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Ventilator Associated Pneumonia (VAP)

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ARHAI Scotland

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Key Information

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Document information	Description
Description:	This literature review examines the available professional literature on ventilator associated pneumonia in the healthcare setting.
Purpose:	To inform the Quality Improvement Tool on ventilator associated pneumonia (VAP) in the National Infection Prevention and Control Manual in order to facilitate the prevention and control of healthcare associated infections in NHS Scotland health and care settings.
Target audience:	All NHS staff involved in the prevention and control of infection in NHSScotland.
Update/review schedule:	Updated as new evidence emerges with changes made to recommendations as required. Review will be formally updated every 3 years with next review in 2025.
Cross reference:	National Infection Prevention and Control Manual A previous version of this literature review informed the 2012 VAP bundle published by SICSAG and available on the **SICSAG website**. The current ARHAI Scotland VAP Literature Review update concluded in 2022 and therefore some literature may not be reflected in the 2012 version of the SICSAG VAP bundle.
Update level:	Practice – No significant change Research – Further research is required to fully understand the impact of IPC on the risk of developing VAP. VAP specific research in adult and, in particular, child and neonatal patients is required.

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Version history

This literature review will be updated in real time if any significant changes are found in the professional literature or from national guidance/policy.

Version	Date	Summary of changes
3	July 2022	Merging of adult and neonatal literature reviews. Addition of new research questions. Updated using 2-person systematic methodology.
2	July 2016	The VAP literature review (version 2) was last published in 2016. The neonatal review was last published as version 1 in 2018.
1	2008	The VAP literature review (version 1) was published in 2008.

Approvals

Version	Date Approved	Name	Job Title	Division
3	22 July 2022	NPGE Working Group		

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1. Objectives

The aim is to review the extant scientific literature to inform a quality improvement tool for the prevention of ventilator associated pneumonia (VAP) in health and care settings to inform evidence-based recommendations for practice. The specific objectives of the review are to determine:

- How can VAP be defined within the literature?
- How should the equipment be prepared prior to insertion (for tracheostomy or endotracheal intubation) for infection prevention?
- How should the insertion site be prepared for a tracheostomy as an aspect of VAP prevention?
- Should humidification be considered as a VAP prevention measure?
- When and how often should a filter be used, what type of filter is needed and where should it be placed for VAP prevention?
- How should the tube be secured?
- How often should the circuit be checked for example for movement or other issues that may be associated with VAP?
- How often should sedation be reviewed as an aspect of VAP prevention?
- What position should the patient be in for/during ventilation as an aspect of VAP prevention?
- How should patients in the prone position be managed for VAP prevention?
- When and how often should subglottic secretion drainage be performed for VAP prevention?
- How and how frequently should condensate be cleared as an aspect of VAP?
- How should oral hygiene care be performed as an aspect of VAP prevention, what should be used?

- How often should patients be assessed for weaning and liberation from ventilator as an aspect of VAP prevention?

2. Methodology

This targeted literature review was produced using a defined two-person systematic methodology as described in the National Infection Prevention and Control Manual: Development Process.

This review considered relevant literature for neonatal, paediatric and adult populations. In addition to the published methodology the following eligibility criteria was applied to select relevant studies for this review. Studies, which did not include or reported a limited definition of ventilator-associated pneumonia (VAP) were, excluded (no radiograph, testing or inability to rule out infection prior to intubation). Studies focusing on prophylactic antibiotic use, selective digestive decontamination or specific tube types, such as silver-coated endotracheal tubes, open/closed systems were considered as out-with the scope of this review.

There are a number of aspects related to healthcare delivery that were not within the remit of this review. This includes that staff are appropriately trained and competent in all aspects of the management of mechanically ventilated patients. The recommendations included within this review are made in reference to ventilator-associated pneumonia, however, all recommendations are considered secondary to clinical requirements and the appropriateness of any VAP prevention activities should be evaluated for each patient. Where appropriate, manufacturers guidance, local or national clinical guidance should be followed. Clinical risks, contraindications or other clinical factors should take priority in the care and management of mechanically ventilated patients of all ages.

3. Discussion

3.1 Implications for practice

How can VAP be defined within the literature?

Ventilator associated pneumonia (VAP) is a leading cause of healthcare associated infection (HAI) within intensive care units (ICUs) and results in a high level of morbidity and mortality.[1, 2] Ventilator associated pneumonia can be caused by aspiration of microorganisms from the oropharynx or stomach; contamination within the ICU environment, particularly the immediate environment; use of contaminated equipment, water, hands of healthcare workers; or via humidified non-sterile water or microorganisms from other sites of infection/colonisation[1-3]

Ventilator associated pneumonia is variably defined within the literature. VAP is generally described as a pneumonia occurring as a result of microorganisms which have entered the lower respiratory tract following a patient being mechanically ventilated. [4, 5] Generally, VAP may be considered 48-hours from commencement of mechanical ventilation.[6-9] A diagnostic criteria published by NHS England West Yorkshire critical care and major trauma department defined early and late VAP as a pneumonia occurring within 48 hours of ventilation (early) or after 48 hours (late).[10] When confirming VAP, clinical criteria [7-9] for pneumonia as well as radiography [6-8] and microbiology [6, 9, 11] are considered. The Scottish Intensive Care Society Audit Group (SICSAG) health care associated infection recognises VAP as those infections meeting the European Centre for Disease Prevention and Control (ECDC) criteria. This represents patients who have been ventilated for more than 48 hours before the onset of infection and considers radiological and clinical and microbiological indicators and is part of the national surveillance of healthcare associated infections in ICU. Scottish expert opinion identified during consultation reported that some units use lung ultrasound as part of the diagnosis of VAP in neonates.

How should the equipment be prepared prior to insertion (for tracheostomy or endotracheal intubation) for infection prevention?

The search identified two limited expert opinion guidance documents which described equipment preparation prior to tube insertion for infection prevention.[12, 13] These were limited by a lack of information regarding how the guidance was formulated and the evidence the

guidance is based on. Actions to consider included never reusing single use equipment[12, 13].Therefore, no recommendation for infection prevention can be made on the preparation of equipment prior to insertion of tubing due to a lack of available evidence.

For more information on the safe management of patient equipment, please refer to the **NIPCM**.

How should the insertion site be prepared for a tracheostomy as an aspect of VAP prevention?

No evidence was identified regarding how the insertion site should be prepared for a tracheostomy as a specific aspect of VAP. Current clinical practice guidelines should be consulted and adhered to. Therefore, no recommendation can be made on how the insertion site should be prepared for a tracheostomy as a specific aspect of VAP prevention. Please refer to the **NIPCM** for further guidance on infection prevention and control, including using an aseptic technique.

Should humidification be considered as a VAP prevention measure?

Humidification is generally considered as a method of reducing possible complications such as drying out of respiratory mucosa which can lead to blockage/occlusion. It involves warming and humidifying inspired gases in mechanically ventilated patients. Active humidification provided through heated humidifiers involves warmed and moistened gases passing through a heated water reservoir and may involve heated wires. Passive humidification through heat and moisture exchange involves a condenser which retains heat and moisture from exhaled breath and returns this in inspired breath. Heated water humidifiers may have a risk of bacterial colonisation of condensate within the tubing. The method of humidification therefore may reduce the risk of VAP but this was not clear from the identified literature. This search identified six expert opinion guidance documents published for US,[13-16] Irish,[12] and international settings.[17] There was no consensus on the most effective humidification method for VAP prevention within these guidance documents. A Centers for Disease Control and Prevention (CDC) publication reported that this is an unresolved issue with no clear preferential method in terms of VAP prevention.[13] The American Association for Respiratory Care state that heat and moisture exchangers (HME) should not be used solely as a prevention strategy for VAP, but

rather based on clinical and other factors.[15] For VAP prevention, they previously suggested there was no clear preference regarding the type of humidification used.[14] The same finding was reported in practice guidance for the management of paediatric patients with a tracheostomy to avoid device-associated complications.[16]Based on the identified expert opinion guidance documents, it could be recommended that the type of humidification employed should be based on patient individual clinical requirements and not solely as an aspect of VAP prevention.

Regarding the frequency of humidifier change, there was consensus in published literature that HME should be changed when clinically indicated, visibly soiled or malfunctioning rather than routinely every 48 hours. [12-15, 17] Therefore, this is considered a clinical issue and should be based on clinical decision making and not as an aspect of VAP prevention, specifically. Clinical and manufacturer guidance should be followed, where appropriate, to select a humidification type and tube position. Other aspects of humidification identified within VAP focused expert opinion guidance was considered. The CDC endorsed guidance published by Tablan et al. (2003), this stated sterile water should be used to fill humidifiers where appropriate.[13] It was suggested by the Strategy for the control of AMR in Ireland National Committee (SARI) working group that changing of the humidifier is an aseptic technique.[12] Scottish expert opinion obtained through consultation recommended that gases should always be humidified in neonates.

In summary, humidification may be generally considered as a recommended clinical measure in mechanically ventilated patients. However, there is a lack of clear evidence for either heated humidification or heat and moisture exchanger use, as well as a lack of consensus around the frequency of heat and moisture exchange as a specific aspect of VAP. The type of humidification should be considered in line with individual patient or clinical factors.

When and how often should a filter be used, what type of filter is needed and where should it be placed for VAP prevention?

A filter in the ventilation circuit may provide filtration of inspiratory or expiratory gases from bacterial, viral or other particulate matter. Limited evidence on the use of filters for VAP prevention was identified, with no available evidence on when and how often a filter should be used, the type of filter (viral/bacteria or other) required, and where it should be placed. The evidence from one moderate quality randomised controlled trial carried out in Spain in 2001

indicated that there may be no benefit from the use of two bacterial filters (one in the inhalation and one in the exhalation branch) when compared with patients with no bacterial filters.[18] However, this study had limited generalisability, applicability and potential bias from lack of blinding. Therefore, due to a lack of evidence no recommendation could be made for this question. However, current clinical or manufacturer recommendations for filter use should be used, where applicable.

How should the tube be secured?

No evidence was identified regarding how the tube should be secured in terms of VAP prevention. Clinical guidance and research should be followed to make decisions regarding tube securement. Therefore, no recommendation can be made on how the tube should be secured in terms of VAP prevention.

How often should the circuit be checked for example for movement or other issues that may be associated with VAP?

Only one primary study compared different frequencies of checking the circuit. This study was a non-randomised study conducted in two ICUs in a US-based hospital which compared frequent (x3 per day) versus infrequent (not specified) monitoring of tube cuff pressure - including audible leak or loss of tidal volume - in adult mechanically ventilated patients.[19] The results showed a similar rate of VAP and mortality in a 30-day follow up period for the two groups.[19] Re-admission rates were significantly (P= 0.02) higher in those receiving infrequent monitoring. However, the study was limited by potential bias due to missing follow up data and a lack of randomisation of patients. Overall, the results indicated that there is no clear evidence for the optimum frequency of monitoring of circuits as an aspect of VAP prevention.

Expert opinion in the literature generally agreed that there was no clear benefit of routinely changing a ventilator circuit based on a period of time. Instead, it was recommended that circuits are changed based on clinical requirements including when soiled/malfunctioning for adults [5, 12-14, 17, 20] children and neonates.[21] No clear, optimal frequency of checking the circuit was identified as a specific aspect of VAP prevention. Current manufacturers and clinical guidance/protocols should be adhered to.

How often should sedation be reviewed as an aspect of VAP prevention?

Mechanical ventilation within intensive care is a lifesaving process when needed, however the risk of VAP may be associated with its duration. The sedation required during ventilation can result in a number of adverse effects including prolonged intubation. There is a small (n=5) body of expert-opinion guidance addressing this question, however none were produced specifically for the UK setting and therefore generalisability may be limited. The identified literature showed consensus that sedation in mechanically ventilated patients should be reviewed and interrupted daily, when appropriate (and not contraindicated) to reduce the duration of mechanical ventilation and reduce risk of VAP.[5, 12, 17, 20, 21] The only deviation from this recommendation was presented by the Society for Healthcare Epidemiology of America (SHEA) who suggested it would not be applicable to neonates as sedation would not ordinarily be used for these patients.[21] SHEA did however recommend daily sedation review and interruption, as appropriate, for paediatric patients.[21] No primary studies comparing the frequency of sedation review and measuring VAP incidence were identified, therefore, this body of evidence is considered as limited and subject to bias. In summary, based on the evidence sourced for this research question it is generally agreed that sedation be reviewed and where appropriate interrupted daily so sedation may be halted when appropriate.

What position should the patient be in for/during ventilation as an aspect of VAP prevention?

This review identified nine records which addressed patient positioning during mechanical ventilation as an aspect of VAP. Three of these were systematic reviews all graded moderate quality [22-24] and the remaining six were limited expert opinion guidance documents.[5, 12, 13, 20, 21, 25] The included studies were heterogeneous, covering different combinations of comparisons of positions making it difficult to establish any consistency in findings. These findings are discussed in more detail within the below sections. Please be aware that clinical indicators should be considered when positioning of each patient as well as for managing patients in different positions (e.g., rotations). Local and national clinical guidance should be adhered to. Clinical management, contraindications or other known clinical risks associated with risks of positioning in any patient of any age should take priority. This includes for neonate positioning where clinical risk of fluctuations in cerebral haemodynamic and Intraventricular haemorrhage (IVH) in the first 72 hours in preterm infants should be prioritised.

Semi-recumbent vs Supine

A Cochrane systematic review and meta-analysis identified significantly lower odds of developing clinically suspected VAP when patients were in the semi-recumbent (30° to 60°) position compared to the supine position (P<.01).[23] Wang et al reported a downward trend but did not see a significant difference between the two positions when considering microbiologically confirmed VAP.[23] However, by the authors' definition, clinically suspected VAP included symptoms and a positive tracheal culture whereas microbiologically suspected cases involved multiple sample cultures and minimum thresholds with unclear symptomology. The authors also reported discrepancies and missing information in the definition of VAP overall. For the three studies included in the microbiologically confirmed analysis, the GRADE of evidence was "*very low quality*" and the analysis was subject to high heterogeneity (I^2 = 87%).[23] This raises concerns about the validly of that analysis. The majority of the studies included within the Cochrane Review were conducted in China. It should also be noted that several (n=7) of the studies included within this Cochrane review were not available in English, one was out-with the date range considered within the eligibility criteria for this review and one was unpublished. It is therefore suggested that the findings of this Cochrane review be treated with caution.

45° Semi-Recumbent Position vs 30° Position

There was consensus across all 6 expert opinion pieces identified that head of bed elevation between 30° and 45° is recommended as part of a VAP bundle.[5, 12, 13, 20, 21, 25] This includes a group of 22 experts in intensive care medicine from 11 European countries,[25] and recommendations sponsored by SHEA,[21] both of which supported the recommendation in adult patients despite a varied evidence base. For paediatric patients, the authors recommended the same position as with adults (between 30° and 45°) based on minimal risk of harm and some data suggesting a lowering of VAP rates.[21] However, for preterm neonates placement in a lateral recumbent position (side lying) or Reverse Trendelenburg position (head elevated 15-30°) was recommended, this was based on minimal risk of harm but unknown impact on VAP.[21] These expert opinion pieces are likely subject to bias due to their lack of methodology for obtaining evidence and therefore unknown quality of the evidence sourced;[5, 12, 13, 20, 21] recommendations formed in the absence of evidence;[21, 25] and lack of generalisability, with only one expert opinion piece from a UK setting.[5] Scottish expert opinion highlighted the importance of considering any contraindications for appropriate neonate positioning. This included the risk of IVH in the first 72 hours for preterm infants. There was some agreement that paediatric

patients may be placed in a semi-recumbent position if it is tolerated and not contraindicated for any reason.

Therefore, based on the identified literature it is possible to suggest that for adult patients, without contraindications, head of bed elevation should be between 30° and 45° to prevent VAP. Head of bed elevation at an angle of 45° may be more effective as an aspect of VAP prevention, however 30° is likely more practical and achievable. Scottish expert opinion highlighted that, semi-recumbent positioning may also be considered where appropriate and not contraindicated for any reason in paediatric patients. Where it is not contraindicated and where it is clinically indicated lateral recumbent positioning (side lying) or reverse Trendelenburg positioning (head elevated 15 degrees) may be considered for neonatal patients.

How should patients in the prone position be managed for VAP prevention?

It is accepted that as a result of clinical factors and clinical decision making, some patients may benefit from prone positioning or an alternative position. Recent rapid pandemic-response National Institute for Health and Care Excellence (NICE) guidelines highlight that COVID-19 patients should be considered for prone positioning where clinically appropriate.[26] No considerations were provided in relation to the management of VAP or VAP prevention in these patients. No other available evidence was identified for how patients in the prone position should be managed specifically for VAP prevention. It should be noted that other clinical considerations are listed by the World Health Organization (WHO) in their adaptation of the SARS infection toolkit published in light of the COVID-19 pandemic.[17] However, specific VAP management strategies for prone positioned patients were not clear. It is therefore not possible to make a clear recommendation for how patients should be managed in the prone position as an aspect of VAP due to a lack of available evidence.

When and how often should subglottic secretion drainage be performed for VAP prevention?

A small evidence base was identified addressing the efficacy of subglottic secretion drainage (SSD) as an aspect of VAP prevention. Two randomised controlled trials comparing intermittent SSD with a control (no SSD) were identified. These were conducted in Belgium, France. Damas et al (2015) supported a reduction of 8.8% (p = 0.018) and Lacherade et al (2010) reported a significant reduction in patients with microbiologically confirmed (RR = .58, 95%CI [0.37-0.90], p = 0.02) but not for clinically confirmed VAP (p = 0.26).[27, 28]However, blinding of the health care workers in both studies was not possible, Damas et al (2015) include both suspected and confirmed cases and Lacherade et al (2010) separated clinically and microbiological confirmed cases.[27, 28] Two low-moderate quality systematic reviews with meta-analysis were sourced which included these trials.[29, 30] Six included studies were not available in English, three were published pre-2000, one was an abstract. Both systematic reviews contained the same 17 randomised controlled trials (RCT) and one (Mao et al) included an additional 3 RCTs.[29, 30] Both found a significant reduction in the risk of developing VAP when subglottic secretion drainage was conducted in patients who were mechanically ventilated for >48 hours.[29, 30] It should also be acknowledged that the meta-analyses may be limited due to varied VAP definitions across included studies and moderate/high risk of bias in most of the included studies. However, subglottic secretion drainage was also recommended in patients requiring ventilation for over 48-72 hours within the SHEA guidance as well as in the UK Intensive Care Society VAP prevention bundle.[5, 21]

There was insufficient evidence identified in the literature to accurately assess the impact of conducting subglottic secretion drainage on paediatric and neonatal patients. Although it should be noted that the SHEA guidance generally recommends that subglottic secretion drainage is not conducted in neonates or in children under the age of 10.[21]

Overall, in adult mechanically ventilated patients' subglottic secretion drainage may be considered as an aspect of VAP prevention, where it is not contraindicated and where a patient will be mechanically ventilated for more than 48 hours. However, at present there is insufficient evidence to recommend the use of subglottic secretion drainage in children or neonates as a routine aspect of VAP prevention.

How and how frequently should condensate be cleared as an aspect of VAP?

There was some consistency in the identified literature that the removal of condensate from endotracheal circuits should be conducted by suctioning as clinically indicated.[13, 31] Due to the research being expert opinion and subject to bias, the optimum frequency of condensate removal is not clear. Only one identified study compared the frequency of endotracheal tube suctioning in mechanically ventilated patients.[32] One study conducted in a NICU with infant patients (n=180) compared suctioning 8-hourly (and as needed) with suctioning 4-hourly (and as needed).[32] There was no significant difference in the risk of developing VAP or reintubation rates between the two frequencies (4 or 8 hours).[32] However, most infants (125/180) had a very low birth weight and the study utilised data collected pre-2000, which may be a limitation if changes in care practice have occurred since that time.[32] It could be considered that condensate removal via suctioning should be conducted based on clinical need rather than a pre-specified routine frequency, as an aspect of VAP prevention. However, due to the limited research identified no clear recommendation can be made.

In summary, limited expert guidance suggests that suctioning be used to remove condensate as an aspect of VAP. The optimum frequency of suctioning was not clear within the literature. It may therefore be appropriate to recommend clearing or condensate when clinically relevant.

How should oral hygiene care be performed as an aspect of VAP prevention, what should be used?

Chlorhexidine Oral Care

This literature review identified five systematic reviews with meta-analysis and two primary studies which compared chlorhexidine use with a placebo or control in mechanically ventilated patients. Three of the identified systematic review with meta-analysis were different iterations of the same Cochrane review 'Oral hygiene care for critically ill patients to prevent ventilator associated pneumonia', Shi et al (2013), Hua et al (2016) and Zhao et al (2020).[33-35] The three Cochrane reviews with meta-analysis reported an association with reduced VAP incidence when chlorhexidine (from 0.12-2%) was used compared to when a placebo or usual care was used.[33-35] All also reported no increase in mortality when chlorhexidine was used compared to a control or placebo.[33-35] Cochrane systematic reviews are generally considered as the 'gold

standard' for systematic reviews and the methods used were appraised as high quality. However, generally, the randomised controlled trials included in these reviews had a high risk of bias and as a result, the finding/recommendations made are considered as low-moderate quality only.

Furthermore, Klompas et al (2014) systematically reviewed the evidence for the use of chlorhexidine oral care in ventilated patients, taking into account the potential impact of two large randomised controlled trials in cardiac patients which the authors suggest skewed the data towards a positive effect for chlorhexidine.[36] After stratifying the studies into cardiac and non-cardiac patients it was found that fewer lower respiratory tract infections occurred in cardiac patients randomised to chlorhexidine (RR 0.56 [CI, 0.41-0.77]).[36] However, there was no association between chlorhexidine use and reduced VAP in non-cardiac patients. Importantly, the three studies of cardiac patients did not assess VAP as an outcome but rather nosocomial pneumonia.[36] The outcomes presented within the review should therefore be considered with caution as they are not specific to VAP prevention. The study found no significant association between chlorhexidine use and mortality, however there was a trend towards increased mortality in non-cardiac patients randomised to chlorhexidine (RR = 1.13 [CI0.25-2.14]).[36] This suggests that chlorhexidine oral care may have reduced lower respiratory tract infection in cardiac patients, but it may not do the same in non-cardiac patients. The authors concluded that policies encouraging routine chlorhexidine be re-evaluated; this is despite not providing a clear association between mortality and chlorhexidine use. This study is also limited due to the heterogeneity between studies and quality of included studies. A similar systematic review by Li et al., (2015) reported that the use of chlorhexidine gels/rinses was associated with a significant reduction in risk of developing VAP in mechanically ventilated patients.[37] In a subgroup analysis, the significant difference was reported for cardiac patients (RR = 0.54, CI 0.39-0.74, p<.01) but not for non-cardiac patients (RR = 0.78, CI 0.60-1.20, p=.72).[37] Mortality did not differ significantly between those receiving chlorhexidine or a placebo/control. However, the concentration of chlorhexidine differed between the included studies, considerable heterogeneity was reported and the included studies had a high risk of bias. Additionally, one experimental study with a historical comparator group, compared chlorhexidine (0.12%, twice per day) use to non-chlorhexidine (no oral care or placebo) use and generally supported that the risk of developing VAP was reduced when chlorhexidine was used.[38] Mortality was reported as similar (non-significantly different) between the two groups.[38] This study only included patients post-cardiovascular surgery patients, and may be subject to bias based on a lack of randomisation, blinding and limitations comparing a retrospective control group. A further

randomised controlled trial conducted in adult mechanically ventilated patients which focused on chlorhexidine use, was identified. It was multi-centred study based in the Netherlands and comparing chlorhexidine (2% or 0.12%) use to 4 applications of either chlorhexidine (2%) in petroleum jelly, chlorhexidine (2%) and colisitin (2%) in petroleum jelly or petroleum jelly (control).[39] It reported a reduction in daily risk of VAP for both treatment groups (chlorhexidine only: HR = 0.454; 95% CI, 0.224, 0. 925; p = 0.030). However, significance testing of baseline characteristics between the groups was not clear and therefore baseline risk of VAP may have differed between the groups.

Furthermore, the Society of Healthcare Epidemiology of America (SHEA) 2014 VAP prevention guidance, which supported chlorhexidine use as a VAP prevention measure in mechanically ventilated patients.[21] This guidance acknowledged that there may be a more "pronounced" effect of chlorhexidine in cardiac patients and that the evidence for non-cardiac patients was less clear.[21] The guidance also reported that there was insufficient evidence of a link between higher mortality and chlorhexidine use in mechanically ventilated patients. The CDC's stakeholder guidance published in 2003 stated that no recommendation could be made for chlorhexidine use in all patients due to lack of research but that it may be beneficial for cardiac patients.[13] Other expert opinion guidance by the WHO (2020) COVID-19 clinical care guidelines provided a VAP prevention toolkit.[17] Within the toolkit, it stated that chlorhexidine should be used regularly as an antiseptic gel or mouth rinse. The Health Quality and Safety Commission for New Zealand's VAP prevention bundle also recommends daily oral care with chlorhexidine though the methods used to produce this document are not clear.[20] Berry et al (2011) report insufficient research to draw clear conclusions regarding the use of chlorhexidine in non-cardiac patients but suggested it is recommended with high confidence for cardiac patients.[40]

An expert opinion VAP prevention bundle published in 2016 and supported by the Intensive Care Society did not recommend chlorhexidine be used as a routine aspect of oral care for mechanically ventilated patients.[5] This recommendation appears to have been based on the findings presented above by Klompas et al (2014) as well as NICE (2008) and Price et al (2014) 2014.[36, 41, 42] Recommendations to use chlorhexidine as a routine oral care antiseptic provided by NICE in 2008 were removed from their technical guidance. Specifically it is stated that, "NICE has withdrawn technical patient safety solutions for ventilator-associated pneumonia in adults, because the recommended action in section 1.2 on administering oral chlorhexidine is no longer supported by the evidence, and risks causing harm".[41] Scottish expert opinion

provided during consultation, suggested that there may be insufficient evidence to provide a strong recommendation for the use of chlorhexidine as an aspect of VAP prevention.

A systematic review, published by Price et al (2014), excluding cardiac patients suggested that the risk of mortality may increase when chlorhexidine is used in ICU patients.[42] However, this review was not specific to mechanically ventilated patients, did not address baseline risk of mortality, and was methodologically limited. It was therefore not considered for inclusion in this review or when making recommendations. For information only, Price et al highlighted that mortality may have been higher for patients receiving chlorohexidine. However, mortality was not the primary outcome in any of the included studies and this was reported in only one included study (Munro et al, 2009).[42, 43] The updated Cochrane review by Zhao et al (2020) did not include the Munro et al (2009) because some of the patients included had pneumonia at baseline.[35] The two previous versions of the Cochrane review by Shi et al (2013) and Hua et al (2016) did include the study by Munro et al (2009), however their findings were the same i.e. they found no association between chlorhexidine for oral care and increased mortality.[33, 34]

No high-quality primary research was identified that assessed chlorhexidine effectiveness in reducing VAP in paediatric and neonatal patients. Specific recommendations for these populations are made by SHEA who instead recommend the use of sterile water for oral care in neonates. [21] For paediatric patients, SHEA did not recommended that chlorhexidine be used due to insufficient evidence and one study reporting no difference in VAP rate, length of stay, or mortality.[21] Thus, as a result of insufficient evidence and lack of detail regarding possible adverse effects, no recommendation can be made regarding the use of chlorhexidine in these populations.

In summary, an assessment of the evidence considering use of chlorhexidine for VAP prevention finds that it is likely to be of benefit to patients with regards to reducing VAP incidence. It also reports no significant association with increased mortality. Despite this, there is some lack of constancy in recommending chlorhexidine use as part of VAP prevention. However, it is not transparent why NICE withdrew their technical guidance. If the decision was based on the studies by Price et al (2014) and Klompas et al (2014), this may have been based on limited evidence.[21, 41, 42] Klompas et al (2014) did not identify a significant risk of mortality, only a trend, and the findings of Price et al (2014) are undermined by the fact that the included studies were not designed to assess mortality as an outcome.[21, 42] The differing results identified may have been related to the different inclusion/exclusion criteria with some including cardiac

patients who are often ventilated for ≤24 hours, others not including patients ventilated for under 24 hours. Generally, the criteria for VAP, frequency of oral care, concentration of chlorhexidine (0.12%-2%) and other aspects of oral care (brushing/not brushing) were not consistent between studies and may bias the results of the included reviews. There is an urgent requirement for higher quality randomised controlled trials investigating the impacts of chlorhexidine on mechanically ventilated patients. There is a particular need for studies that account for the risk of attrition bias in their study designs to ensure data are available at later time points where the risk of VAP is greatest. There is also a specific need for more research on specific populations of adult patients (i.e., cardiac/non-cardiac) as well as paediatric and neonatal (including preterm) patients in terms of VAP, mortality, and other outcomes.

Other Oral Care Measures

Tooth brushing with or without chlorhexidine use was compared in the three aforementioned Cochrane reviews, one RCT as well as one recent systematic review.[33-35, 44] Within the most recent Cochrane update, eight studies with a high risk of bias and low confidence supported a possible benefit of brushing compared with non-brushing (RR 0.61 [CI 0.4-0.91] P = 0.01, I^2 = 40%).[35] Only one included study measured VAP with powered tooth brushing but this study had a high risk of bias (Zhao et al., 2020).[35] Silva (et al., 2021) similarly reported a beneficial impact of brushing on VAP outcomes (RR 0.17 [0.55 to 1.06], I^2= 0%).[44] Generally, tooth-brushing studies had insufficient evidence regarding mortality rates. A multi-centred RCT conducted in four Brazilian hospitals compared 12-hourly tooth brushing plus 0.12% chlorhexidine to no brushing and 0.12% chlorhexidine (control).[45] No significance difference in the risk of developing VAP was reported between the two groups. However, this study had a small sample and had limited microbiological data. Specifically, Berry et al. (2011) expert opinion recommendations suggested that brushing with a soft bristled brush can be used to remove debris and plaque twice a day but that mouth swabs may be used as an alternative if brushing is contraindicated.[40] SHEA guidance recommends that in paediatric patients gums be wiped after eating (if relevant) and that if teeth "*erupt*" brushing be conducted twice a day with water. Fluoride toothpaste could also be considered for children over 2 years of age.[21]

There was insufficient evidence regarding the possible benefits or harms of using povidone iodine as an aspect of routine oral care for VAP prevention. Following a systematic review and meta-analysis Li et al. concluded that povidone iodine was not effective in reducing VAP risk (RR=0.51 [CI: 0.09, 2.82] P=.438).[37] However, Zhao et al. (2020) updated Cochrane review

reported that when povidone iodine was compared to saline or placebo use there was a reduction in the risk of developing VAP (RR 0.69 95% CI 0.50 to 0.95, P=.02).[35] However, a high level of heterogeneity was reported (*I*^{2} = 74%).[35] Three studies included in the sub-analysis within Cochrane review compared povidone iodine use to usual care/saline but one was considered as having a high risk of bias.[35] The remaining two were based in France and include adult mechanically ventilated patients either receiving oral care with povidone iodine (10%) or a placebo or sterile water.[46, 47] Seguin et al (2006) showed no significant difference in the prevalence of VAP between the groups but a significant reduction in the rate or VAP (P = 0.003).[47] However, it may have some risk of bias. It lacked blinding, was single centred and significance testing of the baseline differences between the study groups was not clear. Seguin et al (2014) indicated that there was no difference in risk of VAP.[46] There was a lack of information on the comparability of the six French ICU's included.

The use of saline rinsing or swabbing was also considered in four studies included in Zhao et al (2020) but all had a high risk of bias and high heterogeneity (RR 0.47 95% CI 0.37 to 0.62, P<.001, I^2 = 84%).[35] Saline rinse compared to usual care (RR 0.60 [CI 0.39-0.91] P<.05, I^2= 64% 2 studies) and saline rinse plus swab versus swabbing alone (RR 0.41 [CI 0.23 to 0.72] P=.002, I^2= 0%, 2 studies) were showed to reduce VAP but these studies also had a high risk of bias.[35] Other studies with a high risk of bias compared bicarbonate rinse with tooth brushing; triclosan rinsing, furacilin, hydrogen peroxide or other branded products.[35] Due to the high level of bias and small number of studies on these topics, no conclusions regarding their effectiveness are drawn.

In summary, there is insufficient evidence regarding the possible benefits of tooth brushing as a VAP prevention measure as well as to other possible adverse outcomes. There is also insufficient evidence regarding the use of agents such as saline, povidone iodine or hydrogen peroxide as a routine aspect of VAP prevention. Therefore, it is not possible to make a recommendation regarding tooth brushing, or use of saline swab/rinse, povidone iodine or hydrogen peroxide in mechanically ventilated patients as an aspect of routine VAP prevention.

How often should patients be assessed for weaning and liberation from ventilation as an aspect of VAP prevention?

The duration of intubation may be associated with an increased risk of VAP; to reduce a patients' risk they should be liberated from a ventilator as soon as clinically possible. This

literature review identified five expert guidance documents which considered weaning and liberation from a ventilator as part of VAP prevention strategies. The results of these records may not be generalizable and only one considered neonatal and paediatric patients. Furthermore, as level four evidence, the results are subject to bias. The Society for Healthcare Epidemiology of America (SHEA) guidelines recommend a daily assessment of readiness to extubate (spontaneous breathing trials) in patients without contraindications; this strategy has been found to be associated with extubation 1-2 days earlier compared to usual care.[21] This is supported by other expert guidance created in response to the COVID-19 pandemic.[17] SHEA also recommend daily assessment for extubation/liberation for both paediatric (moderate confidence) and neonatal patients but spontaneous breathing trials were not recommended in preterm/neonatal patients (assessed as low confidence by the experts).[21] Guidelines created by SARI supported daily assessment of readiness for weaning.[12] Whereas, the American Association for Respiratory Care (AARC) provided clinical practice guidance which did recommended spontaneous breathing trials but did not clearly identify an optimum frequency of checking and rather supported assessment for discontinuing ventilator support based on clinical parameters.[48]

Furthermore, Scottish expert opinion recommended that spontaneous breathing trials may be considered, where appropriate in paediatric patients. But, that they should not be recommended as a VAP prevention strategy for neonatal patients.

Therefore, limited evidence supports that mechanically ventilated patients should be checked daily for the appropriateness of weaning and liberation. Where not contraindicated, daily spontaneous breathing trials for adult and paediatric patients may be considered to assess readiness for weaning and liberation from mechanical ventilation.

3.2 Implications for research

The following research questions were also considered for this review:

- What administrative checks should be in place prior to ventilation for the prevention of VAP?
- What PPE should be worn for the procedure for the prevention of VAP?

- How and when should hand hygiene be performed throughout the procedure as a measure of VAP prevention?
- What administrative checks should be in place for the prevention of ventilator associated pneumonia?
- What PPE should be worn and when for VAP prevention?
- How and when should hand hygiene be performed for VAP prevention?

However, following a search of the available literature, no primary studies or VAP specific guidance clearly addressed these questions. While general infection prevention and control (IPC) and good clinical practice recommendations were sourced, these were not specific to preventing VAP. It is therefore recommended that current clinical guidance and relevant IPC measures (as outlined in the NIPCM) are adhered to wherever relevant.

Ordinarily, evidence which investigates bundled care approaches would be excluded from ARHAI reviews as they are not able to assess the effectiveness of a single components of the intervention in isolation. However, two records identified through this review attempted to consider the impact of a VAP bundle in a UK setting. This included an interrupted time series, which discussed VAP incidence in a UK tertiary care centre following the implementation of a bundle of care (head elevation, oral care, suctioning, ranitidine, 4-hourly documentation). The study aimed to reduce VAP incidence rate in a paediatric ICU whilst measuring compliance.[49] No paediatric cases of VAP were detected after the bundle was introduced, yet previous VAP rates were not considered. Additionally, Morris et al (2011) published a before and after study in a Scottish hospital which implemented a VAP prevention bundle (sedation hold and weaning protocols, head raised position, chlorohexidine oral care) in 2008-2009.[50] The results of this study supported a significant reduction in VAP for patients requiring mechanical ventilation for $\geq$ 48 hours, $\geq$6 days and $\geq$14 days.[50] The rate of mortality also decreased after the bundle was introduced by a significant level for all patients mechanically ventilated for $\geq$48 hours, $\geq$6 days and >14 days.[50] Thus, evidence from one UK and one Scottish hospital suggested that a VAP bundle may be beneficial in reducing VAP in these settings. However, lack of blinding, concealment and randomisation are limitations of both of these studies.[49, 50]

As such, it is advised that future primary research investigates the specific aspects of PPE, hand hygiene and administrative checks which may be relevant for VAP prevention. Other topics, which were identified through searching, but that were not covered as part of this review

were the implications of utilising different tubing types (such as silver-coated), selective digestive decontamination and peptic ulcer prophylaxis via antibiotic prophylaxis and wider antibiotic, or pre/probiotic prophylaxis as well as open versus closed suction.

A number of gaps in the current evidence have been identified as a result of this review, which may have implications for future research priorities. Future research should aim to investigate each aspect of VAP prevention individually. Issues identified within the literature included the lack of consistency in diagnosing and describing VAP. This may mean it is difficult or inappropriate to compare studies for the purpose of guideline production. In attempting to identify risk factors to target in a quality improvement tool it was noted that some studies included potential confounding factors, such as the underlying impact of VAP on mortality, patient population (cardiac/non-cardiac), period of time ventilated or gestational age; it is important that future studies adjust for these and similar risk factors in multivariate analysis. Furthermore, the optimum frequency, application method, concentration and impact (including mortality and VAP) of chlorhexidine for the prevention of VAP remains an important, unresolved topic which requires high quality evidence. These may look to provide more consistency in the interventions used as well as the measured outcomes to reduce heterogeneity and understand the impact of these factors on the efficacy of oral care. Future high quality research should address these gaps to understand the most effective measure to prevent VAP in a health and care setting.

4. Recommendations

This review makes the following recommendations based on an assessment of the extant scientific literature on the prevention of ventilator associated pneumonia (VAP) in the health and care setting.

No recommendation was made for the following questions:

How should the equipment be prepared prior to insertion (for a tracheostomy or endotracheal intubation) for infection prevention?

How should the insertion site be prepared for a tracheostomy as an aspect of VAP prevention?

When and how often should a filter be used, what type of filter is needed and where should it be placed for VAP prevention?

How should the tube be secured?

Therefore, other clinical guidance and judgements should be made adhering to local or national (where appropriate) protocols/guidance.

What methods of humidification should be considered as a VAP prevention measure?

For the prevention of ventilator associated pneumonia (VAP), there is no recommendation for the preferential use of either heated humidification or heat and moisture exchangers. The use of humidification and the method employed should be based on clinical assessment of each patient across all patient groups.

(Category C)

How often should the circuit be checked for example for movement, or other issues that may be associated with VAP?

No recommendation can be made regarding the optimum frequency of checking the circuit as an aspect of VAP prevention. Manufacturers, local protocols and clinical guidance should be followed for all patients of any age.

Minimize breaks in the ventilation circuit and consider changing if visibly soiled or malfunctioning.

(Category C)

How often should sedation be reviewed as an aspect of VAP prevention?

Patient sedation should be reviewed each day and stopped, if applicable.

(Category C)

What position should the patient be in for/during ventilation as an aspect of VAP prevention?

All patient positioning should be based on individual clinical factors.

For adult patients, without contraindications, head of bed elevation should be between 30° and 45° to prevent VAP. Head of bed elevation at an angle of 45° may be more effective as an aspect of VAP prevention, however an angle of 30° is likely more practical and achievable.

(Category C)

Paediatric patients:

Where it is not contraindicated, and where it is tolerated, paediatric patient may be placed in a semi-recumbent position (between 30° and 45°).

(Category C)

Neonatal patients:

Where it is not contraindicated (for example the risk of intraventricular haemorrhage in first 72 hours for preterm infants), and where it is clinically indicated, a lateral recumbent position (side lying) or Reverse Trendelenburg position (head elevated 15°) may be considered for neonatal patients.

(Category C)

When and how often should subglottic secretion drainage be performed for VAP prevention?

In adult ventilated patients subglottic secretion drainage should be considered as an aspect of VAP prevention, where it is not contraindicated and where a patient will be mechanically ventilated for more than 48 hours.

(Category B)

Paediatric or neonatal patients:

No recommendation for subglottic secretion drainage in paediatric and neonatal patients.

How and how frequently should condensate be cleared as an aspect of VAP?

Where clinically indicated and not contraindicated, condensate can be removed by suctioning in patients who are mechanically ventilated.

(Category C)

How should oral hygiene care be performed as an aspect of VAP prevention, what should be used?

Individual patient requirements should be considered when implementing oral care. Oral care should be conducted daily in mechanically ventilated patients.

(Category C)

The use of chlorhexidine may be considered, unless contraindicated for any reason, in adult patients, particularly cardiac patients.

(Category B)

Paediatric/neonatal patients:

Chlorhexidine should not be used as a part of routine oral care for the prevention of VAP for neonatal/preterm patients or children. Sterile water may be used as part of neonatal oral care.

(Category C)

How often should patients be assessed for weaning and liberation from ventilator as an aspect of VAP prevention?

All patients should be assessed daily for the appropriateness of weaning and liberation.

(Category C)

Where not contraindicated, the use of daily spontaneous breathing trials should be considered for adult patients and where appropriate for paediatric patients to assess readiness for weaning and liberation from mechanical ventilation.

(Category C)

Neonatal patients:

Spontaneous breathing trials are not recommended in neonatal patients as an aspect of VAP prevention.

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Appendix 1: Grades of recommendation

Grade	Descriptor	Levels of evidence
Mandatory	'Recommendations' that are directives from government policy, regulations or legislation	N/A
Category A	Based on high to moderate quality evidence	SIGN level 1++, 1+, 2++, 2+, AGREE strongly recommend
Category B	Based on low to moderate quality of evidence which suggest net clinical benefits over harm	SIGN level 2+, 3, 4, AGREE recommend
Category C	Expert opinion, these may be formed by the NIPC groups when there is no robust professional or scientific literature available to inform guidance.	SIGN level 4, or opinion of NIPC group
No recommendation	Insufficient evidence to recommend one way or another	N/A

Appendix 2: PRISMA Flow Diagram[51]