ORAL HYGIENE INTERVENTIONS FOR THE PREVENTION OF HEALTHCARE-ASSOCIATED INFECTIONS

AND

THE IMPACT OF HEALTHCARE-ASSOCIATED INFECTIONS ON PATIENTS HOSPITALIZED WITH OROPHARYNGEAL CANCERS OF LIP, MOUTH, AND PHARYNX.

by

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Gugoi, my daughter,
Minu, my wife,
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Background

Healthcare-associated infections (HAI) are a significant concern in the United States, about 1 in 25 patients acquire HAI in any health care facility, including hospital, ambulatory surgical center, end-stage renal disease centers and in the long-term care facilities. [1] The risk for developing the HAIs include catheters, surgery, injections, unhygienic setting, communicable disease, and overuse of antibiotics. [1, 2] The prevention strategy put forward by the Centers for Disease Control and Prevention (CDC), including a set framework for the state HAI prevention plans and judicious use of antibiotics. [3]

The oral cavity is a natural environment for an enormous quantity of microbes and as such an ecological niche for opportunistic and pathogenic microorganisms that can lead to risk for cross-contamination and infection. The risk of these infections is increased in hospitalized patients when oral cavity bacteria are aspirated. Data suggests that aggressive oral hygiene interventions that lessen oral bacterial colonization reduce the risk of ventilation associated pneumonia (VAP). [1] When ventilation is found to be one of the risk factors for aspiration pneumonia, the mainstream record suggests, the focus has always been on VAP.

Enhanced oral care has always been a focus towards reducing the VAP while reducing the risk of pneumonia through enhanced oral care in non-VAP (NVAP) setting is a hypothetical prevention strategy to be tested for, as pneumonia-causing microbes are always present in the oral cavity. Hence, we investigate the likelihood of Oral care intervention in preventing the NVAP is true with an experimental hypothesis that reflects that there will be an observed effect for our experiment.

There appear to be a gap in the literature concerning the comparative effectiveness of oral care interventions (OCI) as a medium to reduce HAI, such as VAP and non-ventilator associated pneumonia (NVAP). Furthermore, the characteristics of these HAIs among those patients undergoing major oropharyngeal procedures are poorly defined relative to their impact on health outcomes and costs. Henceforth, we undertook three studies to estimate these gaps,

i) The effect of enhanced oral care interventions for the prevention of NVAP: A systematic review and meta-analysis of randomized controlled trials and non-randomized trials. (Published, April 24th, 2020 issue of the British Dental Journal),

ii) Network meta-analysis to assess the comparative effectiveness of oral care interventions in preventing ventilator-associated pneumonia in critically ill patients. (Submitted to the journal of BMC Oral Health),

and, iii) The impact of healthcare-associated infections on patients hospitalized with oropharyngeal cancers of lip, mouth, and pharynx – A National inpatient sample 2017 database study. (In preparation).

We performed a pairwise meta-analysis by assembling aggregate patient data (APD) from completed studies that have been published in the medical literature. Limitations might arise, such as - addressing some queries which are not focused in original publications; information about the adequacy of randomization; adjustment for the same variables across studies; ability to address long-term outcomes; exploration of heterogeneity at the patient level and subgroup analyses of patient-level data. These are some of the limitations of the aggregate patient-level meta-analysis, and to tackle these challenges individual patient data meta-analysis is most suitable, we tried to get the individual patient data from the authors to make our study findings robust, but this was time-consuming, and only a few responded. Other limitations of PMA which might equally arise is the publication bias, which arises as a result of lack of studies published with negative effects, primarily due to studies with small sample size and lacking power; no difference between intervention and control groups; and complications or adverse events in the study group. [5]

Some of the ways of dealing with these challenges

- We decided priori to perform a pairwise meta-analysis focusing on the randomized, non-randomized trials and observational study
- We searched for different databases apart from the primary databases for grey literature.
- To reduce the effect of small-study effects and heterogeneity, we have priori decide to use the Hartung, Knapp, Sidik, and Jonkman (HKSJ) adjustment for the random-effects model. Simulations have shown that the HKSJ method performs

better than DerSimonian Laid (DL), especially when there is the heterogeneity, and when number of studies in the meta-analysis is small.

- To assess the publication biases - Funnel plot, trim and fill and Eggers plot are effective in detecting these tasks. We have not performed a publication biases as there were less than ten studies included in our study cohort.

Our second project focused on the Network Meta-analysis (NMA). The possible challenges in performing the NMA are the extension of clinical and methodological homogeneity to comparisons (or transitivity assumptions) across groups of studies that compare treatments, and secondly consistency or the statistical manifestation of transitivity. [6] Ways of dealing with these challenges, we performed an NMA on a robust recently published pairwise meta-analysis. We believe that selecting the previously published PMA [4] represents a current, comprehensive, and inclusive review of the topic. The PMA was screened from most of the massive databases, most of them were searched until 2015 and 2016. We believe that we followed strict assumptions and standardization, as this is the first NMA. The transparency, reproducibility, and detailed documentation of our findings can be appropriately appraised when the readers can compare both the studies.

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Research 1a.

Enhanced oral hygiene interventions as a risk mitigation strategy for the prevention of non-ventilator associated pneumonia:
A systematic review and meta-analysis of randomized controlled trials and non-randomized trials.

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Enhanced oral hygiene interventions as a risk mitigation strategy for the prevention of non-ventilator associated pneumonia: A systematic review and meta-analysis of randomized controlled trials and non-randomized trials.

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Abstract

Background. Healthcare-acquired pneumonias are a significant risk for nursing home and hospital patients. While oral care interventions (OCI) have been found to be effective in reducing the risk of ventilator-associated pneumonia (VAP), their utility in mitigating non-ventilator-associated pneumonias (NVAP) remains unknown. We

performed a structured meta-analysis of randomized and non-randomized clinical trials of enhanced oral hygiene procedures on NVAP.

Methods: We searched PubMed and Embase to include clinical trials (randomized and non-randomized), and observational (retrospective and prospective), and quasi experimental studies examining the effect of any method of OCI on incidence of NVAP.

Results. After quality assessment and consensus agreement between authors we synthesized 6 randomized clinical trials (RCTs) (3891 patients), two non-randomized trials (2993 patients); and separately assessed a retrospective trial (143 patients) and a quasi-experimental study (83 patients). Most studies, performed in nursing homes, did not show a significant association between OCI and NVAP prevention (RR random 0.89, 95% CI 0.64-1.25, p value 0.50). Likewise, the non-randomized trials failed to show an association between NVAP risk and OCI (RR random 1.42, 95% CI, 0.70-2.88, p value 0.32). However, in the subgroup analysis comparing dental professional involvement in care vs usual care, reduced NVAP risk was demonstrated (RR random 0.65,95% CI 0.43-0.98, p value 0.03).

Conclusions. Study results suggest that professional dental care may have some benefit among NVAP patients. The lack of consistent OCI protocols, data in hospitalized patients, and robust RCTs do not allow definitive conclusions about the contribution of OCI in mitigating NVAP risk.

1.0 Introduction

Pneumonias acquired in acute and chronic healthcare facilities are a significant risk for patients. A 2015 survey reported that hospital-acquired infections affect approximately 3.2% of patients hospitalized in the United States (1) or 1,184,000 cases this year, at costs exceeding $40,000,000,000. Among hospital-acquired infections, pneumonias are the most common with an overall incidence of 21.8%. (2-4) Pneumonia is also clinically the most significant infection among the approximately 1.7 million nursing home patients in the United States with an incidence of 0.3 to 2.3 episodes per 1000 resident care days. (5)

Pneumonias in these populations are typically categorized based on their association with ventilator use. Ventilator-associated pneumonias (VAP) have been best studied and protocols have been developed which have lowered their risk. In contrast, the prevalence of non-ventilator-associated pneumonias (NVAP) has remained essentially unchanged. (1) Classical hospital-acquired pneumonias are defined as those that develop after 48 hours of hospital admission. (6) While the definition for NVAPs can also be applied to nursing home patients, there are marked differences between the two populations including length of stay [nursing home 13.7 months (7) vs. 6.1 days for acute care hospitals (8)], demographics and co-morbidities. Nonetheless, given the potential importance of the oral cavity as a bacterial source for NVAP generally we included both populations in the analysis but analyzed them separately.

The physiologic and healthcare costs of NVAPs are significant and have been well-described.(2, 4, 8) The microbial etiology of NVAP has been ascribed to pathogens associated with the upper aerodigestive tract for which four potential routes of contamination have been hypothesized: aspiration of oropharyngeal secretions, food or gastric contents, inhalation of infectious aerosols, contiguous spread of infection or hematogenous spread from non-pulmonary sources to the lung. (9) The primary source of pathogens of pulmonary infections is suggested to be associated with aspiration of colonized secretions from the oropharynx. However, given the bacterial spectrum reported for NVAP, it is impossible to ignore the nose, nasopharynx or sinuses as also being important. A relationship between NVAP risk and dentate state is unresolved. (10)

Intensive oral care interventions (OCI) regimens that reduce the oral cavity bacterial load has been suggested to be effective in mitigating NVAP risk. The individual elements comprising these regimens have not been consistent and range dramatically in their intensity. However, trends in outcomes potentially support their utility. If professionally delivered oral care regimens are to be considered for universal standard of care for NVAP prevention, several critical questions require answers: 1. Is the nursing time, effort and instrumentation needed for an expanded oral hygiene program justified by a cost/benefit analysis; i.e. how effective are expanded oral hygiene programs in modifying risk of NVAP? 2. Are there specific risk factors which can prospectively identify patients at NVAP risk and how do these patients specifically respond to oral hygiene programs? 3.When is the optimum time to initiate oral care interventions , i.e.

are programs which commence at the time of admission effective, or should oral hygiene programs begin earlier, and if so, how much earlier, and 4. Are the pathogens observed in NVAP found in the oral biofilm, where are the primary depots of pathogens and which OCI best target those depots? As a first step, we performed a structured meta-analysis in which we assessed randomized and non-randomized clinical trials and observational studies that investigated the relative efficacy of enhanced OCI Program on NVAP.

2. Methods

2.1 Search strategy and inclusion criteria

Using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement, (11) a systematic literature appraisal was performed. The literature search was done in PUBMED (inception until January 2019) and EMBASE (1990 to January 2019) using inclusive search terms (See Supplementary Appendix 1). The searches included all study designs: clinical trials (randomized and non-randomized), observational studies (retrospective and prospective), and quasi experimental studies. Title and abstracts were independently screened by two investigators (KS, SS) and disagreements regarding eligibility were discussed. Cross-referencing and supplementary literature searches were performed to examine references in topic-related previous published reviews and by manually searching bibliographies of the included articles and similar articles. Full-text screening of selected publication was done by two examiners and discrepancies were resolved by discussion.

For each selected study, the study characteristics were extracted by two assessors which were then corroborated by a third researcher.

Inclusion criteria:

Experimental and observational studies were included based on the following criteria: 1.) reporting NVAP as a primary outcome; 2.) conducted on hospitalized/chronic care facility adults > 18 years of age and were not diagnosed having pneumonia at the time of admission; 3.) intervention or exposure to enhanced oral care, whether matched with placebo, usual care or comparable medication for preventing NVAP; 4.) provided data in the form of point estimates and measure of 95% confidence intervals (CIs) or the data were required to be available to calculate those measures. Studies were excluded if they did not provide specific NVAP results as were those that used the term "hospital-acquired pneumonia (HAP)" but did not differentiate NVAP from VAP. We also excluded the studies which were not published in English Language, and results published as abstracts or poster presentations. If data from the same patient cohort was published more than once, we only included the study which most informed our outcome.

2.2 Data extraction

Data were extracted from eligible studies, independently, using pre-specified data extraction forms. For each included record, study characteristics were recorded by two independent members of the team and discrepancies were resolved by discussion. Characteristics included methods, country, setting, duration of follow-up, sample size, number of patients randomized, number of patients evaluated, inclusion and exclusion

criteria, diagnosis of NVAP, intervention (type, dose, and frequency of oral care), control (type, dose, and frequency of oral care), outcome measures involving incidence of NVAP secondary endpoints, and funding source.

2.3. Quality of studies

Reviewers independently extracted and assessed the risk of bias for randomized controlled trials (RCTs), the random sequence generation (selection bias); allocation concealment (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data (attrition bias); selective reporting (reporting bias) and other bias (example, funding bias).

The quality of randomized controlled trials was assessed using the Risk of Bias tool from the Cochrane Collaboration and the quality of observational studies was assessed using the Newcastle-Ottawa Scale (NOS). (12, 13) Case definition met the selection/outcome criteria if recorded in health-services/study databases as actual diagnoses and did not meet the NOS criteria if self-reported and/ or gathered by questionnaire. A similar approach was taken with ascertainment of enhanced oral care to meet relevant NOS criteria if recorded as prescriptions in health-services/study databases and did not meet NOS criteria if self-reported and/or gathered by an unvalidated questionnaire. For loss-to follow up we considered any study with ≤10% loss-to follow up adequate. The remaining NOS criteria were followed routinely.

2.4. Subgroup analyses

We performed three subgroup analyses. In the first, we evaluated the effectiveness of chemical disinfection on NVAP risk, in the second, we compared the differences in effectiveness between enhanced oral hygiene regimens in which a dental profession (dentist/dental hygienist) vs. those which were administered solely by non-dentally qualified individuals and in the third, we evaluated the effectiveness of the enhanced oral hygiene regimens on the outcome of mortality due to NVAP.

2.5 Statistical analysis

Statistical analyses were based on comparing rates of total NVAP events between the enhanced OCI group and the control group. If the studies did not report the number of NVAP events and/or the total number of participants in the enhanced OCI group and the control group, we used RR, OR, and a measure of variance 95% Confidence interval (CIs) to produce summary relative risk estimates and measure of variance 95% CIs. Due to the expected clinical heterogeneity between studies, we decided a priori to use a DerSimonian and Laird (DL) random effects model for all analyses.(14) Testing for heterogeneity between the studies was performed using Cochran's Q test (15) and the I_2 test. (13) A p value < 0.05 or an I_2 higher than 50% were considered significant evidence for heterogeneity. Additionally, we used the Hartung-Knapp-Sidik-Jonkman (HKSJ) (16) to retrieve more adequate error rates. Simulations have shown that the HKSJ method performs better than DL, especially when there is heterogeneity and the number of studies in the meta-analysis is small. (16-20) Subgroup analysis was performed to assess whether there were differences between professional dental care

and usual care; use of antimicrobial chlorhexidine and usual care; and mortality due to pneumonia in enhanced OCI versus usual care. All statistical analyses were performed using R Studio, Version 1.1.456 (RStudio: Integrated Development for RStudio. RStudio, Inc., Boston, MA URL).

Visual assessment using Funnel and Egger's plots for publication bias wasn't performed as we had only less than 10 studies included in the meta-analysis.

3. Results

Our initial search provided 16,611 records; duplicates of 6223 were removed with the Endnote software X9.1.1 version. After title and abstract screen, 5921 unrelated records were excluded, culminating in 302 records that were assessed for eligibility using full text screening. Eleven studies were identified as meeting our inclusion criteria. Our search strategy led to identification of 7 clinical trials, 2 non-randomized clinical trials, 1 quasi-randomized and 1 retrospective cohort study. [Figure 1]

Characteristics of the included studies are listed in **Table 1**. Seven RCTs (21-27) are included in our analysis of which five (21-23, 26, 27) were conducted in nursing homes, one (24) in stroke rehabilitation unit, and one (25) in intensive care unit (ICU). One study was not included in the qualitative assessment because of non-estimable risks both in the intervention and the control group. (24) A total of 3891 patients were included in the overall analysis. Among the non-RCTs (28, 29), one study (28) (number analyzed, 2890) was done in non-intensive acute care hospital setting and the other (29) in nursing home residents. Among the other experiment

designs, one study was quasi experimental trial (30) (number analyzed, 83) in a neurosurgical population outside the critical care environment and the other study was a retrospective analysis (31) (number analyzed, 143), done in nursing home residents. We employed a per-protocol analysis (PPA) to understand the superior effects of treatment as PPA provides an estimate of the true efficacy of an intervention recognizing that PPA interpretation to actual practice may be confounded by an overstated treatment weight. [32]

3.1 Meta-analysis of enhanced oral care in preventing NVAP- RCTs

The meta-analysis on the 6 RCTs was performed using the DL and HSKJ methods. The DL method demonstrated a pooled relative risk of 0.89, (95% CI: 0.64-1.25, p value=0.50, I_2 =65.2%, p value$_{het}$ =0.01, tau^2= 0.08). **[Figure 2]** HKSJ adjustment of the confidence intervals provided similar results. Since fewer than 10 studies were included in the quantitative synthesis, publication bias assessment was not performed.

3.2 Effect of oral chlorhexidine (CHX) in the prevention of NVAP

Subgroup analysis was performed to assess the effect of oral chlorhexidine rinsing on the prevention of NVAP (n= 3 studies). Using the DL method, the combined effect size was 1.05 (95% CI, 0.69 to 1.60, p value=0.80; I_2=76.6%, tau^2= 0.08 with p value$_{het}$=0.01, suggesting that the addition of chlorhexidine to an enhanced oral care regimen was ineffective in preventing NVAP. **[Figure 3].**

3.3 Dental professional involvement in enhanced oral care in prevention of pneumonia

Subgroup analysis of the impact of dental professional involvement (dentist or hygienist) in enhanced oral care versus usual oral care in the prevention of NVAP (n= 3 studies) revealed a pooled relative risk of 0.65 using the DL method (95% CI, 0.43 to 0.98, p value = 0.03, I^2=*0%*, tau^2= 0 with p $value_{het}$=0.9). It appeared that oral care in which a dental professional was involved favorably reduced NVAP risk (risk reduction of 35%). [**Figure 4**].

3.4 Effects of enhanced oral care in the prevention of mortality due to pneumonia

There was no impact of enhanced oral care in reducing NVAP-related mortality (n= 4 studies); pooled relative was 0.80 (95% CI, 0.40 to 1.63), p value = 0.54, I^2= 83%, tau^2 = 0.38 with p $value_{het}$= 0.00 based on the DL method. **[Figure 5]**

3.5 Non-randomized clinical trials

Assessment of the two non-randomized clinical trials performed with DL method showed the pooled relative risk 1.42 (95% CI, 0.70 to 2.88) p value = 0.32, I^2= 74%, tau^2 = 0.19 with p $value_{het}$= 0.05. **[Figure 6].**

3.6 Other studies

Two additional studies were included in the meta-analysis, a retrospective and a quasi-experiment study. The retrospective analysis noted an odds ratio of 1.21 (95% CI 0.99-1.48), with a p value of 0.6. The quasi experimental study showed relative risk of 0.25 (95% CI 0.06, 1.02) p value of 0.05.

Discussion

The oral cavity is a documented source of pathogens which might contribute to NVAP risk. Consequently, enhanced oral hygiene regimens aimed at reducing the oral bacterial load have been proposed as a risk mitigation strategy. While standard patient-performed oral hygiene is an integral part of a proactive health maintenance routine, definitive evidence of the health and cost benefits of more aggressive regimens on NVAP risk is critical for making the case for widening its implementation. Our aim was to assess clinical trial outcomes in this space using a meta-analysis strategy. Our findings in the effectiveness of enhanced oral care on preventing NVAP were null.

Most studies were performed in nursing home patients. While there are clearly substantive differences noted above between nursing home and acute care patients, they share risk of acquired bacterial pneumonias for which the overall pathogenesis is similar. (5) Thus, both patient cohorts serve as platforms upon which to assess the impact of procedures to reduce the oral bacterial burden as a mitigating strategy. Importantly, despite their dissimilarities, learnings from each group may be applicable and relevant to the other. Collectively the per protocol analysis of enhanced oral hygiene (OH) failed to demonstrate a statistically significant impact on NVAP (pooled RR of 0.89, CI: 0.64-1.25, p value 0.50) risk, which was diverse from that reported in an earlier meta-analysis of 4 RCTs (RR 0.61, CIs 0.40, 0.90, p value 0.02). (35) When the evaluation was limited exclusively to nursing homes (n=5) the impact of OH on NVAP RR was 0.90, CIs 0.63, 1.28, p value 0.56. It is noteworthy that enhanced OH negatively

impacted risk in one U.S. study (RR of HVAP was 1.36). (27) Aside from the patient population and location of each trial, the intensity of the oral hygiene intervention was not uniform and varied principally in two ways: who performed the oral hygiene intervention and whether an antimicrobial rinse was included in the OH regimen.

The results of two non-RCTs trials support enhanced OH as an effective strategy to reduce NVAP risk, but in specific patient groups. A statistically significant reduction in NVAP incidence was reported in a neurosurgical patient cohort. (30) Given the typical functional impediments associated with these patients, the finding is not surprising. A retrospective medical chart review in nursing home patients (31) concluded that enhanced OH performed by a dedicated nursing assistant (n=78) significantly reduced HVAP outcomes compared to no oral care (n=65).

Our subgroup analysis comparing health care provider credentialing impact on outcomes showed the standard enhanced oral hygiene regimens (21,23,25) in which dental professionals were involved appeared to be more effective than those rendered by other providers in reducing NVAP risk (Figure 4). This effect is comparable to previous meta-analysis. (33) While this data supports the concept that effective oral microbial debridement favorably impacts NVAP risk, the conclusion that formal dental training results in demonstrably superior outcomes could be misleading as the effect might not be specifically attributed to variances in technical competencies, but rather to focus and time spent on the oral hygiene process. Whereas non-dental professionals typically number oral care as one of many patient-related daily tasks, the sole emphasis

of the dental professionals was on mouth hygiene. The observation that oral care delivered by a dedicated nursing assistant produced equivalent NVAP-risk supports this argument. (7) Competing time demands for services may limit nurses' capacity to deliver optimal mouthcare. (28) Additional studies are necessary to more fully investigate the impact of provider qualifications on NVAP risk modification since the cost implications of dedicated oral health aides, regardless of their qualification, is not trivial.

Two non-RCT studies in acute care hospital patients were informative. Among 90 elderly patients admitted emergently for lower limb fractures, ten percent of patients developed NVAP. (10) While the authors found that pathogen colonization of the mouth was higher in patients who developed NVAP, it was insufficient to explain differences between VAP and NVAP groups. Whereas NVAP risk was not associated with being dentate, tooth number, or heavy dental or denture plaque, it was associated with a specific bacterial carriage which the authors concluded was present prior to hospital admission.

In perhaps the largest study in an acute care hospital population, (control n=1,487; experimental n=1,403), NVAP development was compared between patient self-brushing (control; n = 1,487)) and enhanced nurse-delivered oral care (experimental arm; n=1,403, three times per day toothbrushing with a fresh toothbrush and daily use of an antiseptic rinse). Despite the designated oral care regimen, no impact on NVAP rates were seen between the control (1.7%) and test groups (1.8%). Critically, despite study-specific training and daily monitoring, nursing compliance was only 1.6 times per

day, only slightly better than patient self-brushing frequency (1.2 times per day). However, when subjects from both arms were pooled and compared based on whether they developed NVAP, the odds ratio for NVAP decreased by 40% when toothbrushing increased by once per day regardless of who performed the procedure. Importantly, this finding suggests that patient-directed education programs and provision of oral care kits may be a valuable and cost- effective approach to NVAP control.

Given the challenges of cost and compliance with professionally delivered oral hygiene-based approaches, chemical disinfection offers a non-procedural alternative to reduce both the tooth-borne and mucosal oral bacterial burden. The latter clearly plays a role in VAP risk and reduction of mucosal bacteria such those residing on the tongue provides an important target for sustained anti-bacterial efficacy. (34) Chlorhexidine remains the most popular agent for this purpose. However, in contrast to its reported efficacy in preventing VAP, its efficacy mitigating NVAP risk was inconsistent across the 3 RCTs (RR 1.05) we evaluated (22, 25, 27), perhaps because of differences in dose response effects and/or the impact of concurrent treatment. (35)

The contrasting efficacy of chlorhexidine rinses between NVAP and VAP is interesting. One might speculate the antimicrobial prophylaxis in the form of a topical agent is effective in preventing colonization of the ventilator tubes in the same way that similar agents favorably impact catheter-centric infections. In the case of VAP, oral plaque accumulation could be exacerbated with placement of ventilation apparatus, especially in the premolar and molar areas.(36) In non-ventilated patients, the microbiome and the

environment is more fluid and subject to dilution effects of saliva which might negatively impact efficacy.(37,38) It is also possible that the time to onset which defines NVAP reduces the potential prophylactic efficacy of antimicrobials by compressing the time in which they might effectively impact NVAP outcomes.

Evaluation of the NVAP literature indicates that NVAP risk is not equivalent for all patients. (39) High rates of NVAP are consistently noted in post-operative cancer patients, patients with neurological diseases and the elderly. The finding that dentate state (dentulous vs. edentulous and number of teeth) is not a clear risk determinant contradicts an oral hygiene strategy that focuses solely on tooth-borne bacteria. (10) It is possible that a patient's oral health status may be a risk component to the extent that it reflects bacterial load. However, whether there is equivalent contribution to hospital associated pneumonia amongst the different microbiological ecoenvironments in the mouth (i.e. tooth-borne bacteria vs. mucosal bacterial niches like the dorsal tongue) is unclear. (39, 40) Likewise, the comparative effectiveness of different oral hygiene interventions on impacting bacterial pathogens is unresolved. (41) Our analysis confirms the need for additional study to fully assess the benefit of OCI, optimize its timing and personalize the intensity of OCI based individualizing risk/benefit. It seems obvious that a "one size – fits all" approach for OCI would likely result in being excessive for many patients, but inadequate for others. Given the frequency and impact of NVAP, additional study is warranted.

Conclusion

In the Introduction we noted four question to which answers would better define NVAP risk and intervention strategies. Given NVAP's potential clinical and economic burden, there is surprisingly little definitive documentation in the form of randomized-controlled trials (RCTs) which speak to the efficacy of directed intervention methods. Most of the RCTs reported were done in nursing homes – most in Japan – and they conclude that structured enhanced OH regimens effectively reduced the rate of NVAP, and that enhanced OH delivered by dental professionals were most effective. Therefore, the generalizability of the results is limited. As a proof-of-concept, the results of such studies can be concluded to be positive with an overall reduction in NVAP rates of greater than 10%, but their broad translatability to the general hospital population is unclear. While good oral hygiene for hospitalized patients should be as consistent as handwashing and bathing, the current body of clinical research defining extended oral interventions as they relate to VAP risk, and the comparative effectiveness of various oral care interventions is incomplete. Given the impact of NVAP large, structured, randomized trials in which specific interventions are tested are critical.

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Authors role

1) SK and STS: Design, methods, data collections, analysis and preparation of paper.
2) SP: Analysis and preparation of paper.

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Figure and Tables

Figure 1. Flow diagram showing summary of literature search and study selection.

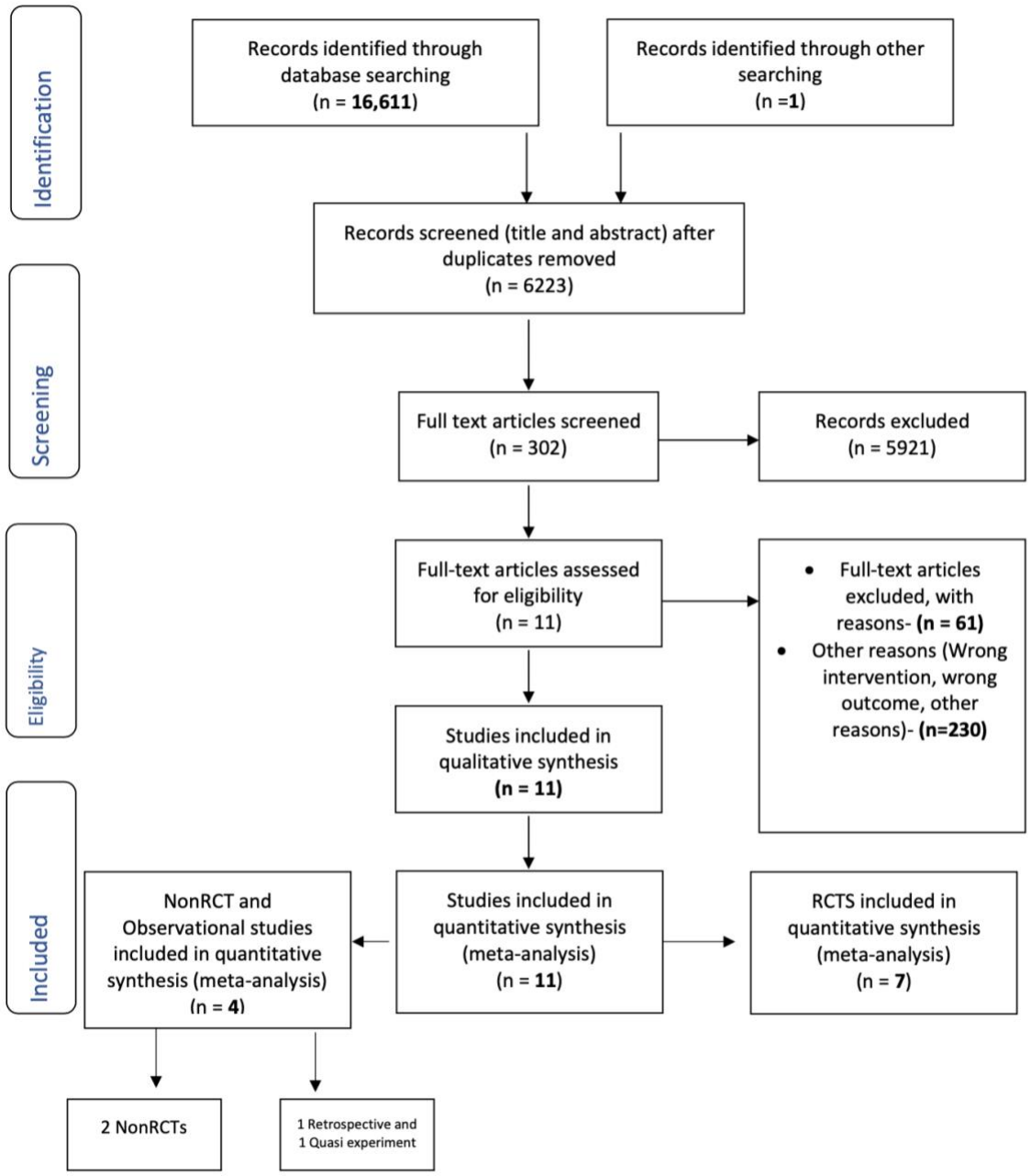


Table 1.

REFERENCE, YEAR	*COUNTRY*	*YEAR*	*STUDY SETTING*	*DURATION*	*NUMBER OF PARTICIPANTS*	*INTERVENTION TYPE*	*CONTROL*
ADACHI 2002	Japan	2002	Nursing homes	24 months	Number evaluated: 88	Professional care	Usual oral care
BOURIGAULT 2011	France	2011	Nursing homes	18 months	Number evaluated: 2513	Chlorhexidine oral rinse and enhanced oral care	Usual oral care
JUTHANI-MEHTHA 2015	USA	2015	Nursing homes	30 Months	Number evaluated: 575	Chlorhexidine oral rinse and enhanced oral care	Usual oral care
LAM 2013	Hong Kong	2013	Stroke rehabilitation unit	31 months	Number evaluated: 81	Professional care with Chlorhexidine oral rinse	Oral hygiene instruction
OHSAWA 2003	Japan	2003	Nursing homes	24 months	Number evaluated: 49	Povidone iodine oral rinse and Professional care	Usual oral care
PANCHABHAI 2009	India	2009	ICU (medical and surgical)	8 months	Number evaluated: 300	Chlorhexidine and usual care	Potassium permanganate rinse
YONEYAMA 2002	Japan	2002	Nursing homes	24 months	Number evaluated: 366	Professional care and povidone iodine oral rinse	Usual oral care

Characteristics of the individual studies

Randomized controlled trials

Non-randomized controlled trials and other studies

REFERENCE, YEAR	*COUNTRY*	*YEAR*	*STUDY DESIGN*	*DURATION*	*NUMBER OF PARTICIPANTS*	*INTERVENTION TYPE*	*CONTROL*
HOLLAR 2017	Netherlands	2017	Controlled trial	12 months	103	Enhanced oral care and chlorhexidine oral rinse	Usual oral care
MCNALLY 2019	USA	2019	Controlled trial	3.5 months	2890	Enhanced oral care and cetylpyridinium oral rinse	Usual oral care
BASSIM 2008	USA	2008	Retrospective study	79 weeks	143	Enhanced oral care	Usual oral care
ROBERTSON 2013	Canada	2013	Quasi experiment	6 months	83	Enhanced oral care	Usual oral care

Figure 2. Forest plot of the RCTs [Enhanced oral hygiene maintenance for the prevention of non-ventilated pneumonia (Comparison: Enhanced oral care versus usual care, Outcome: Prevention of pneumonia)].

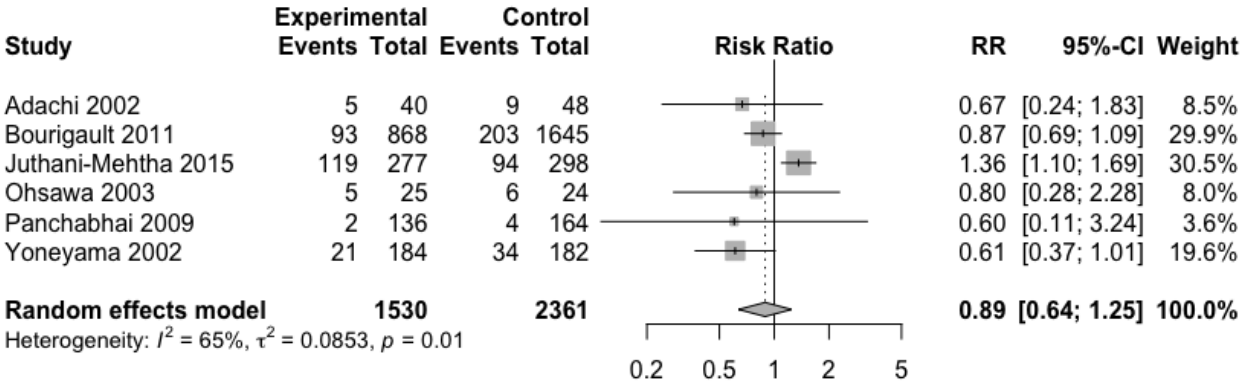


Figure 3. Forest plot of the subgroup analysis of the RCTs [Enhanced oral hygiene maintenance for the prevention of non-ventilated pneumonia (Comparison: Chlorhexidine for oral care versus usual care Outcome: Prevention of pneumonia)].

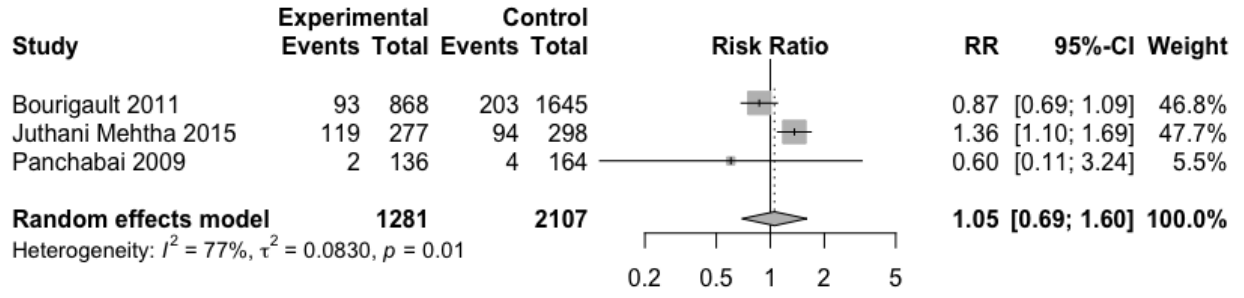


Figure 4. Forest plot of the subgroup analysis of the RCTs [Enhanced oral hygiene maintenance for the prevention of non-ventilated pneumonia (Comparison: Professional Dental care versus usual care, Outcome: Prevention of pneumonia)].

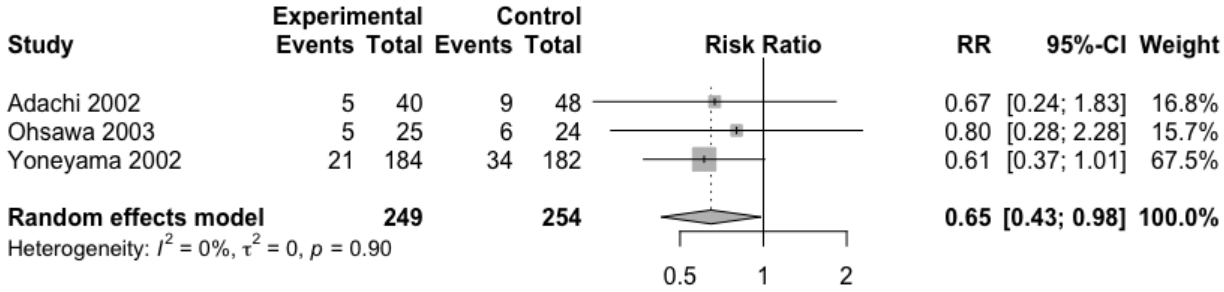


Figure 5. Forest plot of the subgroup analysis of the RCTs [Enhanced oral hygiene maintenance for the prevention of non-ventilated pneumonia, (Comparison: Enhanced oral care versus usual care, Outcome: Prevention of mortality due to pneumonia)].

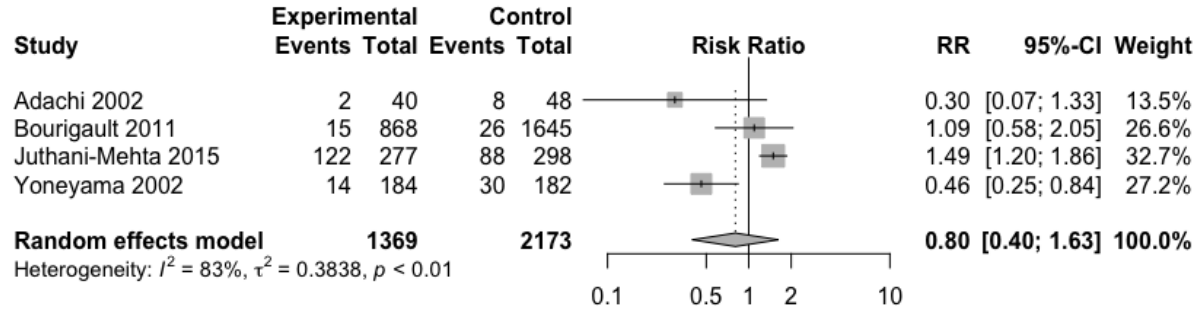
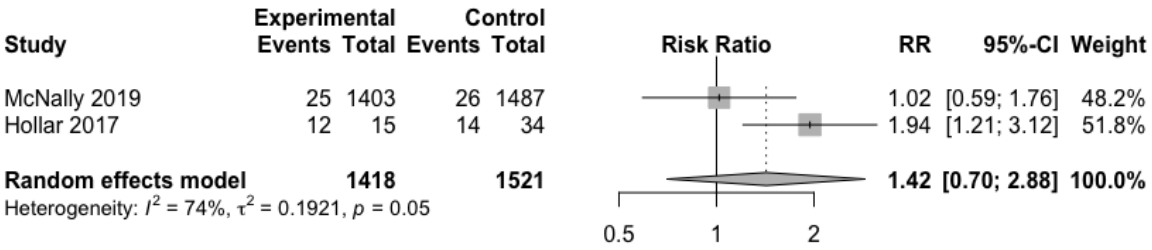


Figure 6. Forest plot of the nonRCTs [Enhanced oral hygiene maintenance for the prevention of non-ventilated pneumonia**.** Comparison: Enhanced oral care versus usual care, Outcome: Prevention of pneumonia)].



Supplementary Table

Detailed characteristics of the individual studies included in the meta-analysis

RCT

REFERENCE, YEAR	*COUNTRY*	*YEAR*	*STUDY SETTING*	*DURATION*	*N*	*INTERVENTION TYPE*	*CONTROL*	*BIAS*	*FUNDING*
ADACHI 2002	Japan	2002	Elderly living in nursing homes	24 months	Number evaluated: 88	Method of oral hygiene treatment focused mainly on **mechanical cleaning** with scaling with hand scalers once a week by dental hygienists Routine care consisted of brushing of the teeth with an electric brush with an automatic water supply. Assisted cleaning after each meal by staffs or caregivers.	caregiver-provided usual oral care Swabbing with a sponge brush and denture cleaning after each meal by residents	*RS - unclear, AC- unclear, BP- High risk, OA- unclear, OD- unclear, SR- low risk, OR- low risk.*	Grant from Tokyo Dental College
BOURIGAULT 2011	France	2011	Nursing homes	18 months	Number evaluated: 2513	**Bucco dental health care professional care** brushing teeth, buccal mucosa and tongue (three times a day and after each meal) + mouthrinse (**chlorhexidine**) + dental visit	usual mouth care (not stated in detail)	*RS - unclear, AC- unclear, BP- High risk, OA- unclear,*	Colgate-Palmolive and the 'Programme Hospitalier de Recherche Clinique' 2003

						(annual visit to dentists)		*OD-uncle ar, SR-low risk, OR-low risk.*	
JUTHANI-MEHTHA 2015	USA	2015	Nursing homes	30 Months	Number evaluated: 575	Brushing teeth (twice a day) + cleaning denture + mouthrinse (0.12% **chlorhexidine** oral rinse, twice a day) + upright feeding positioning, by **nurses**	usual oral care + usual feeding position (not stated in detail)	*RS - low risk, AC-low risk, BP-High risk, OA-low risk, OD-low risk, SR-low risk, OR-low risk.*	National Institutes of Health, USA
LAM 2013	Hong Kong	2013	Stroke rehabilitation unit	31 months	Number evaluated: 81	Professional OHI with **chlorhexidine** mouth wash use	Oral hygiene instruction	*RS - low, AC-uncle ar, BP-High risk, OA-uncle ar, OD-uncle ar, SR-low risk, OR-low risk.*	Grant from Tokyo Dental College
OHSAWA 2003	Japan	2003	Nursing homes in Japan	24 months of follow-up	Number evaluated: 49	Brushing teeth after each meal assisted by nurses and caregivers along with **povidone iodine** (1.0%) as mouthwash; mechanical plaque control, 2-3 days/week by dentists or dental hygienists.	usual oral care	*RS - low, AC-uncle ar, BP-High risk, OA-low risk, OD-uncle ar, SR-low risk, OR-low risk.*	Not stated

PANCHA BHAI 2009	India	2009	ICU (mixed medical and surgical)	8 months	Number evaluated: 300	**Chlorhexidine** along with usual care	Potassium permanganate	*RS - unclear, AC-unclear, BP-High risk, OA-low risk, OD-unclear, SR-low risk, OR-unclear.*	*Not stated*
YONEYAMA 2002	Japan	2002	Nursing homes in Japan	24 months	Number evaluated: 366	Brushing teeth after each meal assisted by nurses and caregivers along with **povidone iodine** (1.0%) as mouthwash; plaque control once a week by dentists and dental hygienists.	usual oral care	*RS - low, AC-unclear, BP-High risk, OA-low risk, OD-unclear, SR-low risk, OR-low risk.*	Japan Welfare Ministry

Random sequence generation (selection bias) - RS, Allocation concealment (selection bias) – AC, Blinding of participants and personnel (performance bias) All outcomes- BP, Blinding of outcome assessment (detection bias) All outcomes- OA, Incomplete outcome data (attrition bias) All outcomes- OD, Selective reporting (reporting bias) -SR, Other risk-OR.

Non-RCT & Other studies

REFERENCE, YEAR	***COUNTRY***	***YEAR***	***STUDY DESIGN***	***DURATION***	***NUMBER OF PARTICIPANTS***	***INTERVENTION TYPE***	***CONTROL***	***FUNDING***

MCNALLY 2019	USA	2019	Controlled trial	3.5 months	2890	Toothbrushing three times per day, each toothbrush was coated with sodium bicarbonate and included a single- use antiseptic oral solution (0.05% **cetylpyridinium chloride**).	Usual oral care	Supported in part by an unrestricted grant and in-kind donation of oral care products from Sage Products, Inc.
HOLLAR 2017	Netherlands	2017	Controlled trial	12 months	103	Receiving daily oral care and 0.05% **chlorhexidine**	Usual oral care	Not stated
BASSIM 2008	USA	2008	Retrospective	79 weeks	143	This included toothbrushing, antiseptic mouthwash use, and oral and denture cleaning for edentulous or partially edentulous residents.	Usual oral care	Dental Research fellowship
ROBERTSON 2013	Canada	2013	Quasi experiment	6 months	83	Change mouth suction equipment every 24 hours, Mouth assessment every 2-4 hours, Cleanse mouth with toothbrush every 12 hours, Cleanse oral mucosa with oral rinse solution every 2-4 hours, moisturize mouth/lips with swab and standard mouth moisturizer every 4 hours, Suction mouth and throat as needed.	Usual oral care	Not stated

Research 1b.

Network meta-analysis to assess the comparative effectiveness of oral care interventions in preventing ventilator associated pneumonia in critically ill patients.

(Submitted in the Journal of BMC Oral Health)

Network meta-analysis to assess the comparative effectiveness of oral care interventions in preventing ventilator associated pneumonia in critically ill patients.

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Manuscript words: 3053

Abstract words: 245

Abstract

Background

In this research, we assessed the efficacy of a novel analytic network metanalysis (NMA) in creating a hierarchy to define the most effective oral care intervention (OCI) for the prevention and management of ventilation-associated pneumonia (VAP).

Methods

We applied NMA to a previously published robust pairwise meta-analysis (PMA). Statistical analyses were based on comparing rates of total VAP events between

intervention groups and placebo-usual care groups. We synthesized a netgraph, reported ranking order of the treatment, and summarized our output by a forest plot with a reference treatment placebo/usual care.

Results

With our inclusion and exclusion criteria for the NMA, we extracted 25 studies (4473 subjects). The NMA included 16 treatments, 29 pairwise comparisons, and 15 designs. Based on the results of multiple comparisons with frequentist ranking probability P scores, tooth brushing (P score fixed of 0.94, P score random of 0.89), toothbrushing with povidone-iodine (P score fixed of 0.91, P score random 0.88), and furacillin (P score set of 0.88, P score random 0.84) were the best three interventions for preventing VAP.

Conclusion

NMA appeared to be an effective platform from which multiple interventions reported in disparate clinical trials could be compared to derive a hierarchical assessment of efficacy in the intervention of VAP. According to the NMA outcome, toothbrushing alone or toothbrushing along with a potent antiseptic mouthwash povidone-iodine was related to the highest response rate in preventing VAP in critically ill patients, followed by furacillin and chlorhexidine 0.2%, respectively.

Background

Oral care interventions (OCI) have been recognized as favorably impacting the risk and course of ventilator-associated pneumonia (VAP) in critically ill patients. [1] A range of preventive strategies have been suggested that include the use of topical (rinse) formulations of antimicrobial agents, such as chlorhexidine (CHX) and povidone-iodine (PI), or mechanical cleansing by healthcare providers. [1-4] Debate persists as to which tactic is most clinically- and cost-effective. A number of randomized trials (RCTs) have been completed to address this uncertainty. [4] In almost all cases, these RCTs have used a standard clinical trial pairwise design in which a placebo or best care was compared to a test agent or regimen. While this approach provides snapshot outcomes for a specific intervention, it lacks the ability to hierarchically assess or rank the efficacy of each in the context of all of the responses studied.

To address this deficiency, we explored the utility of a novel approach in which network meta-analysis (NMA) was applied to a previously published comprehensive pairwise meta-analysis (PMA). [5] NMA, also known as multiple treatment comparison or mixed treatment comparison, is a method of generalization of conventional pairwise meta-analysis whereby the network statistically combines direct and indirect evidence from trials [7] to yield inter-study intervention comparisons. Besides, NMA expresses the relative effectiveness of interventions among all tests and then rank orders them. We explored the utility of NMA as a means of comparing different OCIs to identify those most useful for mitigating VAP in critically ill patients.

Concepts of Network Meta-Analysis

For clinical trials, conventional PMA typically focuses on pairwise comparisons of an active treatment vs. placebo or usual care to assess the superiority of the test agent vs. a control. If the investigation seeks to compare multiple active agents simultaneously, the sample size must increase, leading to extended accrual times, extraordinary expense, and efficacy assessment challenges. In contrast, NMA utilizes a multiple comparison methodology which enables the interventions of one trial to be contrasted with the active responses of other trials, while maintaining the internal randomization of the direct and indirect comparisons.

For example, when two active OCIs like chlorhexidine (CHX) and Toothbrushing (Tb) are independently compared for efficacy against a saline control in two different trials then randomized comparison in the trial 1, CHX and saline provides a direct estimate of the treatment effects of CHX and Saline, measured on the scale as a log odds ratio. We then denote this approach as $\theta_{\text{CHX Saline direct}}$. Trial 2, provides information on the direct comparison between treatment Tb and Saline, denoted by $\theta_{\text{Tb Saline direct}}$. Then NMA provides indirect evidence for the comparison of CHX and Tb from the treatment difference CHX and Saline and Tb and Saline as follows:

$$\theta_{CHX\ Tbindirect} = \theta_{CHX\ Saline\ direct} - \theta_{Tb\ Saline\ direct}$$

and the variance of this association is given by the Var ($\theta_{CHX\ Tbindirect}$) = Var($\theta_{CHX\ Saline\ direct}$) + Var ($\theta_{Tb\ Saline\ direct}$). To have the NMA combination for the direct and indirect comparisons, we are assuming that the trial 1 and 2 are independent, the underlying effects are consistent, and any differences in the data are due to random error. The

NMA now has a consequent network having its integer of total treatments, designs (a design refers to each combination of treatment), pairwise comparisons, and its subsequent statistical inferences of all the included studies.

Methods

2.1 PMA selection and description

We selected the pairwise PMA reported by Hua et al. [5] basis on which to build an NMA and assess its potential clinical meaningfulness.

We believe that the report represents a current, comprehensive, and inclusive review of the topic (OCI and VAP) as it was screened from the Cochrane Oral Health's Trials Register (to 17 December 2015); the Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library, 2015, Issue 11); MEDLINE Ovid (1946 to 17 December 2015); Embase Ovid (1980 to 17 December 2015); LILACS BIREME Virtual Health Library (1982 to 17 December 2015); CINAHL EBSCO (1937 to 17 December 2016); Chinese Biomedical Literature Database (1978 to 14 January 2013); China National Knowledge Infrastructure (1994 to 14 January 2013); Wan Fang Database (January 1984 to 14 January 2013) and VIP Database (January 2012 to 4 May 2016).

2.2 Inclusion and exclusion criteria

To assure consistency, we used the same inclusion and exclusion criteria as Hua et al. VAP was defined as pneumonia developing in a critically ill patient who has received mechanical ventilation for at least 48 hours and excluded studies in which patients were not critically ill and were not dependent on mechanical ventilation for less than 48 hours, or if the patients had an acquired respiratory infection at baseline. We accepted study-described definitions for intervention (test) and control groups. Typically controls of a "placebo" were described as usual care or any oral hygiene intervention care. We accepted studies in which saline was included as a component of routine care/placebo but did not include studies in which saline rinsing/swab was described as an active intervention versus placebo-usual care. We noted that amongst hospitalized patients, saline was used as a most common oral rinse and so was included as a component of the usual care procedure, while in clinical trials, saline was used as a most common control drug. Since the use of saline rinsing/swab as an active intervention might affect the NMA analysis and geometry saline-rinsing/swab as a treatment was excluded. We also excluded feasibility studies and cross-over randomized design trials. Chlorhexidine trials were stratified based on concentration (0.12%, 0.2%, 1%, and 2%), with each being considered as a distinct intervention and compared in the network along with other therapies.

2.3 Data collection

We obtained data from studies that met our inclusion and exclusion criteria from the PMA [5] by a standardized data collection form. For the NMA data analysis, we

calculated the treatment effects (TE) and standard error of the treatment effects (SeTE). Variable TE, which was determined by comparing the pairwise treatment effect of treatments treat1 (intervention) and treat2 (control) in each study with variable SeTE as the corresponding standard error. When dealing with the multi-arm studies in which there were more than two treatment arms, we have included each multi-arm study in the dataset as a series of two-arm comparison. Thus, with every comparator in the multi-arm, we have obtained treatment effects and the standard error of the treatment effects for each treatment on the other.

2.4 Statistical analysis

Frequentist methods of comparative effectiveness approach with multiple treatment comparisons [6-11] were used. Statistical analyses were based on comparing rates of total VAP events between the intervention group and the placebo-usual care group. For outcomes, odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using pairwise meta-analysis format, and the log odds ratio was used to calculate the TE and SeTE of all the included studies. We used the R package netmeta for the NMA analysis.

We reported the random and fixed effects ranking order (P scores) of the treatment effectiveness. For ranking order of the interventions, we used the net ranking function of R package by computing the likelihood of one intervention being the best, second best, and so on for a response preventing VAP outcome. Total or generalized

heterogeneity of NMA's whole network was quantified using Cochran's Q total statistics test. Cochran's Q total statistics test is the total sum of the heterogeneity and inconsistency statistics that represents the variability between the NMA direct and indirect comparisons. And for determining the heterogeneity/inconsistencies between designs of the NMA network, we used Q statistics heterogeneity decomposition function. Finally, to compare several treatments to standard treatment was done by placing placebo-usual care as a reference treatment is represented with a forest plot. All statistical analyses were performed using R Studio, Version 1.1.456 (RStudio: Integrated Development for RStudio. RStudio, Inc., Boston, MA).

Results

3.1 Description of the studies

From the Hua et al. study of 38 RCTs (6016 subjects), 25 studies (4473 subjects) met our inclusion criteria. [figure 2] In our cohort, 2254 subjects were randomly assigned to an active OCI and 2219 subjects who were randomly assigned to the placebo or usual care group. The basic characteristics of the studies are described in Table 1.

3.2 Evidence used in the NMA

After assuring the comprehensiveness of the studies included in the analysis, we included 25 trials (this comprises the total number of trials combined in the network), 16 treatments (number of total treatments compared in the network), and 29 pairwise comparisons (the pairwise is a combination of the individual trials in the two-arm and three-arm trials) and there were 15 designs in the network [figure 2].

Figure 3 shows the graphical representation of the NMA. The size of the nodes is proportional to the number of studies evaluating each intervention, and the width/thickness of the edges indicates inverse standard error of the direct treatment comparisons, and the shading indicates a three-arm study. For example, Figure 2 compares the effectiveness of three different chlorhexidine concentrations (CHX 0.2%, 1%, and 2%). The difference in thickness/density of connecting edges suggests that CHX 0.2% has superior evidence than CHX 1% based on supporting study data. Importantly, this visual graphical representation of the thickness or density does not indicate the statistical significance of the comparison. The most common comparator across all trials was the placebo or usual care arm which appears as the network's most common node. While the majority of studies were two-arm trials, two, 3-arm trials were included in our network (shaded region in the netgraph).

A forest plot [Figure 4] shows the fixed effects model for each intervention having compared with a reference treatment placebo/usual care. In NMA, the forest plot's importance is to compare several treatments to a common comparator, also called reference or baseline treatment. We have taken placebo/usual care as the reference treatment for our readers to compare and contrast, and to comprehend the procedures are significantly different to placebo/routine care.

3.3 Results of heterogeneity and consistency

The heterogeneity statistics of the NMA follow the Chi-square distribution, and the chief prerequisite of assessing the variability is to pinpoint studies whose data differ significantly from what the model predicts. Our first aim was to identify the total or generalized heterogeneity of NMA's whole network using Cochran's Q total statistics test and second to determine the heterogeneity/inconsistencies between designs of the NMA network.

Total heterogeneity statistics of NMA network

The heterogeneity statistics of the decompose function of the netmeta package provided the generalized DerSimonian estimator tau2 value of 0.2829, Higgins' I2 value of 55.7%, CIs, 17.5%; 76.2%. The Cochran's Q total statistics showed a value of 27.10 with a degree of freedom (DOF) 12 and a P-value of 0.008.

The heterogeneity/inconsistencies between designs of the NMA network

Q statistics heterogeneity within design showed a value of 25.91 with a DOF 10 and a P-value of 0.0039, and between design heterogeneity/inconsistency value of 1.19 with a degree of freedom 1.19 and a P-value of 0.56. The results show that there is moderate heterogeneity in the NMA network, and considerably very less heterogeneity within designs and between designs.

The relative effect estimates of the ranking of the treatments according to the multiple comparisons are shown in Table 2. Numerals between 0 and 1, with mean 0.5, demonstrate the rank of treatment within the given assortment of competing treatments, where a score of 1 is linked to the best outcome, and a score of 0 is associated with the worst outcome. The hierarchical ranking order of the intervention being the best and worst is introduced by many authors in the Bayesian and frequentist methods. [10, 11] Rucker and Schwarzer introduced ranking order of interventions in the frequentist NMA as P scores, which are analogs to the Bayesian method, surface under the cumulative ranking curve. [10] These values are derived from the effect estimates and their variances. The P scores are based on the frequentist's method point estimates and the standard error of the network meta-analysis estimates under normality assumption and calculated as means of one-sided p-values. [10, 11, 13, 14, 15]. Numerous studies are using ranking order in NMA so as to display a ranking from the network, which is a better way to present the interventions in terms of the effect estimates. [10, 11, 13, 14, 15] Most commonly, the effect estimates might get affected with some ambiguity, and we will rarely know in placing a particular trial in the first order or second order. Hence, we classified the ranking first three interventions as best, second three-best interventions as next best, and so on. Based on the ranking order, we found that tooth brushing was the most effective intervention for preventing VAP vs. placebo or usual treatment, which was the worst. The best three interventions were tooth brushing (P score fixed of 0.94, P score random of 0.89), tooth brushing with povidone-iodine (P score fixed of 0.91, P score random 0.88), and furacillin (P score fixed of 0.88, P score random 0.84). CHX of 0.2% concentrations (P score fixed of 0.65, P score random of

0.65) ranked as the second-best interventions in the network along with Biotene (P score fixed of 0.6, P score random 0.54) and potassium permanganate (P score fixed of 0.53, P score random 0.54). While chlorhexidine 0.2%, a recommended oral care product for preventing VAP in critically ill patients, has a P score of 0.65 fixed and 0.65 random.

Discussion

We applied NMA to an existing and robust pairwise meta-analysis to assess the utility of this novel analytic in defining a hierarchical comparison to determine the effectiveness of oral interventions in preventing VAP. [5] Our results suggest that the application of NMA to a conventional meta-analysis provides additional actionable information relative to preventing VAP by comprehensively comparing treatment options otherwise sequestered in pairwise comparisons.

These results have to be taken with caution as the assumptions are based on the results of multiple comparisons. This novel technique allows us to presume direct and indirect comparisons performed in a structured statistical framework. Although the inferences are from low risk and unclear risk of bias RCTs, the estimated network and ranking of treatment are thus liable to have distinctions as discussed in this NMA and previous pairwise meta-analysis. [5] A potential value of the method is its informative function relative to directing future studies and, in this case, a specific trial assessing preventive interventions for VAP in critically ill patients. The NMA

is a comprehendible way of combinations which stem the possibility of consolidating a future test from the network. Consequently, the NMA, when compared to pairwise meta-analysis, weighs the logical possibilities, even within the network, maintains the internal randomization of the individual trails.

In comparison with the published pairwise meta-analysis, the NMA showed a divergent finding concerning the ranking probabilities from the multiple comparisons. [3-5] This is the first NMA in this regard to reporting on comparative effectiveness research on oral care intervention for preventing VAP. In contrast to the standard of care where CHX is described as the best oral care intervention to prevent VAP, NMA demonstrated the superiority of tooth brushing or mechanical cleaning. This finding is especially significant given the recent results associated with CHX toxicity. [16] We also determined that toothbrushing intervention when combined with a mouthwash is superior compared to a mouthwash alone; toothbrushing with PI is superior to any other mouthwash or ranking second in the first three-best interventions. This is the first time showing the excellent benefit of the furacillin as a mouthwash in preventing the VAP. Furacillin belongs to the nitrofuran class and is a potent antimicrobial organic compound. It is efficient against gram-positive bacteria and gram-negative bacteria. Studies show furacillin effective against many bacterial and fungal entities when applied topically. [17] Although there aren't many studies on this intervention, this network warrants a possible pilot trial. The PMA showed weak evidence of the PI superior to saline in preventing VAP and inadequate confirmation of the toothbrushing preventing VAP in critically ill patients. [5] The NMA shows

toothbrushing alone or toothbrushing along with PI are the best interventions according to the clinical comparative effectiveness research.

There is a lack of comparative effectiveness research and vagueness with regard to OCI in preventing VAP among critically ill patients, and NMA is never performed. While our results support the usefulness of NMA as a tool to optimize collective analyses of meta-analyses for comparative effectiveness research, it does have limitations. For justifying the rationality of findings and to minimalize error, NMA is designed methodically and conducted carefully. Transporting the high-quality systematic search and search results of the Hua et al. study [5], we established our inclusion and exclusion criteria for building the NMA network. We argue that this way we pragmatically compared the PMA to the NMA and reflected on its comparative effectiveness research. Observing little evidence-based research on OCI on preventing the VAP in critically ill patients after the Hua et al. study and using the Hua et al. research supplemented NMA construction, which defends the thorough literature search along with assessing the risk of bias and quality of evidence. But challenges of the NMA persists when comparing the studies with low and unclear-risk biases. In summary, this research accomplishes to provide comparative effectiveness of OCIs in preventing VAP in critically ill patients when combining direct and indirect evidence by having a transitivity assumption that studies are independent and underlying effects are somewhat consistent.

Conclusions

As meta-analysis is considered the epitome of the evidence-based clinical medicine, NMA is an extension positioned in this framework. Given the challenges of the proof of concept of existing oral care intervention in preventing VAP, and lack of head to head robust trials of the best available treatment modalities, this approach is exceptional. We followed stern assumptions and standardization, and our study cohort was based on the largest pairwise meta-analysis of oral care intervention in preventing the VAP. The transparency, reproducibility, and detailed documentation of our findings can be appropriately appraised. According to the NMA outcome, toothbrushing alone or toothbrushing along with a potent antiseptic mouthwash povidone-iodine was related to the highest response rate in preventing VAP in critically ill patients, followed by furacillin and chlorhexidine 0.2%, respectively.

List of abbreviations

- **Abbreviations in the manuscript.**

VAP – Ventilation associated pneumonia

OCI – Oral care interventions

NMA – Network meta-analysis

PMA – Pairwise meta-analysis

RCT – Randomized controlled trials

CHX – Chlorhexidine

Tb – tooth brushing

TE – Treatment effects

SeTE – Standard error of the treatment effects

PI – Povidone iodine

- **Abbreviations in the figures**

Tbrush -	Tooth brushing
tbrush_povid -	Tooth brushing with Povidone -Iodine
Fura -	Furacillin
chx_.2% -	Chlorhexidine 0.2%
potas	Potassium permanganate
biotene	Biotene
povid	Povidone -Iodine
chx_2%	Chlorhexidine 2%
chx_.12%	Chlorhexidine 0.12%
chx_.12%	Chlorhexidine 0.12% with tooth brushing
tricl	Triclosan
chx_1%	Chlorhexidine_1%
chx_2%_toothbrushing	Chlorhexidine_2%_toothbrushing
bica	Sodium Bicarbonate
list	Listerine

plac-us	Placebo or usual care

Declarations

- Ethics approval and consent to participate – NA
- Consent for publication -NA
- Availability of data and material - NA
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- Authors' contributions

  Satheeshkumar PS: Study design, statistical analysis, data interpretation, manuscript drafting, revision, and critical evaluation

  Sonis S: Study design, data interpretation, manuscript revision and critical evaluation.

- Acknowledgements- NA

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Figures &Tables

Figure 1 Showing trial 1 (Chlorhexidine versus Saline) and trial 2 (Toothbrushing versus Saline) pooled for indirect and direct comparisons in the NMA when assuming that the experiments are independent, and the underlying effects are consistent.

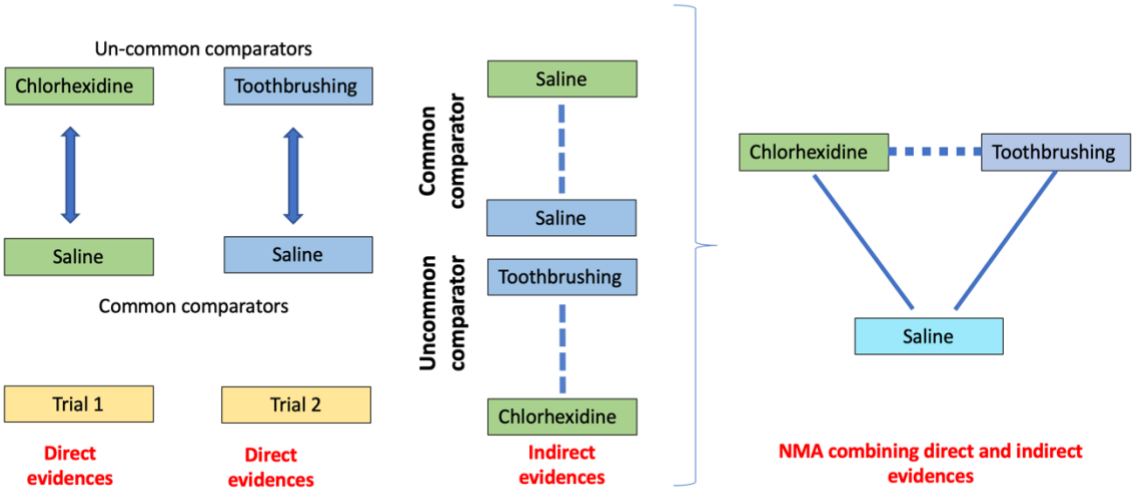

Figure 2. **Flow diagram showing NMA study selection and output.**

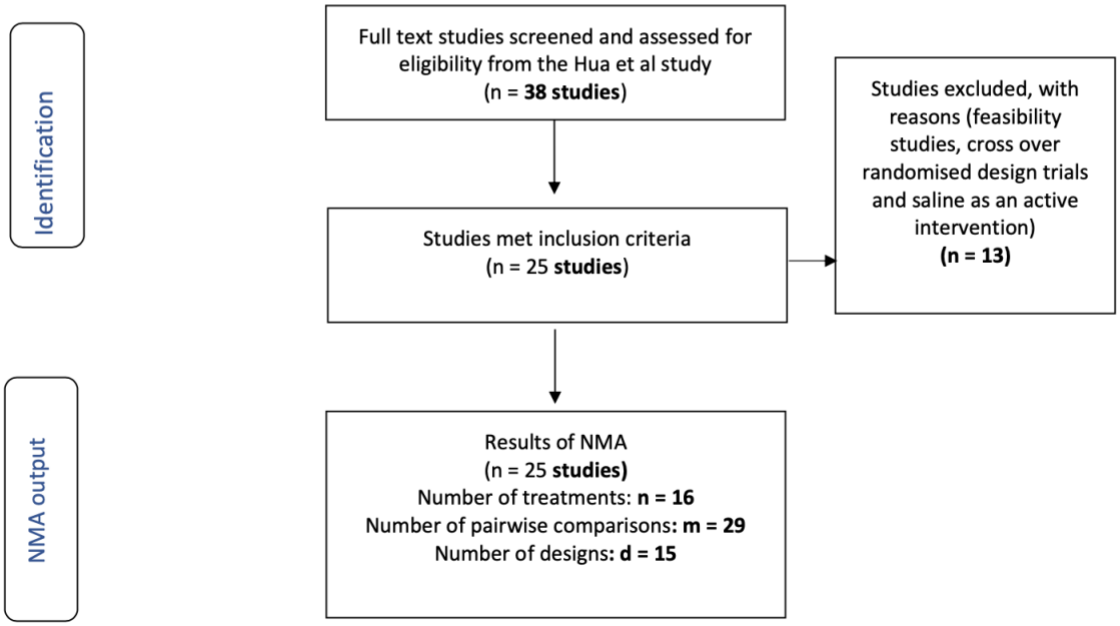

Figure 3. Netgraph of the oral care intervention for the prevention of ventilation associated pneumonia.

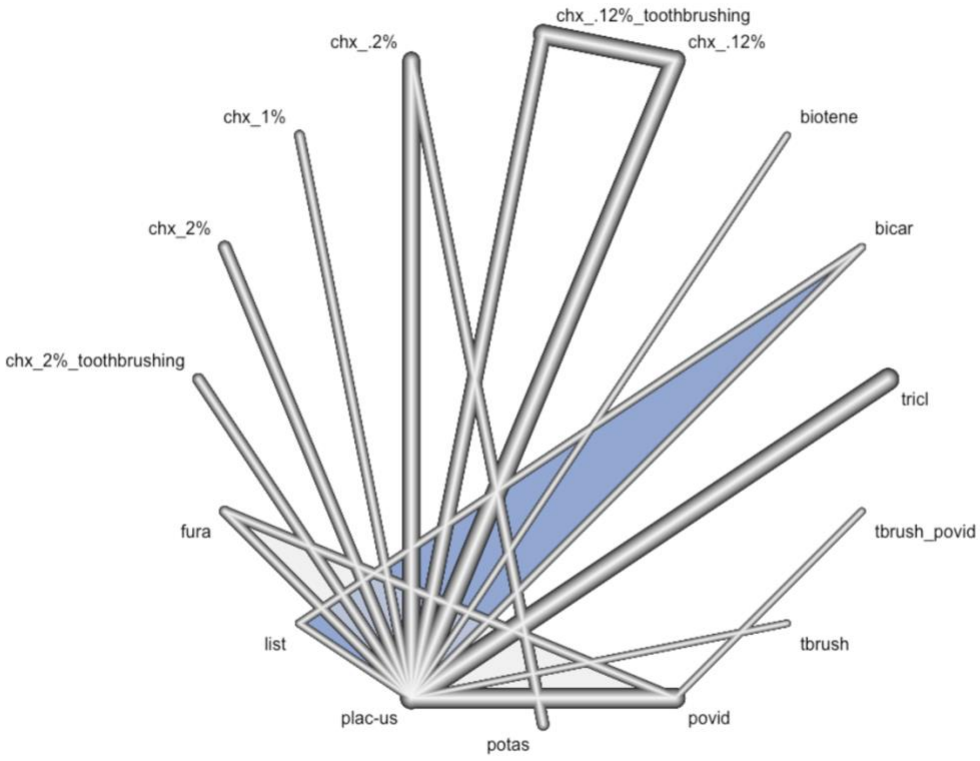

Figure 4. Forest plot of the fixed effect network meta-analysis of the oral care intervention for the prevention of ventilation associated pneumonia, when placing the placebo-usual care as a reference treatment.

Table 2. Ranking order of the treatment

Oral intervention	P-score (fixed)	P-score (random)
Tooth brushing	0.94	0.89
Tooth brushing with povidone-Iodine	0.91	0.88
Furacillin	0.88	0.84
Chlorhexidine (0.2%)	0.65	0.65
Biotene	0.61	0.56
Potassium permanganate	0.54	0.55
Povidone-Iodine	0.53	0.55
Chlorhexidine (2%)	0.59	0.53
Chlorhexidine (0.12%) with toothbrushing	0.46	0.45
Chlorhexidine (0.12%)	0.36	0.39
Triclosan	0.34	0.36
Chlorhexidine (1%)	0.29	0.31
Chlorhexidine (2%) with toothbrushing	0.26	0.29
Bicarbonate	0.25	0.28
Listerine	0.23	0.26
Placebo/usual	0.17	0.21

Supplementary file

Table 1. Characteristics of the included studies.

REFERENCE, YEAR	*NUMBER OF PARTICIPANTS*	INTERVENTION	CONTROL	STUDY TYPE
BELLISMO-RODRIGUES2009	133	Chlorhexidine (0.12%)	Placebo/usual	Two-arm
BERRY2013	271	Bicarbonate rinse + Toothbrushing	Placebo/usual + Toothbrushing	Three-arm
BERRY2013	265	Listerine + Toothbrushing	Placebo/usual + toothbrushing	Three-arm
BERRY2013	260	Listerine + Toothbrushing	Bicarbonate rinse + Toothbrushing	Three-arm
CABOV2010	40	Chlorhexidine (0.2%)	Placebo/usual	Two-arm
DERISO 1996	353	Chlorhexidine (0.12%)	Placebo/usual	Two-arm
FENG2012	139	Povidone-Iodine	Placebo/usual	Three-arm
FENG2012	136	Furacillin	Povidone-Iodine	Three-arm
FENG2012	133	Furacillin	Placebo/usual	Three-arm
FOURRIER2000	58	Chlorhexidine 0.2%	Placebo/usual	Two-arm
FOURRIER2005	228	Chlorhexidine (0.2%)	Placebo/usual	Two-arm
GRAP2011	39	Chlorhexidine (0.12%)	Placebo/usual	Two-arm
JACOMO2011	160	Chlorhexidine (0.12%)	Placebo/usual	Two-arm
KOEMAN2006	257	Chlorhexidine (2%)	Placebo/usual	Two-arm
KUSAHARA2012	96	Chlorhexidine (0.12%) + Toothbrushing	Placebo/usual	Two-arm
LONG2012	61	Tooth brushing + Povidone-Iodine	Povidone-Iodine	Two-arm
LORENTE2012	436	Chlorhexidine (0.12%) + Toothbrushing	Chlorhexidine (0.12%)	Two-arm

MEINBERG2012	52	Chlorhexidine (2%) + Toothbrushing	Placebo/usual	Two-arm
OZCAKA2012	61	Chlorhexidine (0.2%)	Placebo/usual	Two-arm
PANCHABAI2009	171	Chlorhexidine (0.2%)	Potassium permanganate	Two-arm
POBO2009	147	Chlorhexidine (0.12%) + Toothbrushing	Chlorhexidine (0.12%)	Two-arm
SCANNAPIECO 2009	146	Chlorhexidine (0.12%) + Toothbrushing	Placebo/usual	Two-arm
SEBASTIN2012	86	Chlorhexidine (1%)	Placebo/usual	Two-arm
SEGUIN2006	67	Povidone-Iodine	Placebo/usual	Two-arm
SEGUIN 2014	150	Povidone-Iodine	Placebo/usual	Two-arm
STEFANSCU2013	41	Biotene	Placebo/usual	Two-arm
TANTIPONG2008	110	Chlorhexidine (2%) + Toothbrushing	Placebo/usual	Two-arm
YAO2011	53	Tooth brushing	Placebo/usual	Two-arm
ZHAO2012	324	Triclosan	Placebo/usual	Two-arm

Research 2.

The impact of healthcare-associated infections on patients hospitalized with oropharyngeal cancers of lip, mouth, and pharynx.

(In preparation)

The impact of healthcare-associated infections on patients hospitalized with oropharyngeal cancers of lip, mouth, and pharynx.

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Abstract

Background

Healthcare-associated infections (HAIs) increases the burden of illness by the increased length of stay, cost of hospital expenses, and risk of mortality. Oropharyngeal cancer patients are at increased risk of HAIs due to multiple therapeutic interventions and due to the presence of an enormous number of microorganisms in the oro-pharyngeal areas responsible for HAIs. We tried to assess the 2017 trend in differences in outcome among patients with a primary diagnosis of malignant neoplasms of lip, oral cavity, and pharynx (MLOP) with and without HAI.

Methods

Using the United States (U.S.), the National inpatient sample (NIS) database of 2017, we identified all hospitalization with a primary diagnosis of malignant neoplasms of lip,

oral cavity, and pharynx and identified the HAIs among them. We assessed the difference in the cost, length of stay (LOS), and in-hospital mortality among MLOP cancer patients with and without HAI. Association between outcomes (in-hospital mortality, LOS, and hospital charges) and independent variables examined using survey specific multivariable regression analyses.

Result

Among 7,159, 694 (weighted numbers - 20% of the total patients admitted in the U.S. hospitals in the year 2017), 54,934 (unweighted numbers in the U.S.) discharged with a primary diagnosis of the MLOP. Among those 54,934 MLOP patients, 555 (unweighted numbers in the U.S.) patients acquired a minimum of one HAI during their in-hospital stay. The most common HAI was Clostridium difficile infection (36%), followed by central line-associated bloodstream infection (32%), ventilator-associated pneumonia (17%), and catheter-associated urinary tract infection (15%). MLOP patients with HAI had LOS of 6.63 days longer than the non-HAI MLOP patients, confidence intervals (C.I.s), 3.62-9.64, $p < 0.0001$. MLOP patient with HAI had hospitalization charges of 49,383 USD higher than the non-HAI MLOP patients, CIs 20144 USD- 78622 USD, $p < 0.0001$. Mortality was not significantly different among HAI and nonHAI MLOP patients, Odds ratio (OR) 0.63, C.I.s, 0.22- 1.81, a p-value of 0.4.

Conclusion

MLOP patients who acquired HAI were associated with a considerable increase in the length of stay and total charges during their in-hospital stay.

1. BACKGROUND

Cancers of the oro-pharyngeal areas (malignant neoplasms of lip, oral cavity, and pharynx) constitute 3% of all fatalities in the United States (U.S.), and there is approximately 55,000-60,000 number of new cases treated each year in the U.S. alone. [1] Emphatically, malignant neoplasms of lip, oral cavity, and pharynx (MLOP) cancers develop predominantly due to tobacco use and alcohol consumption. However, other implicated risk factors like Human papillomavirus (HPV) infection, Herpes simplex virus, and Epstein-Barr virus infection are also associated. [2, 3] Thus MLOP cancers are preventable to encompass the burden of illness, [4] however, the MLOP cancer treatment necessitates a complex treatment modality involving Radiotherapy (R.T.), chemotherapy (C.T.) and Surgical therapy which affects the quality of life patients. [5, 6] Furthermost, these treatment modalities necessitate more extended hospital stays and continuous economic liability. [7] Subsequently, MLOP cancer patients are also affected by healthcare-associated infections (HAI). [7, 8] The average hospitalization cost of the Head and Neck cancer patients accounts for approximately U.S. $ 18,371, and the average length of stay was 6.6 days. [8] Conversely, the range of problem accompanying with the HAI intertwined with clinical consequences of MLOP cancers are largely indefinite. Henceforth, utilizing the National Inpatient Sample (NIS) database, we tried to obtain the degree of HAIs among MLOP cancer patients by measuring the 2017 trend in the cost, length of stay, and mortality.

2. METHODS

2.1 NIS database

The features of the NIS database have been described in detail previously [9]. NIS obtained from the Health care Cost and Utilization Project of the Agency for Health care Research and Quality (HCUP-AHRQ). And this is the primary publicly accessible all-payer inpatient care database in the U.S. [10] NIS is structured as 20% weighted to represent 94% of all discharges of the U.S. inpatient hospital admissions with the exclusion of observation status and psychiatric hospitals. The NIS has deidentified patient information and considered exempt by the institutional review board. The NIS dataset contains patient demographics, data about comorbidities, in-hospital outcomes, hospital characteristics, insurance status, and hospitalization charges, and cost. Finally, we used inpatient stay discharge weights to create a national estimate for all our results.

2.2 Study population

Beforehand of scheming the study, we documented that the frequent documentation for hospital admissions for oropharyngeal cancers covered in the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD 10 CM) realm was categorized as malignancies of the oral cavity, including lip and

pharynx. Thus, our cohort was identified as malignant neoplasms covering lip, buccal mucosa, tongue, floor of the mouth, gums, hard palate, soft palate, tonsil, major and minor salivary glands, nasopharynx and oropharynx. In our study, we used ICD 10 CM billable codes from C00 to C14 to cover malignant neoplasms of lip, oral cavity, and pharynx. The codes are provided in the supplementary table file. (Supplementary file). Among this cohort of MLOP patients, we used ICD-10-CM billable codes, J95851, T80211A, T80211D, T80211S, T83511A, A0472, to identify hospitalizations with ventilator-associated pneumonia (VAP), central line-associated bloodstream infection (CLABSI), catheter-associated urinary tract infection (CAUTI), and Clostridium difficile infection (CDI). Patient comorbidities were determined using the Elixhauser comorbidity index. The NIS assembles LOS and total charges for hospitalization from every sampled inpatient record calculated in days and U.S. dollars separately. The hospital charges include all the hospital utilization fees charged by the hospital and do not contain the expenses incurred by the physician or typically known as physician's fees, which are billed separately.

2.3 Study measurements

We assessed patient features and clinical characteristics. Patient features included sex, age, race/ethnicity, insurance type, and median household income based on the individual's zip code for that current year grouped into four income quartiles. Clinical characteristics included the admission day (weekend/ weekday), admission type

(elective/nonelective), admission origin (transferred-in, not-transferred), and indicators for whether chemotherapy, radiation, or surgery were performed during the hospitalization. We used the Elixhauser comorbidity index used in the ICD diagnosis codes for categorizing comorbidities, where each comorbidity is dichotomous. And the score from the Elixhauser index was adjusted in the multivariate regression. The variables included in the Elixhauser comorbidity index are listed in the HCUP database. The 2017 NIS MLOP cohort of patients we presented here are stratified as with and without HAI. Table 1 includes MLOP stratified by demographic variables age, sex, race, elective (whether patients electively hospitalized), the payer (whether used the Medicaid, Medicare, other/uninsured, etc.), PL_NCHS (Patient Location whether urban or rural), Indicator of a transfer into the hospital and Median household income for patient's ZIP Code (based on current year). Our study exposure was HAIs among patients admitted for treating oropharyngeal cancers. The outcome of interest included length of hospital stays in days (i.e., the total length of hospital stays of the first admission if it occurred), cost of health services, and in-hospital mortality.

2.4 Statistical analysis

All Statistical analyses were performed using R Studio, Version 1.1.456 (RStudio: Integrated Development for RStudio. RStudio, Inc., Boston, MA). Descriptive statistics were used to describe the baseline hospital and patient characteristics. We used survey-adjusted methods accounting for NIS-specific hospital weighting. Survey

specific design (svydesign) was used for unweighing, aimed to incorporate the survey sampling weights to account for the intricate sampling design used in NIS and to deliver original estimates of the U.S. population in the resulting output.

The svydesign function was best characterized for the combined data frame and the survey design information needed to analyze. Survey specific 'Survey-Weighted Generalized Linear Models' (srvyglm) was used to fit the model (length of stay, total charges, and mortality). The srvyglm was undertaken to appropriately fit a generalized linear model from the intricate survey design of the NIS. We have fitted adjusted and unadjusted srvyglm models for LOS, total charges, and mortality. For the multivariable srvyglm models of LOS, total charges, and mortality, we have adjusted for the age, sex, payer type, patient location, race, an indicator of a transfer into the hospital, median household income and comorbidity score. For the mortality model (binomial), we fitted a family referring quasibinomial to the srvyglm, which avoids a warning about non-integer numbers of successes. The `quasi' versions of the family objects give the same point estimates and standard errors and do not provide the error or warning in the output of the model. All analyses were two-tailed and statistical significance was determined using $P < 0.05$.

3. RESULTS

In 2017, the NIS documented a total of 54, 934 MLOP cancer discharges from the total patients admitted in the U.S. hospitals in 2017; amongst those MLOP discharges, 555 MLOP patients acquired HAI. [Figure 1] Overall, the most common HAI was CDI (36%), followed by CLABSI (32%), VAP (17%), and CAUTI (15%). [Figure 3]

Patient demographics with hospital characteristics among MLOP hospitalization stratified with and without HAI (Table 1). There was no difference in the event of the HAIs and nonHAI among the MLOP cohort based on age, gender, payer type, whether rural or urban, and according to the race. The mean age of the MLOP-HAI and nonHAI were 63 and had a male predisposition in both the sections (72% and 71%). Whites were predominantly affected in the HAI (74.5%) and nonHAI strata (76.9%), whereas Blacks were 10% and 6.5 % in the nonHAI and HAI strata. Nearly 95% of the HAI hospitalization was billed to Medicare (48%), Medicaid (23%), and private insurance (27%); the trend was approximately similar in the nonHAI strata. We documented that the Patient Location: NCHS (National Center for Health Statistics) Urban-Rural Code was comparably distributed in both HAI and nonHAI sections.

We found that Median household income for patients ZIP code (based on the current year) was significantly different in the HAI and nonHAI MLOP patients ($p < 0.001$), and the HAI events were higher in the lowest income quartile. Amongst, HAI, 72% patients belong to 0-25th percentile, and 26th-50th percentile, whereas amongst nonHAI strata, patients are distributed equally in quartiles. The Elixhauser comorbidity index had a significant difference ($P < 0.001$) with the HAI and nonHAI strata.

The unadjusted multivariable regression analysis showed the mean difference in the total charges among MLOP patients with HAI compared to the MLOP patients without HAI was the U.S. $ 54005 CIs 23378 – 84632 USD, p < 0.0001. Correspondingly, the mean difference in the hospital length of stay among MLOP patients with HAI compared to the MLOP cancer patients without HAI was 7.7 days C.I.s, 4.7 - 10.6 days, p < 0.0001. Mortality was not significantly different in the MLOP patients with HAI compared to the MLOP cancer patients without HAI (OR of 0.83, CIs 0.3 – 2.26, p-value = 0.71). [Table 2]

The adjusted multivariable regression analysis showed the mean difference in the total charges among MLOP patients with HAI compared to the MLOP patients without HAI was U.S. $ 49,383 CIs 20144 USD- 78622 USD, p < 0.0001. Correspondingly, the mean difference in the hospital length of stay among MLOP patients with HAI compared to the MLOP cancer patients without HAI was 6.63 days C.I.s, 3.62-9.64 days, p < 0.0001. Mortality was not significantly different in the MLOP patients with HAI compared to the MLOP cancer patients without HAI (OR of 0.63, CIs 0.21-1.80, p-value = 0.4). [Table 3]

4. DISCUSSION

This national-wide study of MLOP patients demonstrates that the occurrence of 1 HAI was associated with a considerable increase in cost and length of

stay. When matched to the cohort of MLOP patients with no HAI, we determined that the mean charges of patients with MLOP and HAI were 2.7 times higher, and the length of stay was 6.63 days longer. Further, there was no change in mortality in both the cohort.

To our knowledge, this is the first nationwide inpatient hospitalization study addressing the burden of HAI among the MLOP patients. Thus, ICD 10 CM codes comprising MLOP patients and HAI were never used in combination with oropharyngeal cancer research. We confirmed ICD 10 CM codes by comparing the disease prevalence with other published studies and with the public data. [1], [8], [11] By doing so, ICD 10 CM codes seemed more reliable, and results were consistent in identifying hospital discharges with MLOP and HAI diagnosis in the 2017 NIS cohort. Nosology (the systematic classification of diseases) has always been fascinating in its extensive and comprehensive use of ICD codes, demonstrating a significant role in healthcare. [12] Thus, this research study leveraged these strengths to add to the prevailing literature a novel perspective of the burden of HAI on MLOP patients.

Head and Neck cancer hospitalization cost, according to the nationwide 2014 NIS database study, was $20,985 per discharge on average, causing a total national inpatient hospitalization cost liability of $1.5 billion [8]. In their study, it is noteworthy that head and neck hospitalizations associated with the oral cavity were the most expensive on average and also had the maximum cases. After adjusting for the covariates in the regression analysis, head and Neck cancer hospitalizations with laryngeal involvement

was accompanied with the highest average cost and longest average LOS. This might be due to multiple factors, including the longest healing time or associated with the hospital-associated infection and when management is inclusive or R.T., CT, and Surgical therapy. [13, 14] In patients who underwent total laryngectomy alone for laryngeal cancer (L.C.) treatment, the median length of stay was 8.0 days (range, 0-130 days). [13] The extended LOS and readmission with surgical site infection are particularly significant among the head and neck cancer patients with laryngeal involvement. [13-15] In our study, we did not assess the laryngeal cancer encumbrance and associated HAI, as previous research points outcome of the burden of hospitalization-LOS, total charges, and readmission metrics among L.C. patients are distinctive. [15] [16]

In a significant descriptive longitudinal study performed with the NIS database from 2000 to 2008 on the hospitalization-level factors of MLOP patients [17], there was an increase in trend in the MLOP hospitalization. The mean length of stay decreased from 7.3 days to 6.7 days in the years from 2000 to 2008, and the total charges trend showed an exponential increase over the nine years. [17] In their study, there was a trend of increase in the mortality; each year increase in age was associated with increased odds of death (odds ratio (OR) 1.0417, 95% CI 1.0335-1.0499, P < .0001). Complications (including postoperative pneumonia and postoperative complications) were recorded in their study; postoperative pneumonia was the most frequently occurring complication (5.6%), followed by bleeding (2.6%), bacterial infection (2.1%), and mycoses (2.1%). [17]

HAIs are one of the major impediments in the health care system as of today. [18] A report published in 2000 from the Institute of Medicine informed 44,000 – 98,000 patients died each year when exposed to the healthcare system. [18] Since then, the focus was to prevent the HAI; it has passed two decades, and according to CDC, "1 in 25 U.S. hospital patients is diagnosed with at least one infection related to hospital care alone; additional infections occur in other healthcare settings." [19] The Most common HAI in our study cohort was the CDI (36%), followed by CLABSI (32%), VAP (17%), and CAUTI (15%). According to the estimate published in 2013, CLABSI accounts for $45,814 (95% CI, $30,919-$65,245), followed by VAP at $40,144 (95% CI, $36,286-$44,220), surgical site infections at $20,785 (95% CI, $18,902-$22,667), CDI at $11,285 (95% CI, $9118-$13,574), and CAUTI at $896 (95% CI, $603-$1189). And the total annual costs for the five major infections were $9.8 billion (95% CI, $8.3-$11.5 billion). [20] Exposure to multiple treatment regimens; use of multiple devices and catheters; lack of identification of high risk-population and lack of personalized intervention may increase the risk of complications [20-22]

HAI infection in MOLP patients provides an insight into the age of onset of disease, compromised immune system, miscellaneous management (surgical and R.T), interventions (catheters, ventilators, etc.), and increased length of stay leads to multiple complications and increased burden of illness.

Our results also highlight some crucial differences between whites and non-whites with MLOP (whites accounted for most of the hospitalization). Still, there was no higher variabilities in the HAI and nonHAI strata. HAI events increased in the lowest income quartile compared to the most upper-income quartiles, and there was a significant difference in the HAI and nonHAI levels (P = 0.001). The distribution of the comorbidity in both HAI and nonHAI levels was significantly different. A discrepancy indicates that the comorbidities might influence the burden of the HAI in the MLOP patients (P< 0.001). The majority of the hospitalization (80%-90%) were not transferred into the hospitals in both the strata. And there was a difference in the transfer-in-from different acute care hospitals in both the levels. ELECTIVE in Table 1 indicates whether the admission to the hospital was elective; this information was derived from the type of access; there was a difference in the HAI and nonHAI strata. All our results are comparable to other National database studies previously conducted. [17] [8]

HAI infections among the MLOP patients are perceptive that infectious complications would indicate poorer outcomes, but, knowing the possibility and degree of this burden from the clinical characteristics, patient features, and comorbidities would be beneficial in prediction. [23-28] Although the NIS database is excellent, many factors affect the dataset, the observational nature of the dataset, limitations with administrative claims data set, failure to demonstrate causal inference, along with hospital coding method, and inaccurate representation of the outcome are some inherent limitations. [29-30]

The HAI burden among MLOP patients is significant when compared to hospitalized patients in different settings showed a similar trend of increased LOS and hospitalization cost. [11, 31-33] Our research outcomes would complement the patient cohort with the risk of HAI burden.

1. As a platform, the strength of these findings would help predict risk factors and modeling in oncology and non-oncology settings concerning oral and maxillofacial diseases.

2. The economic burden of cancer is a significant concern in the U.S., and when intertwined with HAI, MLOP patients are more susceptible to this setback. Thus, actions for preventing HAI among cancer patients are required at every phase of hospital care.

3. A similar trend in the increase of LOS and hospitalization costs are comparable to hospitalized gynecology-oncology patients, [34] cardio-thoracic surgery patients, [32, 11] and in non-oncology pediatric care settings. [33] While HAIs are comparable to other backgrounds, the occurrence of HAIs among MLOP patients might also depend upon significant factors like comorbid conditions, age at diagnosis, stage of cancer, and the microbial etiology of MLOP cancers.

4. Amongst cancer patients, it is uncertain whether HAIs serves as a risk factor for recurrence, secondary neoplasms, and survival. Mostly, these aspects of HAIs are

unknown and generally requires actionable practices in oncology and non-oncology setting.

5. CONCLUSION

The burden of Healthcare-associated infections in MLOP patients are mostly preventable, our study indicates the U.S. 2017 MLOP patient cohort who acquired HAI, was associated with a considerable increase in the length of stay, and total charges during their in-hospital stay.

Limitations of the study

1. Claims data

The most significant limitations of the claims data are the accurateness of billing codes when used to classify diagnoses and procedures. Coding inaccuracy leads to destabilizing the reliability and correlation, although it varies by disease characterizations and definitions, and the procedures in the data source may exaggerate this. Relating or comparing findings with multiple studies on the same associations' measure might effectively reduce these selection biases. Generally, it is assumed that when procedure codes are combined with diagnostic codes, the results are more reliable, demonstrating the thoroughness of the claims and internal validation. Some of the other potential problems arising with claims data are that data are stored in raw-from and not in ready to use form. And in terms of the scarce in-depth details and

de-identification, which prevents the follow-ups and gathering of other additional variables, which might increase the risk of residual confounding. In the case of NIS data, we believe that it is the best available in terms of the readiness to use. We have used the ICD 10 CM codes comprising oropharyngeal cancer patients and HAI, which were never used in combination with Head and Neck cancer research. We confirmed ICD 10 CM codes by comparing the disease prevalence with other published studies and with the public data. This way, we believe that we have used accurate billable codes for our research.

2. Claims data on the bias of results

Analytical questions may arise regarding the external validity, selection bias, confounding, misclassification bias, and causality, as the inferences are derived from observational data obtained from the third-party documents. The evidence comprised in insurance data is often incomplete or sometimes will be adjusted, therefore, formulating it for the disease and risk factors, causation, and treatment sometimes might be misleading. Carefully researching the data, which itself is a rigorous task, offers to minimize errors. By adjusting the variables in the multivariable regressions, balancing covariates by propensity score and instrument variable analysis-based methods for variable adjustment are being utilized to balance the confounding elements among the patient cohort being analyzed, which are inherently different at baseline. With the comparison with the other studies and clinical judgment, we have carefully adjusted the

variables in the multivariable regression analysis. Thus, we believe that we have regulated some of the confounding biases which might influence the outcome.

3. Cross-sectional nature of the NIS data

With the cross-sectional quality of the claims data, finding an association might be appropriate, which in turn will depend on the assumptions for the exposure and outcome of the study. Still, causality or causal inference would be inappropriate or even impossible. The weakness of such studies would be interrelated whether the results followed exposure in time.

Additionally, the claims data provide a snapshot of the disease processes and other health-related characteristics at an in-hospitalization timepoint. Thus, we have utilized the methodology which can be used to assess the in-hospital burden of HAI of a population (oropharyngeal cancer patients) at a given time point.

4. Generalizability

Occasionally generalizability of results might be challenging and problematic, a significant consideration appeared when dealing with the dental data, in 2012, approximately 60 % of the U.S. population had dental insurance, and a majority of them were healthier and having a higher income than those didn't have insurance. [36-38] And thus, inferences from such studies could only be applied to those populations where they have insurance coverage. We initially decided to use the oropharyngeal

procedure to identify the codes from the CDT procedure (The CDT dental code is a set of procedural systems for oral health and dentistry). We noted that dental claims data are predominantly vulnerable to misclassification because they are not based on the diagnosis, which is very different from the NIS data. From the previously published report, we noted that periodontal and oral surgical procedures are often not submitted in the ICD codes.

We then decided to use the inpatient sample data were a major procedure like oropharyngeal cancer treatment are undertaken. Thus, the generalizability of the claims data might largely depend on disease classification in the diagnosis codes and procedure codes platform.

5. Residual confounding

Even with the adjustment of the covariates in the regression approach, there might be undetectable confounding biases, such as unmeasured or residual confounding elements. We have used a multivariable regression-based approach to fit our model and considered judging each clinically relevant variable by selectively evaluating the change in the exposure-outcome estimate. Other methods like automated selection methods in regression, stratification, and propensity score methods might be useful to adjust for the confounding.

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Figures & Tables

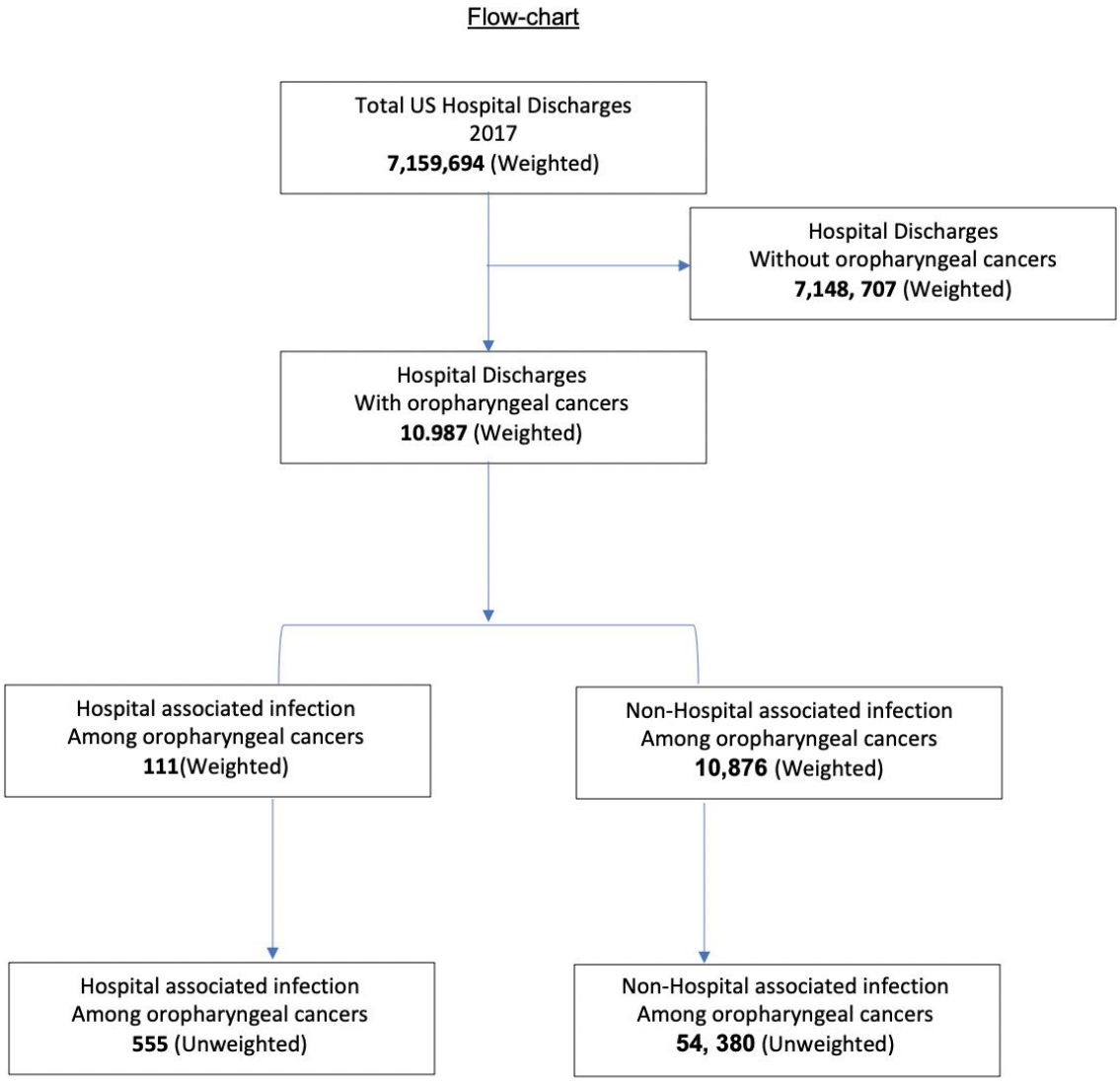

Figure 1. Flow chart of the cohort selection from the NIS; sample size presented with weighted and unweighted numbers.

Figure legend – The flow chart shows - Weighted number of patients (this is the 20% of total number of patients admitted in the entire US hospital) and the Unweighted number of patients (represents total number of patients in the US hospitals after unweighing with svydesign).

Table 1. Baseline characteristics of MLOP patients comparing HAI with non-HAI

Characteristics	nonHAI	HAI	P-value
Age (mean (SD))	63.35 (13.48)	62.82 (15.00)	0.710
Female (%)	15765.0 (29.0)	155.0 (27.9)	0.812
Race (%)			0.405
1. White	39120.0 (74.5)	415.0 (76.9)	
2. Black	5660.0 (10.8)	35.0 (6.5)	
3. Hispanic	3430.0 (6.5)	55.0 (10.2)	
4. Asian or Pacific Islander	1930.0 (3.7)	20.0 (3.7)	
5. Native American	245.0 (0.5)	0.0 (0.0)	
6. Other	2115.0 (4.0)	15.0 (2.8)	
Expected primary payer (%)			0.278
1 Medicare	27020.0 (49.8)	260.0 (46.8)	
2 Medicaid	8490.0 (15.6)	125.0 (22.5)	
3 Private insurance	15780.0 (29.1)	145.0 (26.1)	
4 self-pay	1210.0 (2.2)	5.0 (0.9)	
5 No charge	140.0 (0.3)	5.0 (0.9)	
6 Other	1645.0 (3.0)	15.0 (2.7)	
Elective (%)	19900.0 (36.7)	110.0 (19.8)	<0.001
Patient Location: NCHS Urban-Rural Code (%)			0.036
1 "Central" counties of metro areas of >=1 million population	15690.0 (29.0)	110.0 (20.2)	
2 "Fringe" counties of metro areas of >=1 million population	13985.0 (25.8)	110.0 (20.2)	
3 Counties in metro areas of 250,000-999,999 population.	11045.0 (20.4)	145.0 (26.6)	
4. Counties in metro areas of 50,000-249,999 population.	5165.0 (9.5)	55.0 (10.1)	
5. Micropolitan counties	4860.0 (9.0)	60.0 (11.0)	
6. Not metropolitan or micropolitan counties.	3415.0 (6.3)	65.0 (11.9)	
Indicator of a transfer into the hospital (%)			0.001
0. Not transferred in or newborn admission indicated by ATYPE=4	49525.0 (91.3)	460.0 (82.9)	
1. Transferred in from a different acute care hospital	2970.0 (5.5)	75.0 (13.5)	
2. Transferred in from another type of health facility	1720.0 (3.2)	20.0 (3.6)	
Median household income for patient's ZIP Code (based on current year)			0.001
1. 0-25th percentile	15110.0 (28.3)	180.0 (33.3)	
2. 26th to 50th percentile (median)	13985.0 (26.2)	215.0 (39.8)	
3. 51st to 75th percentile	12800.0 (24.0)	80.0 (14.8)	
4. 76th to 100th percentile	11445.0 (21.5)	65.0 (12.0)	
Weighted Charlson score (mean (SD))	20.86 (12.24)	24.92 (11.89)	<0.001

Abbreviations: SD, Standard deviation; NCHS, National Center for Health Statistics.

Figure 2. Difference in the outcome measures of HAI and nonHAI cohort of oropharyngeal patients.

Abbreviation: 95% CI, 95% confidence interval; MD, mean difference; OR, odds ratio.

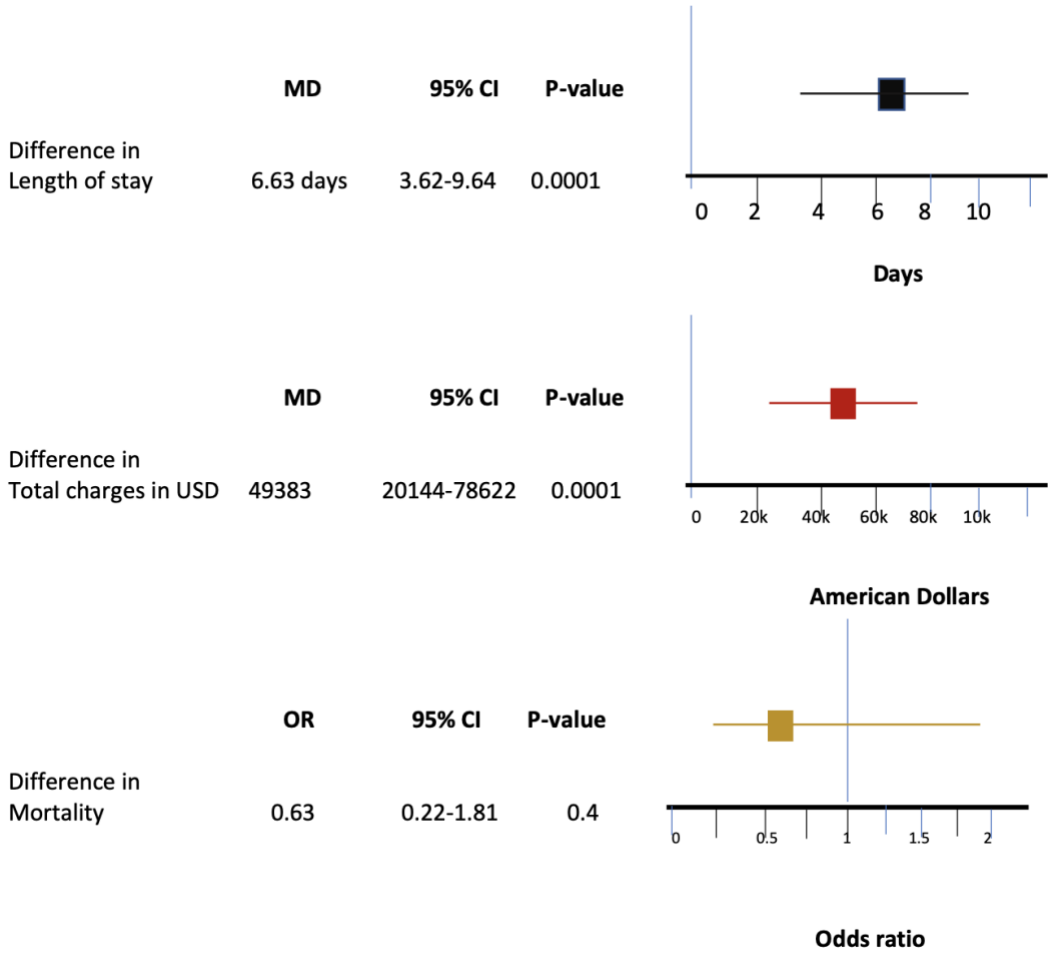

Figure legend – Results of the adjusted multivariable regression analysis, i) the mean difference in LOS of HAI and non-HAI patients - 6.63 days longer in HAI, CIs, 3.62-9.64, p < 0.0001;

ii) the mean difference in total inpatient hospital expenses of HAI and non-HAI patients - US $ 49,383 higher in HAI, CIs 20144 USD- 78622 USD, p < 0.0001;

ii) the odds of mortality (OR of 0.63, CIs 0.21-1.80, p value = 0.4) among MLOP patients with HAI compared to the MLOP cancer patients without HAI.

Table 2. Unadjusted outcome measures among patients having oropharyngeal cancers and hospital associated infections

Outcome	Hospital associated infection = 555	Confidence interval	P value
Mean length of stay	7.7 days	4.7 - 10.6 days	< 0.001
Total Charges	54005 USD	23378 – 84632 USD	< 0.001
Mortality	0.83 (OR)	0.3 - 2.26 (OR)	0.71

Table 2 legend - Results of the unadjusted multivariable regression analysis, i) the mean difference in LOS of HAI and non-HAI patients - 7.7 days longer in HAI, CIs, 4.7 - 10.6 days, p < 0.0001;

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Table 3. Adjusted outcome measures among patients having oropharyngeal cancers and hospital associated infections

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Table 3 legend – Results of the adjusted multivariable regression analysis, i) the mean difference in LOS of HAI and non-HAI patients - 6.63 days longer in HAI, CIs, 3.62-9.64, p < 0.0001;

ii) the mean difference in total inpatient hospital expenses of HAI and non-HAI patients - US $ 49,383 higher in HAI, CIs 20144 USD- 78622 USD, p < 0.0001;

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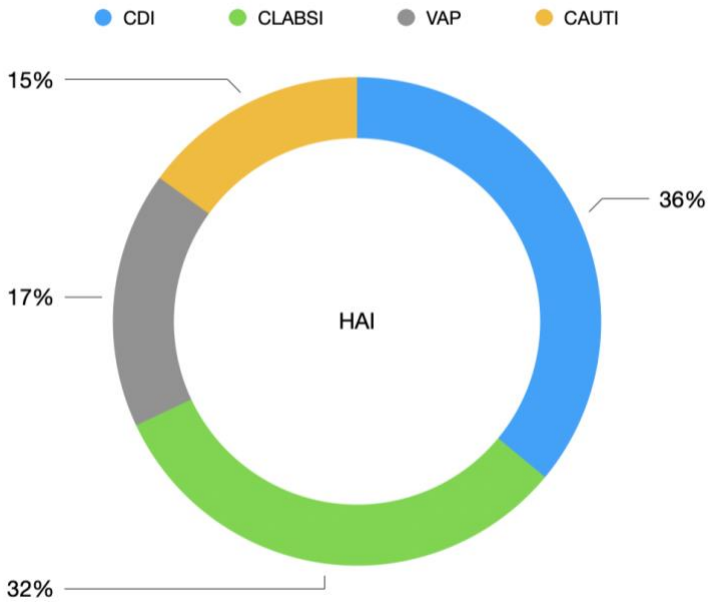
Figure 3. Prevalence of the HAI among the US 2017 Oropharyngeal cancers.



Supplementary file

ICD 10 billable Codes for Malignant neoplasms of lip, oral cavity and pharynx

(C00-C14).

- C00.0 - Malignant neoplasm of external upper lip **BILLABLE CODE**
- C00.1 - Malignant neoplasm of external lower lip **BILLABLE CODE**
- C00.2 - Malignant neoplasm of external lip, unspecified **BILLABLE CODE**
- C00.3 - Malignant neoplasm of upper lip, inner aspect **BILLABLE CODE**

- C00.4 - Malignant neoplasm of lower lip, inner aspect **BILLABLE CODE**
- C00.5 - Malignant neoplasm of lip, unspecified, inner aspect **BILLABLE CODE**
- C00.6 - Malignant neoplasm of commissure of lip, unspecified **BILLABLE CODE**
- C00.8 - Malignant neoplasm of overlapping sites of lip **BILLABLE CODE**
- C00.9 - Malignant neoplasm of lip, unspecified **BILLABLE CODE**

Malignant neoplasm of base of tongue (C01)

- C01 - Malignant neoplasm of base of tongue **BILLABLE CODE**

Malignant neoplasm of other and unspecified parts of tongue (C02)

- C02.0 - Malignant neoplasm of dorsal surface of tongue **BILLABLE CODE**
- C02.1 - Malignant neoplasm of border of tongue **BILLABLE CODE**
- C02.2 - Malignant neoplasm of ventral surface of tongue **BILLABLE CODE**
- C02.3 - Malig neoplasm of anterior two-thirds of tongue, part unsp **BILLABLE CODE**
- C02.4 - Malignant neoplasm of lingual tonsil **BILLABLE CODE**
- C02.8 - Malignant neoplasm of overlapping sites of tongue **BILLABLE CODE**
- C02.9 - Malignant neoplasm of tongue, unspecified **BILLABLE CODE**

Malignant neoplasm of gum (C03)

- C03.0 - Malignant neoplasm of upper gum **BILLABLE CODE**
- C03.1 - Malignant neoplasm of lower gum **BILLABLE CODE**
- C03.9 - Malignant neoplasm of gum, unspecified **BILLABLE CODE**

Malignant neoplasm of floor of mouth (C04)

- C04.0 - Malignant neoplasm of anterior floor of mouth **BILLABLE CODE**
- C04.1 - Malignant neoplasm of lateral floor of mouth **BILLABLE CODE**
- C04.8 - Malignant neoplasm of overlapping sites of floor of mouth **BILLABLE CODE**
- C04.9 - Malignant neoplasm of floor of mouth, unspecified **BILLABLE CODE**

Malignant neoplasm of palate (C05)

- C05.0 - Malignant neoplasm of hard palate **BILLABLE CODE**
- C05.1 - Malignant neoplasm of soft palate **BILLABLE CODE**
- C05.2 - Malignant neoplasm of uvula **BILLABLE CODE**
- C05.8 - Malignant neoplasm of overlapping sites of palate **BILLABLE CODE**
- C05.9 - Malignant neoplasm of palate, unspecified **BILLABLE CODE**

Malignant neoplasm of other and unspecified parts of mouth (C06)

- C06.0 - Malignant neoplasm of cheek mucosa **BILLABLE CODE**
- C06.1 - Malignant neoplasm of vestibule of mouth **BILLABLE CODE**

- C06.2 - Malignant neoplasm of retromolar area **BILLABLE CODE**
- C06.80 - Malignant neoplasm of ovrlp sites of unsp parts of mouth **BILLABLE CODE**
- C06.89 - Malignant neoplasm of overlapping sites of oth prt mouth **BILLABLE CODE**
- C06.9 - Malignant neoplasm of mouth, unspecified **BILLABLE CODE**

Malignant neoplasm of parotid gland (C07)

- C07 - Malignant neoplasm of parotid gland **BILLABLE CODE**

Malignant neoplasm of other and unsp major salivary glands (C08)

- C08.0 - Malignant neoplasm of submandibular gland **BILLABLE CODE**
- C08.1 - Malignant neoplasm of sublingual gland **BILLABLE CODE**
- C08.9 - Malignant neoplasm of major salivary gland, unspecified **BILLABLE CODE**

Malignant neoplasm of tonsil (C09)

- C09.0 - Malignant neoplasm of tonsillar fossa **BILLABLE CODE**
- C09.1 - Malig neoplasm of tonsillar pillar (anterior) (posterior) **BILLABLE CODE**
- C09.8 - Malignant neoplasm of overlapping sites of tonsil **BILLABLE CODE**
- C09.9 - Malignant neoplasm of tonsil, unspecified **BILLABLE CODE**

Malignant neoplasm of oropharynx (C10)

- C10.0 - Malignant neoplasm of vallecula **BILLABLE CODE**
- C10.1 - Malignant neoplasm of anterior surface of epiglottis **BILLABLE CODE**
- C10.2 - Malignant neoplasm of lateral wall of oropharynx **BILLABLE CODE**
- C10.3 - Malignant neoplasm of posterior wall of oropharynx **BILLABLE CODE**
- C10.4 - Malignant neoplasm of branchial cleft **BILLABLE CODE**
- C10.8 - Malignant neoplasm of overlapping sites of oropharynx **BILLABLE CODE**
- C10.9 - Malignant neoplasm of oropharynx, unspecified **BILLABLE CODE**

Malignant neoplasm of nasopharynx (C11)

- C11.0 - Malignant neoplasm of superior wall of nasopharynx **BILLABLE CODE**
- C11.1 - Malignant neoplasm of posterior wall of nasopharynx **BILLABLE CODE**
- C11.2 - Malignant neoplasm of lateral wall of nasopharynx **BILLABLE CODE**
- C11.3 - Malignant neoplasm of anterior wall of nasopharynx **BILLABLE CODE**
- C11.8 - Malignant neoplasm of overlapping sites of nasopharynx **BILLABLE CODE**
- C11.9 - Malignant neoplasm of nasopharynx, unspecified **BILLABLE CODE**

Malignant neoplasm of pyriform sinus (C12)

- C12 - Malignant neoplasm of pyriform sinus **BILLABLE CODE**

Malignant neoplasm of hypopharynx (C13)

- C13.0 - Malignant neoplasm of postcricoid region **BILLABLE CODE**
- C13.1 - Malig neoplasm of aryepiglottic fold, hypopharyngeal aspect **BILLABLE CODE**
- C13.2 - Malignant neoplasm of posterior wall of hypopharynx **BILLABLE CODE**
- C13.8 - Malignant neoplasm of overlapping sites of hypopharynx **BILLABLE CODE**
- C13.9 - Malignant neoplasm of hypopharynx, unspecified **BILLABLE CODE**

Malig neoplasm of sites in the lip, oral cavity and pharynx (C14)

- C14.0 - Malignant neoplasm of pharynx, unspecified **BILLABLE CODE**
- C14.2 - Malignant neoplasm of Waldeyer's ring **BILLABLE CODE**
- C14.8 - Malig neoplm of ovrlp sites of lip, oral cavity and pharynx **BILLABLE CODE**

Summary

Summary of the research

Paper 1, 2 and 3, conclusions

Oral care interventions (OCI) that reduce oral bacterial load have been suggested to be effective in mitigating the risk of ventilation associated pneumonia (VAP). However, very little was known about the oral care intervention in the risk of non-ventilation associated pneumonia (NVAP). Our research in this space estimated that NVAP risk is not equivalent for all hospitalized patients. When considering the NVAP's burden, there is very little conclusive evidence in the form of randomized-controlled trials (RCTs). RCTs on oral hygiene intervention performed by a dental professional to prevent the NVAP risk were conducted in nursing homes in Japan, and they conclude that structured enhanced oral regimens effectively reduced the rate of NVAP and that enhanced OCI delivered by dental professionals were most effective. Therefore, the generalizability of the results is limited. As a proof-of-concept, the results of such studies can be concluded to be positive with an overall reduction in NVAP rates of greater than 10%, but their broad translatability to the general hospital population is unclear.

A patient's oral health status may be a risk component to the extent that it reflects bacterial load. However, there is an equivalent contribution from patient's comorbidities, length of stay, type of the facility (acute and chronic care setting), and other factors that might increase the risk of Healthcare-associated infection (HAI), this needs to be analyzed in detail. And there is an extreme paucity in distinguishing the burden of HAIs in this area of research. Our analysis confirms the need for additional studies to assess

the benefit of OCI on all HAI risk fully, and also to characterize the burden of HAI outcome on the oropharyngeal procedures.

Given the challenges of existing oral care intervention in preventing VAP, and lack of head to head robust trials of the best available treatment modality, the approach of the Network meta-analysis (NMA) to assess the comparative effectiveness of oral care interventions in preventing ventilator-associated pneumonia in critically ill patients is exceptional. We followed stern assumptions and standardization, and our study cohort was based on the largest pairwise meta-analysis of oral care intervention in preventing the VAP. According to the NMA outcome, toothbrushing alone or toothbrushing along with a potent antiseptic mouthwash povidone-iodine was related to the highest response rate in preventing VAP in critically ill patients, followed by furacillin and chlorhexidine 0.2%, respectively.

The outcomes from first and second research show that oral hygiene maintenance directed to the mechanical cleaning (scaling and root planing performed by a dental professional in the NVAP setting, toothbrushing alone and toothbrushing along with a potent mouthwash in VAP setting) was very much superior to the chemical disinfection alone in reducing the microbial counts in the oral cavity whether in VAP patients or in non-VAP patients. The mechanical cleaning performed by a dental professional in NVAP patients reduced the 35% risk. The approach of mechanical cleansing by the dental professionals in NVAP patients reduced the active microbial pooling when patients who were hospitalized without a device (endotracheal tube) in the

oral cavity. This scenario is entirely different when patients are ventilated with an active device in the oral cavity, as in the case of VAP. Oral hygiene procedures like scaling and root planning are never possible to perform when patients are ventilated, and reduction of the oral biofilm and dental plaque accumulation utilizing a toothbrushing alone or in combinations with a potent chemical mouthwash is more suitable, than a chemical mouthwash alone.

Some studies have suggested that improved oral hygiene may be useful in reducing its incidence [1-8]. However, when hospitalized, there is a disproportionate accumulation of dental biofilm and pooling microbes to drive throughout the oral and laryngeal airway space. [1-9] It is worth noting, the dental deposits alone contain around 100 million bacteria per one cubic millimeter of dental plaque. [8,9] There could be a difference in the acute care setting and the long-term care setting when accounting for the microbial pooling in the lungs. In both cases, dental biofilm could be a significant responsible factor for the development of pneumonia. [9]

Ventilated patients with no access to clear oral secretion may aspirate or cough, are at risk of developing VAP, aspiration of oral secretion contaminated by oral microbes, may potentially serve as a reservoir for pneumonia. [9,10,11] Whereas in the NVAP cases, where mostly elderly care setting is included having reduced salivary secretions, decreased cough reflex, followed by swallowing disorders and reduced skill to perform oral hygiene, may explain the risk. [12, 13]. However, it is also debatable whether there is a difference in the dentate and edentate group, which was not

evaluated since enough data was not available to perform this analysis. Studies on oral health status and VAP provides an insight into those areas where the oral hygiene wasn't performed due to the mechanical ventilation device, especially the posterior buccal teeth surface prone to microbial pooling, studies found these to be risk factors for pneumonia. [1-3, 14, 15] Our first and second research suggests that mechanical cleansing alone or along with a potent mouthwash reduced the oral biofilm and oral plaque formation, and substantiality reduced the risk of pneumonia among the VAP and NVAP groups.

To assess the characteristics of the HAI, we performed a descriptive study to assess the differences in outcome among patients with a primary diagnosis of malignant neoplasms of the oropharyngeal area with and without hospital-associated infection (HAI). To our knowledge, this is the first nationwide inpatient hospitalization study addressing the burden of HAI among oropharyngeal cancer patients.

The most common HAI was Clostridium difficile infection (36%), followed by central line-associated bloodstream infection (32%), ventilator-associated pneumonia (17%), and catheter-associated urinary tract infection (15%). Oropharyngeal cancer patients with HAI had a length of stay of 6.63 days longer than the non-HAI patients. Oropharyngeal cancer patients with HAI had hospitalization charges of 49383 USD higher than the non-HAI oropharyngeal cancer patients.

Our analysis was limited to oropharyngeal cancers of the 2017 US national hospitals, although it provided an overview of the difference in the outcome of the HAI and non-HAI. We were not sure whether oropharyngeal procedures definitively had any consequence on the difference in HAI outcomes. Hence, we further analyzed the 2017 inpatient sample data for additional studies outlined below, and findings of all studies are remarkable and publishable.

1) **Characteristics of the healthcare-associated infections among those who underwent Orthognathic surgery - Ongoing study.**

2) **Healthcare-associated infections among patients undergoing treatment for chemotherapy and radiation-induced ulcerative mucositis - Ongoing study.**

3) **The differences in outcome among patients hospitalized with a primary diagnosis of malignant neoplasms of lip, oral cavity, and pharynx with and without Ulcerative Mucositis (UM) – Ongoing study.**

Limitations

1. Owing to the increasing concern in the dissemination of the oral microbes into the systemic distribution, focusing on preventing systemic illness with enhanced oral care may add value in recent years to come. However, there would always be a concern in the VAP and NVAP prevention protocols and oral care stances. Along with other

comorbidities, oral microbiota may unquestionably influence the general health of the patients.

2. Our research supports the concept that adequate oral microbial debridement favorably impacts NVAP risk. However, the reason for the difference in response between dental vs. non-dental professionals may not be specifically attributed to differences in competencies, but slightly reflective of focus and time spent.

Whereas non-dental professionals typically have oral care as one of many patient-related daily tasks, the only focus of the dental professionals was oral care, and thus the time-spent and outcome motivation was likely to be more direct. The observed impact on NVAP-related outcomes when care was delivered by a nursing assistant dedicated to providing OCI as a primary task supports this argument. Competing time demands for nursing services may limit their capacity to provide optimal mouthcare. Additional studies are necessary to more thoroughly investigate the impact of provider qualifications on NVAP risk modification since the cost implications of dedicated oral health aides, regardless of their requirement, is not insignificant.

3. Chemical disinfection presumably offers a non-procedural opportunity to reduce oral bacterial burden. In contrast to its reported efficacy to prevent VAP, the effect of chemical disinfection on NVAP risk was inconsistent across the 3 RCTs (Relative risk (RR), 1.05). Recent studies suggest an increased risk of NVAP with chlorhexidine use

(RR 1.36), and some showed either a marginally protective effect (RR 0.87) or a substantive effect (RR 0.60). There is a lack of studies estimating the chlorhexidine concentrations.

4. Chlorhexidine has been widely used in the general population for many years, and chlorhexidine resistance is an emerging topic recently, but research on chlorhexidine resistance on VAP and NVAP population is very limited.

5. Our study on the comparative effectiveness of the oral care products in preventing ventilation associated pneumonia was limited to the systematic search until 2016, and there might be other RCTs in this area with robust findings.

6. **Small numbers of studies** in a meta-analysis possibly lead to more heterogeneity; and more generally, for numerous dissimilar therapeutic interventions, the pooled effect estimates of meta-analyses of larger studies are more reliable when compared with the smaller studies. [16] This was one of the chief limitations with the first pairwise meta-analysis research, and we attempted to get as much evidence from the non-randomized trials and observational studies to test our hypothesis. Since there were a smaller number of trials in this area of research in the hospitalized population, we expect to have more trials in the future both as a randomized and non-randomized experiment to test the hypothesis.

7. **Publication bias**, which is known as the 'file drawer problem,' [17] This phenomenon occurs when statistically insignificant or no effect studies are not published, and hence do not appear in the meta-analysis. Preventing publication bias could be done by setting a search strategy to include grey literature, conference abstracts, and university thesis, with the limited time, we couldn't do this search strategy. We might have included funnel plot, eggers plot, trim, and fill method to detect publication bias since fewer than ten studies were included in the quantitative synthesis, publication bias assessment was not performed.

8. **Limitations of sub-group analyses and limitations of generalizability.**

Considering the over-all pooled effect estimate, which is often affected by effect modifiers, the subgroup analysis is best to assess the consistency of treatment across multiple groups. Subgroup analysis is a beneficial technique, but they have limitations and pitfalls, primarily when referring to the generalizability of the findings. The results of the subgroup analysis may sometimes misleading if not powered enough to conclude. And similarly, the subgroup analysis findings would lead to influence the inferences of the causal conclusion derived from the randomized controlled trial. [18]

In our first research focusing on the oral care intervention preventing non-ventilated pneumonia (NVAP), the quantitative synthesis of meta-analysis didn't show significant findings of oral care intervention in preventing the NVAP; the subgroup analysis, where a dental professional who performed analysis showed a meaningful result. Although these findings may not be generalizable, and more studies are needed to assert this finding through randomized and non-randomized controlled trials.

But we believe that the patient cohort where a dental professional performed oral hygiene would have spent a sufficient time to reduce the oral microbial content through mechanical cleaning than others. In place of the concept that oral microorganism responsible for pneumonia are present in the oral cavity and requires less than 48 hours to colonize in the mouth, structured mechanical cleaning is beneficial. The patient cohorts were a dental professional involved resulted in higher responses in the reduction of pneumonia upon which to assess the impact of procedures to reduce the oral bacterial burden serves as an explanatory.

Conclusion

Ongoing professional dental care is the most effective preventive measure for non-ventilated pneumonia for patients in long-term care facilities. Preventing oral deposits in hospitalized patients by means of mechanical plaque and debris removal might reduce the risk of pneumonia by means of a reduction in pneumonia-causing microorganisms in the oral cavity.

Structured oral care, along with other preventive efforts, are warranted for hospitalized patients at risk of HAI. Additional randomized clinical trials are needed to validate the utility of oral care interventions as a preventive strategy for HAI.

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Appendix I

First research is assigned to the *April 24th* issue of the BDJ.

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Enhanced oral hygiene interventions as a risk mitigation strategy for the prevention of non-ventilator-associated pneumonia: a systematic review and meta-analysis

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Key points

- Ongoing professional dental care is the most predictably effective preventive intervention for non-ventilated pneumonia (NVAP) for patients in long-term care facilities.
- Structured oral care may be warranted for hospitalised patients at risk of NVAP.
- Additional, prospective, randomised, controlled clinical trials are needed to validate the utility of oral care interventions as a preventive strategy for NVAP.

Abstract

Background Healthcare-acquired pneumonias are a significant risk for nursing home and hospital patients. While oral care interventions (OCIs) have been found to be effective in reducing the risk of ventilator-associated pneumonia (VAP), their utility in mitigating non-ventilator-associated pneumonias (NVAP) remains unknown. We performed a structured meta-analysis of randomised and non-randomised clinical trials of enhanced oral hygiene procedures on NVAP.

Methods We searched PubMed and Embase to include clinical trials (randomised and non-randomised), and observational (retrospective and prospective) and quasi-experimental studies examining the effect of any method of OCI on incidence of NVAP.

Results After quality assessment and consensus agreement between authors, we synthesised six randomised clinical trials (3,891 patients), two non-randomised trials (2,993 patients), and separately assessed a retrospective trial (143 patients) and a quasi-experimental study (83 patients). Most studies, performed in nursing homes, did not show a significant association between OCI and NVAP prevention (RR random 0.89, 95% CI 0.64–1.25, p value 0.50). Likewise, the non-randomised trials failed to show an association between NVAP risk and OCI (RR random 1.42, 95% CI, 0.70–2.88, p value 0.32). However, in the subgroup analysis comparing dental professional involvement in care vs usual care, reduced NVAP risk was demonstrated (RR random 0.65, 95% CI 0.43–0.98, p value 0.03).

Conclusions Study results suggest that professional dental care may confer some benefit among NVAP patients. The lack of consistent OCI protocols, data in hospitalised patients and robust randomised clinical trials do not allow definitive conclusions about the contribution of OCI in mitigating NVAP risk.

Introduction

Pneumonias acquired in acute and chronic healthcare facilities are a significant risk for patients. A 2015 survey reported that hospital-acquired infections affect approximately 3.2% of patients hospitalised in the United States,[1] or 1,184,000 cases this year, at costs exceeding $40,000,000,000. Among hospital-acquired infections, pneumonias are the most common with an overall incidence of 21.8%.[2,3,4] Pneumonia is also clinically the most significant infection among the approximately 1.7 million nursing home patients in the United States, with an incidence of 0.3 to 2.3 episodes per 1,000 resident care days.[5]

Pneumonias in these populations are typically categorised based on their association with ventilator use. Ventilator-associated pneumonias (VAPs) have been best studied and protocols have been developed which have lowered their risk. In contrast, the prevalence of non-ventilator-associated pneumonias (NVAPs) has remained essentially unchanged.[1] Classic hospital-acquired pneumonias are defined as those that develop after 48 hours of hospital admission.[6] While the definition for NVAPs can also be applied to nursing home patients, there are marked differences between the two populations, including length of stay (13.7 months for nursing homes[7] vs 6.1 days for acute care hospitals),[8] demographics and co-morbidities. Nonetheless, given the potential importance of the oral cavity as a bacterial source for NVAP, we generally included both populations in the analysis, but analysed them separately.

The physiologic and healthcare costs of NVAPs are significant and have been well-described.[2,4,8] The microbial aetiology of NVAP has been ascribed to pathogens associated with the upper aerodigestive tract, for which four potential routes of contamination have been hypothesised: aspiration of oropharyngeal secretions, food or gastric contents; inhalation of infectious aerosols; contiguous spread of infection; or haematogenous spread from non-pulmonary sources to the lung.[9] The primary

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source of pathogens of pulmonary infections is suggested to be associated with aspiration of colonised secretions from the oropharynx. However, given the bacterial spectrum reported for NVAP, it is impossible to ignore the nose, nasopharynx or sinuses as also being important. A relationship between NVAP risk and dentate state is unresolved.[10]

Intensive oral care interventions (OCIs), regimens that reduce the oral cavity bacterial load, have been suggested to be effective in mitigating NVAP risk. The individual elements comprising these regimens have not been consistent and range dramatically in their intensity. However, trends in outcomes potentially support their utility. If professionally delivered oral care regimens are to be considered for universal standard of care for NVAP prevention, several critical questions require answers:

1. Is the nursing time, effort and instrumentation needed for an expanded oral hygiene programme justified by a cost/benefit analysis; that is, how effective are expanded oral hygiene programmes in modifying risk of NVAP?
2. Are there specific risk factors which can prospectively identify patients at risk of NVAP and how do these patients specifically respond to oral hygiene programmes?
3. When is the optimum time to initiate OCIs; that is, are programmes which commence at the time of admission effective, or should oral hygiene programmes begin earlier, and if so, how much earlier?
4. Are the pathogens observed in NVAP found in the oral biofilm, where are the primary depots of pathogens and which OCIs best target those depots?

As a first step, we performed a structured meta-analysis in which we assessed randomised and non-randomised clinical trials, and observational studies that investigated the relative efficacy of enhanced OCI program on NVAP.

Methods

Search strategy and inclusion criteria

Using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement,[11] a systematic literature appraisal was performed. The literature search was done in PubMed (inception until January 2019) and Embase (1990 to January 2019) using inclusive search terms (see Appendix 1). The searches included all study designs: clinical trials (randomised and non-randomised), observational studies (retrospective and prospective) and quasi-experimental studies. Title and abstracts were independently screened by two investigators (KS and SS) and disagreements regarding eligibility were discussed. Cross-referencing and supplementary literature searches were performed to examine references in topic-related previously published reviews, and by manually searching bibliographies of the included articles and similar articles. Full-text screening of selected publications was done by two examiners and discrepancies were resolved by discussion. For each selected study, the study characteristics were extracted by two assessors which were then corroborated by a third researcher.

Inclusion criteria

Experimental and observational studies were included based on the following criteria:

1. Reported NVAP as a primary outcome
2. Conducted on hospitalised/chronic care facility adults >18 years of age who were not diagnosed as having pneumonia at the time of admission
3. Intervention or exposure to enhanced oral care, whether matched with placebo, usual care or comparable medication for preventing NVAP
4. Provided data in the form of point estimates and measure of 95% confidence intervals (CIs), or the data were required to be available to calculate those measures.

Studies were excluded if they did not provide specific NVAP results, as were those that used the term 'hospital-acquired pneumonia (HAP)' but did not differentiate NVAP from VAP. We also excluded the studies which were not published in English and those with results published as abstracts or poster presentations. If data from the same patient cohort was published more than once, we only included the study which most informed our outcome.

Data extraction

Data were extracted from eligible studies, independently, using pre-specified data extraction forms. For each included record, study characteristics were recorded by two independent members of the team and discrepancies were resolved by discussion. Characteristics included methods, country, setting, duration of follow-up, sample size, number of patients randomised, number of patients evaluated, inclusion and exclusion criteria, diagnosis of NVAP, intervention (type, dose and frequency of oral care), control (type, dose and frequency of oral care), outcome measures involving incidence of NVAP secondary endpoints, and funding source.

Quality of studies

Reviewers independently extracted and assessed the risk of bias for randomised controlled trials (RCTs), the random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias (for example, funding bias).

The quality of RCTs was assessed using the 'Risk of Bias' tool from the Cochrane Collaboration and the quality of observational studies was assessed using the Newcastle-Ottawa Scale (NOS).[12,13] Case definition met the selection/outcome criteria if recorded in health services/study databases as actual diagnoses and did not meet the NOS criteria if self-reported and/or gathered by questionnaire. A similar approach was taken with ascertainment of enhanced oral care to meet relevant NOS criteria if recorded as prescriptions in health services/study databases and did not meet NOS criteria if self-reported and/or gathered by a non-validated questionnaire. For lost to follow-up, we considered any study with ≤10% lost to follow-up adequate. The remaining NOS criteria were followed routinely.

Subgroup analyses

We performed three subgroup analyses. In the first, we evaluated the effectiveness of chemical disinfection on NVAP risk, in the second, we compared the differences in effectiveness between enhanced oral hygiene regimens in which a dental profession (dentist/dental hygienist) vs. those which were administered solely by non-dentally qualified individuals and in the third, we evaluated the effectiveness of the enhanced oral hygiene regimens on the outcome of mortality due to NVAP.

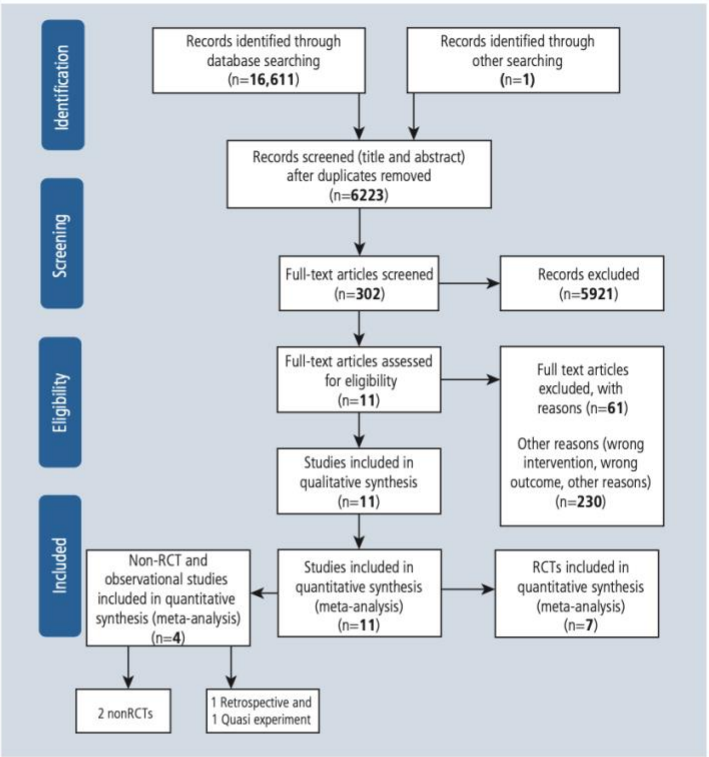
Statistical analysis

Statistical analyses were based on comparing rates of total NVAP events between the enhanced OCI group and the control group. If the studies did not report the number of NVAP events and/or the total number of

participants in the enhanced OCI group and the control group, we used RR, OR and a measure of variance 95% CIs to produce summary relative risk estimates and measure of variance 95% CIs. Due to the expected clinical heterogeneity between studies, we decided *a priori* to use a DerSimonian and Laird (DL) random effects model for all analyses.[14] Testing for heterogeneity between the studies was performed using Cochran's Q test[15] and the I^2 test.[13] A p value <0.05 or an I^2 higher than 50% were considered significant evidence for heterogeneity. Additionally, we used the Hartung-Knapp-Sidik-Jonkman (HKSJ) method[16] to retrieve more adequate error rates. Simulations have shown that the HKSJ method performs better than DL, especially when there is heterogeneity and the number of studies in the meta-analysis is small.[16,17,18,19,20] Subgroup analysis was performed to assess whether there were differences between professional dental care and usual care, use of antimicrobial chlorhexidine (CHX) and usual care, and mortality due to pneumonia in enhanced OCI versus usual care. All statistical analyses were performed using RStudio, Version 1.1.456 (RStudio: Integrated Development for RStudio; RStudio, Inc., Boston, MA URL).

Visual assessment using Funnel's and Egger's plots for publication bias was not performed as we had less than ten studies included in the meta-analysis.

Fig. 1 Flow diagram showing summary of literature search and study selection



Results

Our initial search provided 16,611 records; duplicates of 6,223 were removed with the EndNote software X9.1.1 version. After title and abstract screen, 5,921 unrelated records were excluded, culminating in 302 records that were assessed for eligibility using full-text screening. Eleven studies were identified as meeting our inclusion criteria. Our search strategy led to identification of seven clinical trials, two non-randomised clinical trials, one quasi-randomised and one retrospective cohort study (Fig. 1).

Characteristics of the included studies are listed in Table 1 (see online supplementary information for further detail). Seven RCTs[21,22,23,24,25,26,27] are included in our analysis, of which five[21,22,23,26,27] were conducted in nursing homes, one in a stroke rehabilitation unit,[24] and one in an intensive care unit (ICU).[25] One study was not included in the qualitative assessment because of non-estimable risks, both in the intervention and the control group.[24] A total of 3,891 patients were included in the overall analysis. Among the non-RCTs,[28,29] one study (number analysed: 2,890) was done in a non-intensive acute care hospital setting,[28] and the other in nursing home residents.[29] Among the other experiment designs, one study was a quasi-experimental trial (number analysed: 83) in a neurosurgical population outside the critical care environment,[30] and the other study was a retrospective analysis (number analysed: 143) conducted in nursing home residents.[31] We employed a per-protocol analysis (PPA) to understand the superior effects of treatment, as PPA provides an estimate of the true efficacy of an intervention, also recognising that PPA interpretation to actual practice may be confounded by an overstated treatment weight.[32]

Meta-analysis of enhanced oral care in preventing NVAP – RCTs

The meta-analysis of the six RCTs was performed using the DL and HSKJ methods. The DL method demonstrated a pooled relative risk of 0.89 (95% CI: 0.64–1.25, p value = 0.50, I^2 = 65.2%, p $value_{het}$ = 0.01, tau^2 = 0.08) (Table 2). HKSJ adjustment of the CIs provided similar results. Since fewer than ten studies were included in the quantitative synthesis, publication bias assessment was not performed.

Effect of oral CHX in the prevention of NVAP

Subgroup analysis was performed to assess the effect of oral CHX rinsing on the prevention of NVAP (n = 3 studies). Using the DL method, the combined effect size was 1.05 (95% CI, 0.69 to 1.60, p value = 0.80; I^2 = 76.6%, tau^2 = 0.08 with p $value_{het}$ = 0.01, suggesting that the addition of CHX to an enhanced oral care regimen was ineffective in preventing NVAP (Table 3).

Dental professional involvement in enhanced oral care in prevention of pneumonia

Subgroup analysis of the impact of dental professional involvement (dentist or hygienist) in enhanced oral care versus usual oral care in the prevention of NVAP (n = 3 studies) revealed

a pooled relative risk of 0.65 using the DL method (95% CI, 0.43 to 0.98, p value = 0.03, I^2 = 0%, tau^2 = 0 with p $value_{het}$ = 0.9). It appeared that oral care in which a dental professional was involved favourably reduced NVAP risk (risk reduction of 35%) (Table 4).

Effects of enhanced oral care in the prevention of mortality due to pneumonia

There was no impact of enhanced oral care in reducing NVAP-related mortality (n = 4 studies); pooled relative was 0.80 (95% CI, 0.40 to 1.63), p value = 0.54, I^2 = 83%, tau^2 = 0.38 with p $value_{het}$ = 0.00 based on the DL method (Table 5).

Non-randomised clinical trials

Assessment of the two non-randomised clinical trials performed with DL method showed the pooled relative risk 1.42 (95% CI, 0.70 to 2.88) p value = 0.32, I^2 = 74%, tau^2 = 0.19 with p $value_{het}$ = 0.05 (Table 6).

Other studies

Two additional studies were included in the meta-analysis: a retrospective and a quasi-experiment study. The retrospective analysis noted an odds ratio of 1.21 (95% CI 0.99–1.48), with a p value of 0.6. The quasi-experimental study showed relative risk of 0.25 (95% CIs 0.06, 1.02) p value of 0.05.

Discussion

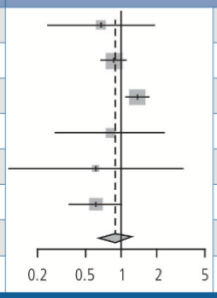
The oral cavity is a documented source of pathogens which might contribute to NVAP risk. Consequently, enhanced oral hygiene regimens aimed at reducing the oral bacterial load have been proposed as a risk mitigation strategy. While standard patient-performed oral hygiene is an integral part of a proactive health maintenance routine, definitive evidence of the health and cost benefits of more aggressive regimens on NVAP risk is critical for making the case for widening its implementation. Our aim was to assess clinical trial outcomes in this space

Table 1 Characteristics of the individual studies

Reference (year)	Country	Study setting	Duration	Number of participants evaluated	Intervention type	Control
Randomised controlled trials						
Adachi (2002)[21]	Japan	Nursing homes	24 months	88	Professional care	Usual oral care
Bourigault (2011)[22]	France	Nursing homes	18 months	2,513	CHX oral rinse and enhanced oral care	Usual oral care
Ohsawa (2003)[23]	Japan	Nursing homes	24 months	49	Professional care with povidone-iodine oral rinse	Usual oral care
Lam (2013)[24]	Hong Kong	Stroke rehabilitation unit	31 months	81	Professional care with CHX oral rinse	Oral hygiene instructions
Panchabhai (2009)[25]	India	ICU (medical and surgical)	8 months	300	CHX and usual care	Potassium permanganate rinse
Yoneyama (2002)[26]	Japan	Nursing homes	24 months	366	Professional care with povidone-iodine oral rinse	Usual oral care
Juthani-Mehtha (2015)[27]	USA	Nursing homes	30 months	575	CHX oral rinse and enhanced oral care	Usual oral care
Non-randomised controlled trials and other studies						
McNally (2019)[28]	USA	Controlled trial	3.5 months	2,890	Enhanced oral care and cetylpyridinium oral rinse	Usual oral care
Hollaar (2017)[29]	Netherlands	Controlled trial	12 months	103	Enhanced oral care and CHX oral rinse	Usual oral care
Robertson (2013)[30]	Canada	Quasi-experimental	6 months	83	Enhanced oral care	Usual oral care
Bassim (2008)[31]	USA	Retrospective study	79 weeks	143	Enhanced oral care	Usual oral care

Table 2 Forest plot of the RCTs. Review: enhanced oral hygiene maintenance for the prevention of non-ventilated pneumonia. Comparison: enhanced oral care versus usual care. Outcome: prevention of pneumonia

Study	Experimental		Control		Risk ratio	RR	95% CI	Weight
	Events	Total	Events	Total				
Adachi (2002)[21]	5	40	9	48		0.67	(0.24; 1.83)	8.5%
Bourigault (2011)[22]	93	868	203	1,645		0.87	(0.69; 1.09)	29.9%
Juthani-Mehtha (2015)[27]	119	277	94	298		1.36	(1.10; 1.69)	30.5%
Ohsawa (2003)[23]	5	25	6	24		0.80	(0.28; 2.28)	8.0%
Panchabhai (2009)[25]	2	136	4	164		0.60	(0.11; 3.24)	3.6%
Yoneyama (2002)[26]	21	184	34	182		0.61	(0.37; 1.01)	19.6%
Random effects model	**1,530**		**2,361**			**0.89**	**(0.64; 1.25)**	**100.0%**



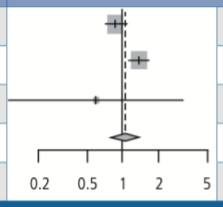
Heterogeneity: I^2 = 65%, tau^2 = 0.0853, p = 0.01

using a meta-analysis strategy. Our findings in the effectiveness of enhanced oral care on preventing NVAP were null.

Most studies were performed in nursing home patients. While there are clearly substantive differences noted above between nursing home and acute care patients, they share the risk of acquired bacterial pneumonias for which the overall pathogenesis is similar.[5] Thus, both patient cohorts serve as platforms upon which to assess the impact of procedures to reduce the oral bacterial burden as a mitigating strategy. Importantly, despite their dissimilarities, learnings from each group may be applicable and relevant to the other. Collectively, the PPA of enhanced oral hygiene failed to demonstrate a statistically significant impact on NVAP (pooled RR of 0.89, CI: 0.64–1.25, p value 0.50) risk, which was diverse from that reported in an earlier meta-analysis of four RCTs (RR 0.61, CIs 0.40, 0.90, p value 0.02).[33] When the evaluation was limited exclusively to nursing homes (n = 5) the impact of oral hygiene on NVAP RR was 0.90, CIs 0.63, 1.28, p value 0.56. It is noteworthy that enhanced oral hygiene negatively impacted risk in one United States study (RR of NVAP was 1.36).[27] Aside from the patient population and location of each trial, the intensity of the

Table 3 Forest plot of the subgroup analysis of the RCTs. Review: enhanced oral hygiene maintenance for the prevention of non-ventilated pneumonia. Comparison: chlorhexidine for oral care versus usual care. Outcome: prevention of pneumonia

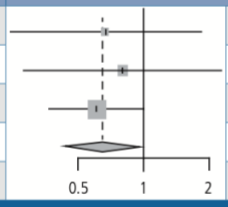
Study	Experimental		Control		Risk ratio	RR	95% CI	Weight
	Events	Total	Events	Total				
Bourigault (2011)[22]	93	868	203	1,645		0.87	(0.69; 1.09)	46.8%
Juthani-Mehtha (2015)[27]	119	277	94	298		1.36	(1.10; 1.69)	47.7%
Panchabhai (2009)[25]	2	136	4	164		0.60	(0.11; 3.24)	5.5%
Random effects model	**1,281**		**2,107**			**1.05**	**(0.69; 1.60)**	**100.0%**



Heterogeneity: I^2 = 77%, tau^2 = 0.0830, p = 0.01

Table 4 Forest plot of the subgroup analysis of the RCTs. Review: enhanced oral hygiene maintenance for the prevention of non-ventilated pneumonia. Comparison: professional dental care versus usual care. Outcome: prevention of pneumonia

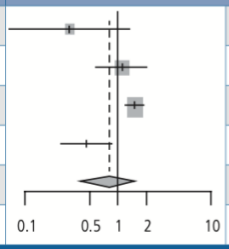
Study	Experimental		Control		Risk ratio	RR	95% CI	Weight
	Events	Total	Events	Total				
Adachi (2002)[21]	5	40	9	48		0.67	(0.24; 1.83)	16.8%
Ohsawa (2003)[23]	5	25	6	24		0.80	(0.28; 2.28)	15.7%
Yoneyama (2002)[26]	21	184	34	182		0.61	(0.37; 1.01)	67.5%
Random effects model	**249**		**254**			**0.65**	**(0.43; 0.98)**	**100.0%**



Heterogeneity: I^2 = 0%, tau^2 = 0, p = 0.90

Table 5 Forest plot of the subgroup analysis of the RCTs. Review: enhanced oral hygiene maintenance for the prevention of non-ventilated pneumonia. Comparison: enhanced oral care versus usual care. Outcome: prevention of mortality due to pneumonia

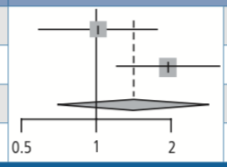
Study	Experimental		Control		Risk ratio	RR	95% CI	Weight
	Events	Total	Events	Total				
Adachi (2002)[21]	2	40	8	48		0.30	(0.07; 1.33)	13.5%
Bourigault (2011)[22]	15	868	26	1,645		1.09	(0.58; 2.05)	26.6%
Juthani-Mehtha (2015)[27]	122	277	88	298		1.49	(1.20; 1.86)	32.7%
Yoneyama (2002)[26]	14	184	30	182		0.46	(0.25; 0.84)	27.2%
Random effects model	**1,369**		**2,173**			**0.80**	**(0.40; 1.63)**	**100.0%**



Heterogeneity: I^2 = 83%, tau^2 = 0.3838, p <0.01

Table 6 Forest plot of the non-RCTs (enhanced oral care in the prevention of NVAP). Review: enhanced oral hygiene maintenance for the prevention of non-ventilated pneumonia. Comparison: enhanced oral care versus usual care. Outcome: prevention of pneumonia

Study	Experimental		Control		Risk ratio	RR	95% CI	Weight
	Events	Total	Events	Total				
McNally (2019)[28]	25	1,403	26	1,487		1.02	(0.59; 1.76)	48.2%
Hollaar (2017)[29]	12	15	14	34		1.94	(1.21; 3.12)	51.8%
Random effects model	**1,418**		**1,521**			**1.42**	**(0.70; 2.88)**	**100.0%**



Heterogeneity: I^2 = 74%, tau^2 = 0.1921, p = 0.05

oral hygiene intervention was not uniform and varied principally in two ways: who performed the oral hygiene intervention and whether an antimicrobial rinse was included in the oral hygiene regimen.

The results of two non-RCTs support enhanced oral hygiene as an effective strategy to reduce NVAP risk, but in specific patient groups. A statistically significant reduction in NVAP incidence was reported in a neurosurgical patient cohort.[30] Given the typical functional impediments associated with these patients, the finding is not surprising. A retrospective medical chart review in nursing home patients[31] concluded that enhanced oral hygiene performed by a dedicated nursing assistant (n = 78) significantly reduced NVAP outcomes compared to no oral care (n = 65).

Our subgroup analysis comparing the impact of healthcare provider credentials on outcomes showed that the standard of oral hygiene regimens[21,23,25] was enhanced for those in which dental professionals were involved, and these appeared to be more effective than those rendered by other providers in reducing NVAP risk (Table 4). This effect is comparable to previous meta-analysis.[34] While this data supports the concept that effective oral microbial debridement favourably impacts NVAP risk, the conclusion that formal dental training results in demonstrably superior outcomes could be misleading as the effect might not be specifically attributed to variances in technical competencies, but rather to focus and time spent on the oral hygiene process. Whereas non-dental professionals typically number oral care as one of many patient-related daily tasks, the sole emphasis of the dental professionals was on mouth hygiene. The observation that oral care delivered by a dedicated nursing assistant produced equivalent NVAP risk supports this argument.[7] Competing time demands for services may limit nurses' capacity to deliver optimal mouthcare.[28] Additional studies are necessary to more fully investigate the impact of provider qualifications on NVAP risk modification, since the cost implications of dedicated oral health aides, regardless of their qualification, is not trivial.

Two non-RCT studies in acute care hospital patients were informative. Out of 90 elderly patients admitted urgently for lower limb fractures, 10% of patients developed NVAP.[10] While the authors found that pathogen colonisation of the mouth was higher in patients who developed NVAP, it was insufficient to explain differences between VAP and NVAP groups. Whereas NVAP risk was not associated with being dentate, tooth number, or heavy dental or denture plaque, it was associated with a specific bacterial carriage which the authors concluded was present before hospital admission.

In perhaps the largest study in an acute care hospital population, NVAP development was compared between patient self-brushing (control n = 1,487) and enhanced nurse-delivered oral care (experimental n = 1,403; tooth brushing three times per day with a fresh toothbrush and daily use of an antiseptic rinse). Despite the designated oral care regimen, no impact on NVAP rates were seen between the control (1.7%) and test groups (1.8%). Critically, despite study-specific training and daily monitoring, nursing compliance was only 1.6 times per day, only slightly better than patient self-brushing frequency (1.2 times per day). However, when subjects from both arms were pooled and compared based on whether they developed NVAP, the odds ratio for NVAP decreased by 40% when tooth brushing increased by once per day, regardless of who performed the procedure. Importantly, this finding suggests that patient-directed education programmes and provision of oral care kits may be a valuable and cost-effective approach to NVAP control.

Given the challenges of cost and compliance with professionally delivered oral hygiene-based approaches, chemical disinfection offers a non-procedural alternative to reduce both the tooth-borne and mucosal oral bacterial burden. The latter clearly plays a role in VAP risk, and reduction of mucosal bacteria such as those residing on the tongue provides an important target for sustained antibacterial efficacy.[35] CHX remains the most popular agent for this purpose. However, in contrast to its reported efficacy in preventing VAP, its efficacy mitigating NVAP risk was inconsistent across the three RCTs (RR 1.05) we evaluated,[22,25,27] perhaps because of differences in dose response effects and/or the impact of concurrent treatment.[33]

The contrasting efficacy of CHX rinses between NVAP and VAP is interesting. One might speculate the antimicrobial prophylaxis in the form of a topical agent is effective in preventing colonisation of the ventilator tubes in the same way that similar agents favourably impact catheter-centric infections. In the case of VAP, oral plaque accumulation could be exacerbated with placement of ventilation apparatus, especially in the premolar and molar areas.[36] In non-ventilated patients, the microbiome and the environment is more fluid and subject to dilution effects of saliva, which might negatively impact efficacy.[37,38] It is also possible that the time to onset which defines NVAP reduces the potential prophylactic efficacy of antimicrobials by compressing the

time in which they might effectively impact NVAP outcomes.

Evaluation of the NVAP literature indicates that NVAP risk is not equivalent for all patients.[39] High rates of NVAP are consistently noted in post-operative cancer patients, patients with neurological diseases and the elderly. The finding that dentate state (dentulous vs edentulous, and number of teeth) is not a clear risk determinant contradicts an oral hygiene strategy that focuses solely on tooth-borne bacteria.[10] It is possible that a patient's oral health status may be a risk component to the extent that it reflects bacterial load. However, whether there is equivalent contribution to hospital-associated pneumonia among the different microbiological eco-environments in the mouth (that is, tooth-borne bacteria vs mucosal bacterial niches like the dorsal tongue) is unclear.[39,40] Likewise, the comparative effectiveness of different oral hygiene interventions on impacting bacterial pathogens is unresolved.[41] Our analysis confirms the need for additional study to fully assess the benefit of OCI, optimise its timing and personalise the intensity of OCI-based individualising risk/benefit. It seems obvious that a 'one size fits all' approach for OCI would likely result in being excessive for many patients, but inadequate for others. Given the frequency and impact of NVAP, additional study is warranted.

Conclusion

In the introduction, we noted four questions to which answers would better define NVAP risk and intervention strategies. Given NVAP's potential clinical and economic burden, there is surprisingly little definitive documentation in the form of RCTs which speak to the efficacy of directed intervention methods. Most of the RCTs reported were done in nursing homes – most in Japan – and they conclude that structured enhanced oral hygiene regimens effectively reduced the rate of NVAP, and that enhanced oral hygiene delivered by dental professionals were most effective. Therefore, the generalisability of the results is limited. As a proof-of-concept, the results of such studies can be concluded to be positive with an overall reduction in VAP rates of greater than 10%, but their broad translatability to the general hospital population is unclear. While good oral hygiene for hospitalised patients should be as consistent as handwashing and bathing, the current body of clinical research defining extended oral interventions as they relate to VAP risk, and the comparative effectiveness of various oral care interventions, is incomplete. Given the impact of NVAP, large, structured, randomised trials in which specific interventions are tested are critical.

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Author contributions

SK and STS: design, methods, data collections, analysis and preparation of paper.

SP: analysis and preparation of paper.

Sponsor's role in manuscript preparation: none.

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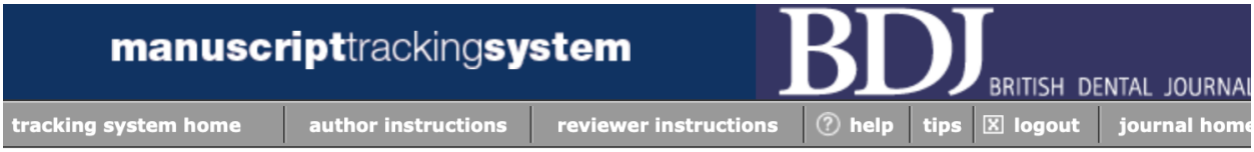
Appendix 1 PubMed and Embase search terms

Search in PubMed (inception until January 2019)	Nursing homes [Title/Abstract] OR intermediate care facilities [Title/Abstract] OR nursing facilities [Title/Abstract] AND elderly care [Title/Abstract] Oral hygiene [Title/Abstract] OR mouth care [Title/Abstract] OR mouthwash [Title/Abstract] OR oral chlorhexidine [Title/Abstract] OR oral povidone-iodine [Title/Abstract] OR tooth brushing [Title/Abstract] OR dental care [Title/Abstract] OR oral antiseptic [Title/Abstract] OR oral rinse [Title/Abstract] Pneumonia [Title/Abstract] OR lung infection [Title/Abstract] OR non-ventilator pneumonia [Title/Abstract] OR respiratory tract diseases [Title/Abstract] OR lung diseases [Title/Abstract] OR hospital-acquired pneumonia [Title/Abstract] OR nosocomial pneumonia [Title/Abstract] Cross infection [Title/Abstract] OR nosocomial infection [Title/Abstract] OR infection, hospital [Title/Abstract] OR health care associated infections [Title/Abstract]
Search in Embase (from 1 January 1990 to January 2019)	'cross infection':ab,ti OR 'nosocomial infection':ab,ti OR 'infection, hospital':ab,ti OR 'health care associated infections':ab,ti) AND [1990-2019]/py ('nursing homes':ab,ti OR 'intermediate care facilities':ab,ti OR 'nursing facilities':ab,ti OR 'elderly care':ab,ti) AND [1990-2019]/py ('oral hygiene':ab,ti OR 'mouth care':ab,ti OR 'oral chlorhexidine':ab,ti OR 'oral povidone-iodine':ab,ti OR 'tooth brushing':ab,ti OR 'dental care':ab,ti OR 'oral antiseptic':ab,ti OR 'oral rinse':ab,ti) AND [1990-2019]/py ('pneumonia':ab,ti OR 'lung infection':ab,ti OR 'non-ventilator pneumonia':ab,ti OR 'respiratory tract diseases':ab,ti OR 'hospital-acquired pneumonia':ab,ti OR 'nosocomial pneumonia':ab,ti) AND [1990-2019]/py 1 AND 2 AND 3 AND 4

Appendix II

Second research submitted in British Dental Journal- transferred to BMC-Oral Health.



Detailed Status Information

Manuscript #	MSS-2020-222
Current Revision #	0
Submission Date	6th Mar 20
Current Stage	Manuscript Transferred
Title	Application of network meta-analysis to assess the comparative effectiveness of oral car interventions in preventing ventilator-associated pneumonia in critically ill patients.
Running Title	Network meta-analysis of oral care interventions in preventing ventilator-associated pneumonia.
Manuscript Type	Research
Manuscript Comment	1. This is the first comparative effectiveness research with respect to oral care interventions in preventing ventilation associated pneumonia 2. The findings of this research are highly important for the future perspective in oral hygiene care in mechanically ventilated patients.
Corresponding Author	PS Satheeshkumar (Harvard University)
Contributing Author	Stephen Sonis
Abstract	Background Oral care interventions (OCI) are considered essential in lessening the risk of ventilator-associated pneumonia (VAP). While preventive and intervention strategies have been suggested, their comparative effectiveness has not been established. In this paper, we assessed the efficacy of a novel analytic, network metanalysis (NMA), in creating a hierarchy to define the most effective OCI for the prevention and management of VAP. Methods We applied NMA to a previously published robust pairwise meta-analysis (PMA). Statistical analyses were based on comparing rates of total VAP events between the intervention groups and the placebo-usual care groups. To ascertain variability/heterogeneity in the included studies of NMA design, we used the heterogeneity statistics decomposition function of netmeta package, R Studio. We synthesized a netgraph, reported ranking order of the treatment and summarized our output by a forest plot with a reference treatment placebo/usual care. Results With our inclusion and exclusion criteria for the NMA, we extracted 25 studies (4473 subjects) from a previously published PMA. The NMA included 16 treatments, 29 pairwis comparisons, and 15 designs. Based on the results of multiple comparisons with frequentist ranking probability P scores, we reported fixed and random effects P scores of the best possible rating of all OCIs preventing VAP in critically ill patients. Tooth brushing (P score fixed of 0.9353, P score random of 0.8892), toothbrushing with povidone-iodine (P score fixed of 0.9091, P score random 0.8801), and furacillin (P score fixed of 0.8798, P score random 0.8358) were the best three interventions. While chlorhexidine 0.2%, a recommended oral care product for preventing VAP in critically ill patients has a P score of 0.6531 fixed and 0.6478 random. Conclusion NMA appeared to be an effective platform from which multiple interventions reported in disparate clinical trials could be compared to derive a hierarchical assessment of efficacy in the intervention of VAP. According to the NMA outcome, toothbrushing alone or toothbrushing along with a potent antiseptic mouthwash povidone-iodine was related to the highest response rate in preventing VAP in critically ill patients followed by furacillin and chlorhexidine 0.2%, respectively.

RESEARCH ARTICLE *Dentistry* *Head & Neck Surgery*

Application of Network Meta-Analysis to Assess the Comparative Effectiveness of Oral Care Interventions in Preventing Ventilator Associated Pneumonia in Critically Ill Patients.

Satheeshkumar PS, Stephen Sonis

DOI: 10.21203/rs.3.rs-23653/v1

Abstract

Background In this research, we assessed the efficacy of a novel analytic, network metanalysis (NMA), in creating a hierarchy to define the most effective oral care intervention (OCI) for the prevention and management of ventilation-associated pneumonia (VAP).

Methods We applied NMA to a previously published robust pairwise meta-analysis (PMA). Statistical analyses were based on comparing rates of total VAP events between intervention groups and placebo-usual care groups. We synthesized a netgraph, reported ranking order of the treatment and summarized our output by a forest plot with a reference treatment placebo/usual care.

Results With our inclusion and exclusion critiera for the NMA we extracted 25 studies (4473 subjects). The NMA included 16 treatments, 29 pairwise comparisons and 15 designs. Based on the results of multiple comparisons with frequentist ranking probability P scores, tooth brushing (P score fixed of 0.9353, P score random of 0.8892), toothbrushing with povidone iodine (P score fixed of 0.9091, P score random 0.8801), and furacillin (P score fixed of 0.8798, P score random 0.8358) were the best three interventions for preventing VAP.

Conclusion NMA appeared to be an effective platform from which multiple interventions reported in disparate clinical trials could be compared to derive a hierarchical assessment of efficacy in the intervention of VAP. According to the NMA outcome, toothbrushing alone or toothbrushing along with a potent antiseptic mouthwash povidone iodine was related to the highest response rate in preventing VAP in critically ill patients followed by furacillin and chlorhexidine 0.2%, respectively