

1. When was the work published?

For this particular assignment, I chose to critique the scientific article titled “Impact of Oral Hygiene Involving Toothbrushing versus Cyclohexidine in the Prevention of Ventilator Associated Pneumonia: A Randomized Study”, written by Claudia Fernanda de Lacerda Vidal, Aurora de Lacerda Vidal and 13 other authors. This study was published in Volume 17 of the academic journal “BMC Infectious Diseases” on Jan 31, 2017.

2. What are the main points in the article? Write a 150-200 word summary of the article that accurately conveys the content of the article.

In this randomized, prospective study, the author analyzes whether toothbrushing, alongside the application of 0.12% cyclohexidine gel, presents any additional benefits in killing oral pathogens, reducing the oral to pulmonary transfer of bacteria and thus limiting the occurrence of ventilator associated pneumonia (VAP) in mechanically ventilated patients, when compared to using the 0.12% cyclohexidine gel alone. For this trial, 213 adults were chosen from a group of 716 mechanically ventilated patients from 4 ICU’s across Brazil and randomly assigned to either the control (cyclohexidine gel) or intervention (toothbrushing and cyclohexidine gel) group. The oral hygiene treatment to all subjects was applied every 12 hrs and changes in each patient’s individual health noted for a 28 day follow-up period, using leukocyte count, body temperature and presence of pulmonary infiltrate to detect the onset of

pneumonia. The researchers also noted if there were any changes in length of ICU stay, duration of mechanical ventilation and mortality rates between the 2 groups.

The results showed that although there was a reduction in the occurrence of VAP when toothbrushing was implemented, the results were not statistically significant ($p=8.4\%$). Similarly although mortality rates and length of ICU stay declined in the toothbrushing group, again the results were not statistically significant ($p=29.6\%$ and 6.4% respectively). Length of mechanical ventilation also decreased when toothbrushing was implemented and here the results were statistically significant ($p=1.8\%$). Overall, toothbrushing did tend to offer additional benefits in preventing VAP and boosting pulmonary health when compared to using cyclohexidine gel alone, but the results were mostly too insignificant due to the small sample size used.

3. Does the work meet the standards to be considered an appropriate academic/scholarly source? Justify your answer.

Yes, the work meets the standards necessary to be considered an appropriate scholarly source. This journal article was peer reviewed prior to being accepted for publication in the journal *BMC Infectious Diseases* (submitted 3 Aug 2015 and accepted 5 January 2017). This gives it an immense amount of scholarly value. Additionally, the article was collaborated and written by multiple authors, all affiliated with renowned hospitals, medical universities and infection control centers, which gives it a whole new level of academic integrity and eliminates research bias that may be present in a single author work. The study itself has been conducted in a professional manner, following

the works of previous researchers. The authors have utilized 25 academic journal articles, meta reviews and studies (listed in the bibliography) before starting their experiment, meaning they have a sound academic baseline. They have also published the article fairly recently, which would ensure the concepts presented are more updated and accurate than something similar published more than 5 years ago.

The results themselves have been analyzed in a statistically logical manner using chi square probability tests on STATA computer software. This gives the results an unbiased amount of accuracy. Add to this the fact that the trial has also been registered into the Brazilian Clinical Trials Registry proves the authors conducted the research in a professional and legal manner. Combining all these reasons, I would not question the academic value of this work and would consider it of high scholarly value.

4. Are the qualifications of the authors appropriate for an academic article?

Briefly describe the authors' qualifications.

Yes, all the 15 authors who partook in writing the article are well qualified to do so. The main author of the article, Claudia Fernanda de Lacerda Vital, not only happens to be a professor at the Federal University of Pernambuco, but is also an active member of the Tropical Medicine Health Sciences Center and the Committee on Infection Control of Hospitals and Clinics. In fact, this study has multiple authors and all 15 of them hail from very credible universities, medical research institutes and hospitals, meaning they most likely have worked with the demographic population in question, ICU patients and pneumonia patients, in the past. To be more exact, 11 of the 15 authors

work at a medical university, 7 are from the Medicine Health Science Center and 4 are from Infection Control Committees across Brazil.

Because most authors are from top of the line research institutes, there is no doubting they are familiar with the experimental design and have the qualifications necessary to conduct a study or write an academic research article on the subject. The fact they are well studied shows well enough in the many references they make to other author's works throughout the article. Furthermore, seeing how they have all worked in hospitals and ICU's, they must have accumulated a diverse level of expertise working with pneumonia patients, understanding the pathophysiology of the disease as well as practicing infection control procedures commonly used to prevent it. Therefore, their experimental design and results will supposedly be less flawed than someone who's conducting a study on VAP patients for the very first time.

5. Is the purpose clearly stated? Restate the purpose of the paper in your own words.

The authors clearly state the purpose of the study in both the abstract and the full text as part of "background" information. According to them, almost half of all infections occurring in ICU units are incidences of Ventilator Associated Pneumonia.

Unfortunately, when ICU patients are mechanically ventilated, the endotracheal tube giving them air acts as a conductor of bacteria from their mouth to their lower respiratory tract, facilitating the onset of nosocomial pneumonia. As a result, the patient has to stay in the ICU longer, which translates into higher hospital costs, more occupied beds and

more suffering for the patient. This vicious cycle can easily be interrupted if adequate oral hygiene methods are implemented to kill oral pathogens and interrupt pulmonary transfer of the bacteria.

Although there has been considerable amount of research done on reducing VAP through the use of cyclohexidine gel/rinse, very little attention has been paid to the effects of toothbrushing on further reducing VAP. It is now believed that toothbrushing, due to its mechanical abrasion mechanism, may be better able to remove biofilm and bacteria from the mouth than a topical application of cyclohexidine alone, which only swishes bacteria around in the mouth. Therefore, the researchers wanted to examine the additional benefits toothbrushing can offer in controlling biofilm, reducing VAP occurrence and improving overall patient health and vitality, which is why they conducted this experiment using 2 groups, the cyclohexidine only group as the control design and toothbrushing and cyclohexidine group as the experimental design.

6. Is the experimental design clearly described? Describe the design in your own words.

The experimental design is very clearly laid out in the methods section of the article. The authors describe everything from the recruitment of the study population to their randomization into one of two study groups, their treatment plan, methods of data collection and statistical analysis. The researchers state that the study population of 213 individuals is picked out from a set of 711 ICU patients based on age, initial pulmonary condition, pregnancy status, intubation length and other qualifying factors. Then the

chosen individuals are placed into either the control or intervention group using a random computer generated list, which makes this a **randomized trial** as stated in the very title of the article. The groups are analyzed for statistical differences to make sure they are not too different. Then they are treated with either the control or experimental therapy every 12 hrs. The nurses administering the oral hygiene treatment to both groups are unaware of whom is receiving the intervention treatment versus who's not, as are the participants, which makes this a **double blind study**. The subjects are followed for a period of 28 days following mechanical ventilation and changes in each patient's health using pneumonia markers such as presence of pulmonary infiltrate and body temp, are recorded periodically. Because the experiment attempts to study patients through a followup period rather a specific point in time, the study can be considered to be of a **longitudinal, prospective design**. After specific traits such as length of ICU stay and days on mechanical ventilation are identified for each patient, the results are gathered and analyzed using the STATA software program to check for significant differences between the 2 groups.

7. Has the sample been appropriately selected? Describe the sample in the study and describe its appropriateness.

I believe the 213 participants that were narrowed down from the list of 716 ICU patients undergoing mechanical ventilation were appropriately selected for the purposes of the study. Among the criteria for inclusion was being aged at least 18 yrs, not being pregnant, not showing any signs of pulmonary infections, being expected to remain on

intubation for at least 48 hrs, not having any chlorhexidine allergy and not being edentulous. Since the study was being conducted on adults, it made sense to exclude patients that were younger than 18. Also since the study was supposed to follow the said individual for 28 days, it was only logical to exclude patients who were weaned off mechanical ventilation or extubated in the first 48 hours. Also, because pregnancy can act as a huge confounding variable due to the hormonal changes it brings, it was again reasonable to reject pregnant individuals for the purposes of the study. Edentulous patients and those allergic to chlorhexidine were also excluded, which was again understandable, considering they could not undergo either therapy due to missing teeth or allergy to the treatment plan. The resultant sample population, with an average age of 59.4-63.2, consisting of similar numbers of males and females, having at least 10 teeth in the mouth and presenting no pneumonia symptoms at the start of therapy, were well qualified for the study.

Next, the study population was randomly assigned to either the control or intervention group based on a computer generated program. Here, however, I believe the authors flawed in choosing 2 statistically similar groups. The mean age of the intervention group, for ex was 4 yrs lower, than that for the control group, which would make them less likely to develop VAP anyway, not just as a result of incorporating toothbrushing. Similarly, the male to female ratio between the 2 groups was not the same or even significantly similar. There were more males in the control group and considering one gender may be more susceptible to acquiring pneumonia than the other, gender may have played an additional role in determining VAP outcome.

Therefore, although the study subjects were recruited appropriately, they were not grouped adequately enough to keep confounding variables from altering results.

8. Have the possible influences on the findings been identified and controls instituted? Describe the use of controls and possible influences.

Prior to conducting the experiment, the researchers realized that there may be differences in operating procedures and treatment administration by the participating nurses. In addition, there may be discrepancies between researchers and the criteria they use to detect the occurrence of pneumonia in each patient. In order to prevent such discrepancies from altering results, the principal investigator extensively trained the researchers from July 2012 to July 2013 to insure they were on the same page and using the same set of criteria to mark results. In addition, the practical nurses were trained to administer the oral hygiene therapy to both groups in a certain way to again insure inter-examiner reliability.

However, despite these measures, the results cannot be considered truly accurate because all confounding variables were not eliminated. For example, it was mentioned that 72% of individuals in the study population suffered from gingivitis or periodontitis (swollen, bleeding gums, periodontal pockets, recession) prior to the start of the experiment. Such diseased individuals would obviously be carrying a heavy oral bacterial load that may not have sufficiently responded to the toothbrush or cyclohexidine therapy and would thus increase the likelihood of the patient contracting VAP. Because it was not mentioned what percentage of perio patients existed in each

group, there's really no knowing upto what extent the results of each group were altered by the patient's current deteriorating oral health. Similarly, despite being grouped randomly, the control group had a higher percentage of pulmonary disease patients (23.2%) than the intervention group (21%). Therefore, the control group, with their already compromised pulmonary health, were more susceptible to contracting pneumonia and staying longer at the hospital, regardless of whether or not they practiced toothbrushing.

Another confounding variable here is the overall diet and medication plan of each patient, which is different based on each patient's systemic conditions. Since certain foods and medications can increase saliva and biofilm production more than others, the oral health of all patients was again not the same at baseline. Moreover, the general health and ability to fight infection would have also been different for each patient based on his antibiotic usage. Therefore, we cannot expect that all incidences of VAP were brought upon either by the absence or presence of toothbrushing and were unaffected by the patients' different diet and medication plans. Due to the presence of such confounding variables, one cannot state controls were rightly instituted in the study.

9.Has the reliability/validity of the article been assessed? Evaluate and state the test/diagnostic results.

The experimental design in this study is only somewhat reliable. Although the authors are very specific on how the study population is recruited and how the

chlorhexidine treatment is applied to the control group (using a swab to cover all tooth surfaces with the 0.12% gel every 12 hrs), they are less clear in describing the oral hygiene method used on the intervention group. They fail to mention whether they apply the gel first or use the toothbrush first for the experimental participants. Furthermore, they do not mention what toothbrushing method or toothpaste is utilized by the nurses for the intervention group. These are important pieces of information, and with them missing, the overall experimental design cannot be reproduced. Without the ability to replicate results, the overall study loses reliability. Although the nurses and professionals used for this study may have been trained well to use standard, uniform operating procedures, as long as these uniform procedures are not mentioned to the reader, the results really cannot be duplicated in the future and the study cannot be considered reliable.

However, the diagnostic criteria used to measure the occurrence of VAP is more valid. The researchers are using a body temp above 37.8°C , a leukocyte count of greater than $10 \times 10^3/\text{mm}^3$ and presence of pulmonary infiltrate in chest radiography to indicate whether or not each individual has contracted VAP. Since a fever, high white blood cell counts and presence of sputum are usually the tell tale signs of pneumonia, this criteria makes sure the researchers are assessing the occurrence of VAP in each patient in a valid way. However, the same cannot be said for the measurement of ICU stay length and mortality rates. Since there may be other systemic conditions that complicate a patient's health and lead to him staying at the hospital longer or even dying, mortality rates and hospital stay length are not valid measures of the patient's

pulmonary health or the overall effectiveness of either oral therapy in reducing VAP. Because mortality rates and length of ICU stay can be affected by various factors unrelated to contracting pneumonia, inclusion of these measures is serving no purpose other than to complicate results here.

Coming to the results themselves, it was discovered that there was a 9.7% reduction in occurrence of ventilator associated pneumonia when toothbrushing was implemented. The overall length of ICU stay also decreased from 13.9 to 11.9 days with toothbrushing and the duration of mechanical ventilation decreased from 11.1 to 8.7 days. These results are analyzed for statistically significant differences using the chi square test for categorical variables and the student t test for continuous variables.

10. Is the experimental therapy compared appropriately to the control therapy?

Describe and evaluate the use of the control group.

In this experiment, the control group was included to see what additional benefits toothbrushing can offer mechanically ventilated individuals over the use of cyclohexidine gel alone. Both groups, including the control, received the cyclohexidine gel application since that is considered the standard hygiene method for killing oral pathogens that may cause pneumonia in mechanically ventilated patients. To correctly analyze if tooth brushing can clear biofilm left untouched by the chlorhexidine gel, it was important to include a control group who used chlorhexidine only, as this would give an idea to the amount of oral pathogens that existed at baseline, i.e. before the toothbrushing.

The control and experimental therapies were not as similar as they could have been. For one thing, the experimental group was slightly smaller (105 individuals) compared to the control group (108 individuals). In addition, the intervention group received rinsing and suction after toothbrushing, which is something the control group did not receive. Because suction and rinsing are not necessarily part of the toothbrushing process but can help eliminate biofilm too, it can be said the control group received a slightly inferior therapy than the intervention group. Furthermore, as previously stated, both groups did not receive the same diet and medications. Since food and drug intake plays a huge role in biofilm buildup, again the control and experimental therapies cannot be considered truly equal.

11. Is the experiment of sufficient duration? Evaluate and explain your reasoning.

Although the experient boasts of being a longitudinal study, it is truly not so. Each study participant is followed for a period of 28 days following initial intubation, in which they are given the oral hygiene treatment and observed for signs of pneumonia. Although 28 days may be enough time to see whether or not pneumonia develops (4 days is the avg. time VAP takes to onset) it is truly not enough time to measure mortality rates. Very few participants will die from pneumonia within 1 month, so using a 28 day period to measure if toothbrushing can help reduce mortality rates in mechanically ventilated patients is simply illogical. Furthermore, many patients stay in the ICU for a period of 11 days or more. So ending the followup period exactly at 28 days doesn't give an accurate measure of how long each study participant stayed in the ICU. In fact,

some participants stay in the hospital even after they leave the ICU for long term care. So just using ICU stay duration to measure a patient's overall health is again illogical.

The data from all participants was gathered and collaborated from July 2013 to Jan 2014, a period of 6 months. This is again not enough time for a longitudinal study since it does not even span for an entire year. Most pneumonia and pulmonary infections occur in the winter when the air becomes cool and dry, and the time period during which the study is conducted indicates summer in Brazil. As a result, the favorable weather may have reduced the overall likelihood of contracting pneumonia or need for mechanical ventilation in both groups, so toothbrushing is no longer the sole variable affecting results here. If I were the researcher, I would undoubtedly follow each study participant for at least 2 months following intubation and conduct the study over the period of one year to ensure I get to include a more diverse ICU entering population.

12. Have the research questions or hypothesis been answered? Restate the research questions/hypothesis in your own words.

At the beginning of the study, the researchers hypothesized that toothbrushing, due to its mechanical cleansing mechanism, may be the most efficient method for removing pathogens from plaque, reducing the oral bacterial load and subsequently reducing the transfer of infection to the lungs and the risk of contracting ventilator associated pneumonia in those receiving mechanical ventilation. They further hypothesized that an oral hygiene regimen that combined toothbrushing with application of 0.12% cyclohexidine gel would work better than just cyclohexidine alone at not only

reducing the occurrence of VAP, but also decreasing the patients' length of mechanical ventilation, duration of ICU stay and mortality rates.

The authors attempted to execute an experimental design that would address all the different aspects of their hypothesis. They tested two different therapies on the control and experimental groups: one group of mechanically ventilated patients received only the cyclohexidine gel treatment (control therapy), while the other group received both toothbrushing and cyclohexidine gel application (experimental therapy).

When the results from the 2 groups were compared, however, they were not statistically significant and did not therefore answer the hypothesis. For example, although there was a 9.7% reduction in occurrence of VAP when toothbrushing was implemented, a p value of 8.4% meant that the difference between the two therapies might be due to chance and not because toothbrushing was offering any additional infection control benefits. Similarly, although there was a 2 day reduction in length of ICU stay and a 6% decrease in mortality rate with toothbrushing, again high p values of 6.4% and 29.6% respectively meant the differences may have again been due to chance and the hypothesis linking toothbrushing to reduced ICU stay remained unanswered.

The only thing that the authors did predict with a high level of certainty was that toothbrushing can decrease the length of mechanical ventilation in intubated patients. Here, the p value of 1.8% was small enough to verify the hypothesis that toothbrushing allows ICU patients to be weaned off the ventilator faster, meaning it does offer some additional benefits. However, the parts of the hypothesis relating toothbrushing to length

of hospital stay, occurrence of VAP and mortality rates remained unanswered due to statistically insignificant, inconclusive results.

13. Do the interpretations and conclusion logically follow the experimental findings? Restate the conclusion, and explain if and how they follow the experimental findings.

In the conclusion the authors state that toothbrushing only significantly reduces the duration of mechanical ventilation. However, it only “tends” to reduce the incidence of VAP and length of ICU stay. This conclusion is scientifically reasonable because the results indicated that there was no statistically significant difference between the 2 groups in incidence of VAP, length of ICU stay, or mortality rates, with p values of 0.084, .064 and .249 respectively. Sure, there was a general reduction in these measures for the intervention group, but without large confidence intervals to verify their claim, the authors can only state that the “tendency” was towards reduction, not that there was an actual sizeable decrease. However, because there was reduction in length of mechanical ventilation for the toothbrushing group with a small p value of 0.018, the authors rightly conclude that toothbrushing directly decreases time patient spends being mechanically ventilated.

The authors further conclude that in order to detect differences of larger magnitude and with more certainty, the study needs to be repeated with a larger sample size. This is again a sound conclusion considering that the size of this study was a mere 200 or so individuals from one geographic location (Brazil) while many other scientific

trials on the same topic have encompassed thousands of participants, spanning the globe. The study population in this trial, due to being solely of Hispanic origin, was not as diverse as the ideal population should be. Therefore, it would only make sense to repeat the trial with a more diverse and large population that is representative of the human race as a whole, so that the results can be applied with a reasonable level of confidence to all of us.

14. Do you agree with the article and the findings? Explain why.

One of the main points the article boasted was that it was a “randomized trial” comparing 2 different oral hygiene therapies in mechanically ventilated patients. However, I disagree with the authors’ method of randomization because the 2 study groups picked randomly were not statistically similar in terms of age, gender, antibiotic usage or initial systemic conditions. Furthermore, the study population included only Hispanic people and no other races, which was not representative of the entire population. Therefore, whatever findings the authors came up with could not have possibly compared the two therapies equally as there were too many confounding variables involved. As a result the findings, due to inadequate randomization of subjects, were inconclusive.

Even though I disagreed with the way the authors grouped their study subjects, I did agree with the way they analyzed results. They used chi square tests to analyze differences between categorical variables such as mortality rates and student t tests to analyze differences between continuous variables such as length of ICU stay. In

addition, they used a computed based software program (STATA version 12) to do calculations to eliminate the possibility of human error from altering results. In the end, the authors used confidence intervals and p values to measure whether their results were worthwhile. I agreed with the rigorous scientific methods used for the analysis of results because this supposedly gave the findings a higher level of certainty.

When the p values were large, as in the case of mortality rates and occurrence of VAP, the authors did not consider those results statistically significant enough to be conclusive. I agreed with this conclusion as well because high p values decrease the credibility of any result. I further agree that this study did not rightly predict the effect of toothbrushing on reducing incidence of VAP or the length of the patient's ICU stay. In the end, the researchers concluded that experiment needs to be repeated again with a larger sample size so results would have a higher confidence interval and lower p value. I again agree with this analysis because I also believe the study population was too small and ethnically similar to provide conclusive results. The only way of giving more validity to the results would be to repeat the experiment and produce more certain results with lower P values this time.

15. What would you change in the article? What would you add or delete? Why?

Things I would do differently if I were conducting the study would be to include a larger study population encompassing more ethnicities and covering more geographical areas. If the effects of toothbrushing on VAP incidence are truly to be analyzed on the human race, it only makes sense to use a study population that is better representative

of us as a whole. I would also extend the followup period from 28 days to 2 months following start of intubation to get a better idea of how toothbrushing affects pulmonary health, length of ICU stay and mortality rates.

Something else I would change about the experimental design would be adding more experimental groups. To get a true sense of which oral hygiene therapy is the best method for removing biofilm and limiting VAP incidence, we should use 4 study groups. The control should receive no implementation of oral hygiene other than rinsing with water, the first experimental group should receive only toothbrushing, the second should receive only chlorhexidine gel application and the last should receive both therapies. Additionally, the authors should make sure to use a higher concentration of chlorhexidine this time (0.2%) because this is the concentration at which the anti-microbial mechanism of the gel has been known to become active. These 4 study groups would allow us to compare chlorhexidine and toothbrushing as infection control methods in a more comprehensive manner.

Additionally, I would try to eliminate confounding variables in the study by making the 4 study groups as statistically similar as possible in terms of age, gender, systemic conditions and antibiotic usage. I would also make sure to exclude all periodontitis and gingivitis patients from the study. Since their deteriorating oral health can transfer infection more easily to the lungs, this may increase their chance of getting VAP and affect results regardless of what oral hygiene therapy they are using. Furthermore, I would make sure all patients in the study are on the same diet and medication plan. Because certain foods can create biofilm that leads to pulmonary infection more easily,

only the same diet across all patients can ensure the patients have the same level of oral and systemic health at baseline.

However, despite the changes necessary, I still believe this was a worthwhile study discussing a very interesting topic. Any experimental flaws can ofcourse be overcome if the study design is further tweaked before repeating the experiment.