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# EVALUATING THE RESPONSE TO COMBINATION THERAPY WITH NEBULIZED AMIKACIN, IV AMIKACIN AND MEROPENEM IN PATIENTS WITH VENTILATOR-ACQUIRED-PNEUMONIA WITH RESISTANT SERRATIA TRACHEAL CULTURES IN ICU OF VALI-E-ASR HOSPITAL IN ZANJAN

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## ABSTRACT

**Background:** There have been reports of increased rates of multi-drug resistant VAP in the ICU of Zanjan Vali-e-Asr hospital. Suggesting an appropriate therapeutic regimen is of paramount importance, which is the main goal of this study. **Method:** This non-randomized uncontrolled semi experimental study was carried out with a total number of 45 patients who were selected from ICU of Zanjan Vali-e-Asr hospital. All patients were diagnosed with Serattia-positive multi-drug resistant VAP and treated with the suggested therapeutic regimen. The effectiveness of the regimen was evaluated through the CPIS before and after the treatment. Thereafter, the results were analyzed by SPSS and STATA software. **Results:** Our data indicate significant changes in body temperature with p value=0.004 (from 37.4±0.6 on the 1st day to 37±0.3 on the 15th day), pulse rate with p value=0.003(from 90.8±16.1 on the 1st day to 83.7±9.1 on the 15th day), systolic blood pressure with p value=0.009 (from 108.8±10.5 on the 1st day to 107.1±8.8 on the 15th day) and creatinine level with p value=0.005(from 1.4±1.3 on the 1st day to 1±0.6 on the 15th day). Although not statistically significant, radiologic changes and the pulmonary secretion both followed an overall improving pattern. The total cure rates on day 7 and day 15 were not statistically significant. **Conclusion:** Our study reports a positive response to our recommended therapeutic regimen in patients with VAP. Our findings also indicate that the antibiotic preference is not dependent on early or late VAP; especially in complicated cases such as patients admitted to ICU. We highly recommend a similar study conducted with the control group.

**KEYWORDS:** Combination Therapy, Nebulized Amikacin, Meropenem, Ventilator-Acquired - Pneumonia, Resistant *Serratia,* ICU.

## INTRODUCTION

Pneumonia is a disease which mainly involves lung tissue. Types of pneumonia include Community Acquired Pneumonia (CAP) and Hospital Acquired Pneumonia (HAP). HAP has a subset named Ventilator Associated Pneumonia (VAP). Together HAP and VAP count as the second most prevalent type of nosocomial infections which have a high rate of mortality and morbidity.[1,2] Since VAP is mostly known to be multi-factorial, diagnosis and treatment of it remains a challenging issue leading to a poor prognosis (2). Abnormal radiologic changes (alveolar infiltrations, airbronchogram view, or the worsening of radiologic changes) along with the CPIS scoring system (36.5<body temperature>38.5, 4000<WBC<11000, tracheal secretions and microbiology) are the diagnostic tools which are commonly used. According to the CPIS scoring system if patients receive a score more than 6 points they are highly likely to have pneumonia.[3,4]

Due to the high prevalence of some pathogens that cause HAP and VAP, the so called core pathogens grouping is formed; which Serratia Marcescens is a part of.[5] The prevalence of Serratia is reported to be as high as 35-80% (Rotstein C. 2008) or as low as 2.78% (Ahmed W. 2014).[6,7]

VAP is treated based on the type; being early onset VAP (up to five days from starting mechanical ventilation) or

late onset VAP (more than five days from starting mechanically ventilation). A lot of studies have been performed concerning mono vs. combination therapy of HAP which has not yet been able to value one above another; however, it has been recommended to use combination therapy in cases of Multi-Drug-Resistant Pathogens.[8,9] The therapeutic regimen suggested for VAP is a combination of one Beta-lactam with one Aminoglycoside and/or one of the new Fluoroquinolones.[10]

## METHODS AND MATERIALS

This is a semi-experimental non-randomized clinical trial conducted in the ICU ward of Zanjan's Vali-e-Asr Hospital between May 2016 and December 2017. Primarily, patients who were hospitalized for at least 48 hours and had been mechanically ventilated for at least 48 hours were suspected to have VAP. Patients who got more than 6 points in the CPIS scoring system (CPIS scoring system is based on tracheal secretions, pulmonary infiltrations in chest X-ray, body temperature, white blood cells, PaO2/FiO2 ratio and microbiology with each item scoring 0-2 with a maximum score of 12) and had a positive culture for MDR Serratia (bronchoscopy was performed early in the morning; BAL was taken and sent to the hospital laboratory) were included. The exclusion criteria consisted of any patient diagnosed with HAP, CAP or suspected to have Tracheobronchitis or any other infectious diseases, malignancies or AIDS, severe neutropenia (NAC<500), probable expiration in coming 7 days, multi-organ failure, diagnosed with TB, MRSA or who were sensitive to beta-lactam and patients with renal failure.

The total period taken for the therapeutic course for each patient was 15 days. Patients were observed on the $7^{th}$ day to see if there was any change in their laboratory results or clinical situation. If any promising changes had occurred, treatment would be continued until the $15^{th}$ day. However, if the patients' situation were worsening, treatment would be discontinued and the patient would be dropped out of the study. The CPIS scoring items together with tracheal secretions, chest X-ray and Creatinine were checked on the day the recommended regimen was first started followed by the $3^{rd}$, $5^{th}$, $7^{th}$ and the $15^{th}$ day.

An empirical regimen for pneumonia was started for the patients until the anti-biogram results were ready. The empirical regimen used in our ICU ward was either Meropenem or Imipenem in combination with a broad-spectrum anti-biotic such as Vancomycin or Fluoroquinolones. After the culture results confirmed MDR Serratia, our recommended regimen was given to the patients: high doses of IV Meropenem (2gr Q 8hrs), infusion of Amikacin (15mg/kg daily, infusion within 6-8 hours) and nebulized Amikacin (250mg Q 12hrs, 2puffs each time). To enhance the absorption of nebulized Amikacin, we used 2 puffs of Salbutamol spray beforehand. The nebulized Amikacin would be given to patients for 3 to 5 days in the beginning of the therapeutic course depending on tracheal secretions (if the tracheal secretions were decreasing the nebulized Amikacin would be stopped after 3 days, if not, the nebulized Amikacin would be continued for 5 days).

Effectiveness of the therapeutic regimen was considered as a decrease in tracheal secretions, relative changes in chest X-ray (the relative changes to pulmonary infiltrations, consolidations or pleural effusion), improvement of CPIS items (fever devolvement, no tachy/brady cardia, normal blood pressure, decreasing or normal range WBC, and the negative BAL cultures) and finally the clinical view of the specialist.

Finally the data were analyzed using independent t-test, chi square test and two sample proportion tests. We used the SPSS version 21 and STATA software.

## RESULTS

A total number of 45 patients were primarily enrolled and 8 patients were dropped out because of the exclusion criteria (3 patients' deaths were probable in 7 days, 1 patient had GI malignancy-gastric cancer, 1 patient had severe renal failure, 1 patient had multi-organ failure and 2 patients decided to change the therapeutic regimen and leave the experiment). The clinical situation of 37 patients who were diagnosed with MDR Serratia positive VAP was compared before and after the recommended regimen was administered. The patients were mostly men older than 65 years and the mean age was 66.67±19.12.

Our data showed no significant relation between early/late onset pneumonia with either age or sex (table-1).

**Table 1: Different types of pneumonia due to age and sex. According to the table most of our patients who have early onset VAP are aged more than 65 years old, however, this difference is not significant. According to sex, most of our patients diagnosed with VAP are males; there is no difference in prevalence of early or late onset VAP per se.**

| Pneumonia | Age | | | Sex | | Significance Level |
|---|---|---|---|---|---|---|
| | <40 | 40-65 | 65< | Male | Female | |
| Early Onset | 2(5.40%) | 6(16.21%) | 14(37.83%) | 14(37.83%) | 8(21.62%) | 0.121 |
| Late Onset | 2(5.40%) | 4(10.81%) | 9(24.32%) | 13(35.13%) | 2(5.40%) | 0.919 |

There were significant changes in temperature, systolic blood pressure, pulse rate and Creatinine in the comparison between the first day and the last day of the therapeutic course (respectively, p value=0.004, p value=0.009, p value=0.003 and p value=0.005) (table-2).

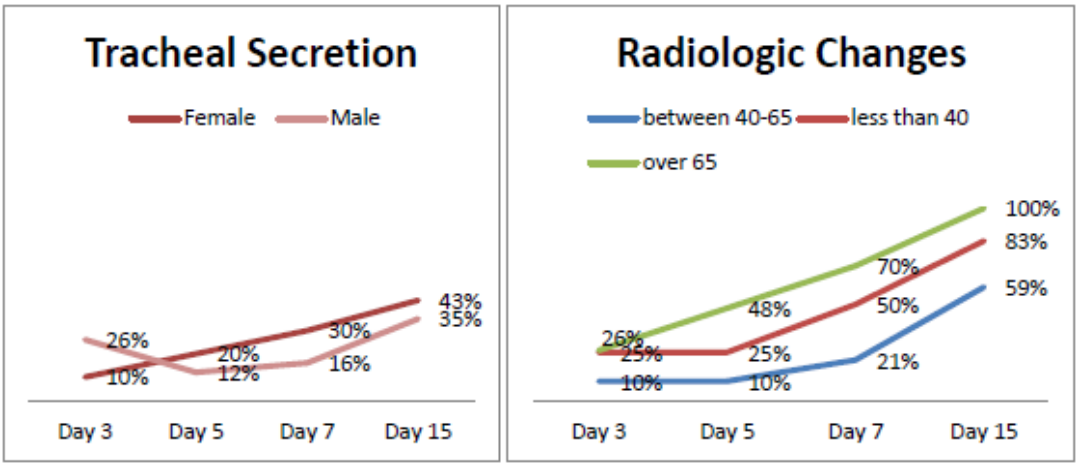
**Table 2: Clinical and para-clinical changes between first and the last day of treatment course. Clinical findings included in CPIS scoring system, Body Temperature, Systolic Blood Pressure and Pulse Rate are significantly decreased after taking our recommended regimen. There is no significant change in WBC which could be explained due the wild normal range and the fact that most patients were neutro/lympho-penic.**

| Variable | Average ( Standard Deviation) | | | | Significance Level |
|---|---|---|---|---|---|
| | Day 1 | | Day 15 | | |
| WBC | 12270±12301.58 | | 9293.33±3114.91 | | 0.199 |
| Body Temperature | 37.423±0.609 | | 37.033±0.332 | | 0.004 |
| Systolic Blood Pressure | 107.80±10.50 | | 108.10±8.848 | | 0.009 |
| Diastolic Blood Pressure | 73.466±6.072 | | 76.90±5.99 | | 0.528 |
| Pulse Rate | 90.80±16.17 | | 83.7±9.16 | | 0.003 |
| Creatinine | 1.436±1.386 | | 1.014±0.675 | | 0.005 |
| Tracheal Secretion | Mild | 24.3% | Mild | 73.3% | 0.602 |
| | Moderate | 56.8% | Moderate | 26.7% | |
| | Severe | 18.9% | Severe | 0% | |
| Radiologic Changes* | No Change | 75.7% | No Change | 56.7% | 0.132 |
| | Better | 21.6% | Better | 36.7% | |
| | Worse | 2.7% | Worse | 6.7% | |

There were no significant changes in tracheal secretions and radiologic changes; however, an overall improvement is seen per se (chart 1, chart 2). Also there were no significant changes between either tracheal secretions or radiologic changes and age or sex (data not shown). No significant data were collected on Creatinine relation with age or sex (data not shown).

**Chart 1 and 2**

Chart one show the tracheal changes according to the sex during the treatment. Although there were no statically significance found, however, the overall improvement is seen in tracheal secretions, mostly in men. Chart two shows the radiologic changes during the treatment. Again, although no statically significance was found, the overall improvement is seen during the treatment. Patients aged more than 65 years, showed almost complete radiologic improvement after taking our recommended regimen.




## DISCUSSION

A total number of 37 patients were included in our study. The aim was to evaluate the effectiveness of our suggested regimen for the treatment of VAP. Our data indicates a decrease of sepsis from 8.1% to 0% from the 1st day to the 15th day. There were no differences regarding the secondary outcomes, including microbiological cure, mortality or renal toxicity. Accordingly, although the overall tracheal secretions were decreased through the therapeutic course, however, due to the invasive character of BAL taking and the tracheal secretions culture, it was not possible for us evaluate the microbiological aspect of our regimen effectiveness. On the other hand, although there was promising data of how our patients responded to the

therapeutic regimen, however, there were unfortunately no promising data of any prolonged or increased life span. This means, although the patients became almost symptom free after 15 days, there was no change in the survival rate (data not shown). Finally, we found no evidence of renal toxicity in any of our patients.[11] Almost all of our patients had the normal range Creatinine during the treatment. Even those who did not have normal ranged Creatinine did not have a toxic level of serum Creatinine. There were also patients who had toxic levels of serum Creatinine whose Creatinine decreased to the normal level after taking the regimen (detailed data not shown). These findings may be due to possible, dehydrated state of patients in ICU or due to the low BMI of our patients, which both may falsely cause a normal serum range for Creatinine. These findings are parallel to the same findings of Montmollin et. al in 2014.[12] There were no significant changes in the cure rate between the 7$^{th}$ day and the 15$^{th}$ day. This finding may suggest a necessity for the treatment course to be 7 days and not as long as 15 full days. There were significant changes in decreased body temperature, systolic blood pressure and pulse rate, which together confirm the effectiveness of the suggested regimen. There were no significant changes in radiographs and pulmonary secretions, however, overall improvements were detected per se.

The data of our study is in parallel with findings of Fernnando et. al in 2015,[13] where they support the effectiveness of nebulized anti-biotic-therapy. In respect to the combination therapy with one Betalactam and one Aminoglycoside, our data is supported by a study of Micheal Wilke et. al in 2014.[14] Moreover, the use of high dose Amikacin in our study is supported by O.Pajot et. al in their study in 2015.[15]

We also reported no relevance between age, sex and the type of pneumonia with the response-rate to the suggested regimen. This indicates it is unnecessary to consider the type of pneumonia to choose the most suitable regimen. This finding of ours opposes previous studies,[6,7] which may not be completely reliable due the absence of a control group and the limited number of participants.

There were 8 patients, whose clinical conditions worsened through the therapeutic course. They died between the 12$^{th}$ and 15$^{th}$ day. They died due to worsening of an underlying disease like GI Bleeding, poisoning, electrolyte or cardio-vascular disorders.

## CONCLUSION

All together our study shows the positive response of patients and the effectiveness of our suggested therapeutic regimen. However, due the lack of a control group and the limited number of participants, we highly recommend further future studies with a control group.

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