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Research Paper

# Evaluating antibiotic therapy for ventilator-associated pneumonia caused by gram-negative bacilli

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ABSTRACT

*Introduction:* Ventilator-associated pneumonias (VAPs) are a complication of mechanical ventilation in the intensive care unit (ICU) that increase length of stay, morbidity, and mortality. While identifying and treating infections early is paramount to improving patient outcomes, more and more data demonstrate limited courses of antibiotics improve outcomes. Prolonged (10–14 day) courses of antibiotics have remained the standard of care for pneumonia due to gram-negative bacilli (GNR). We aimed to review our GNR VAPs to assess risk factors for recurrent GNR infections.

*Methods:* We reviewed trauma patients who developed VAP from 02/2019 through 05/2022. Demographics, injury characteristics, and outcomes were reviewed with a focus on pneumonia details including the cultured pathogen(s), antibiotic(s) used, treatment duration, and presence of recurrent infections. We then compared single episode VAPs to multiple episode VAPs among patients infected by GNRs.

*Results:* Eleven of the fifty trauma patients admitted to the ICU suffered a VAP caused by a GNR. Of these eleven patients, six experienced a recurrent infection, four of which were caused by *Pseudomonas aeruginosa* and two of which were caused by *Enterobacter aerogenes*. Among the patients who received ten days of antibiotic treatment, half suffered a recurrence. Although, there was no difference in the microbiology or antibiotic duration between the recurrences and single episodes.

*Conclusion:* Despite prolonged use of antibiotics, we found that the risk of recurrent or persistent infections was high among patients with VAP due to GNB. Further study is needed to determine optimal treatment to minimize the risk of these recurrences.

*Key message:* Ventilator-associated pneumonia due to gram-negative bacilli is a rare but high morbidity complication in intensive care units. Despite prolonged duration of therapy, these infections still appear to account for many recurrent infections and further study into optimal therapy is warranted.

## Introduction

Every day, Intensive Care Units (ICUs) are tasked with the management of patients requiring invasive mechanical ventilation. Ventilator-associated pneumonias (VAPs) are an inherent risk of prolonged mechanical ventilation that increases patient length of stay, morbidity, and mortality in the ICU [1–5]. Despite gram negative rods (GNRs) making up the minority of VAPs, they are notorious for causing recurrent infections that negatively impact patient outcomes [6]. Common GNR offenders include *Pseudomonas aeruginosa*, *Enterobacter* spp., and *Acinetobacter* spp.

While identifying and treating infections promptly is paramount to improving patient outcomes, data continue to emerge demonstrating improved outcomes from limiting possibly superfluous antibiotics improves by reducing costs, reducing resistance pressure, and by allowing earlier diagnosis of subsequent infections. The landmark paper in 2003 by Chastre et al. established the standard of care for treating VAPs with 7 days (as opposed to 14 days) of appropriate antibiotics [6].

However, Chastre et al. also identified a subset of patients who may not have benefited by limiting antibiotic duration—those caused by GNR bacteria [6]. This high-risk group is therefore an important target for study to identify optimal therapy. In our Surgical ICU (SICU), with a

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large trauma population, it is standard practice to use 10–14 days of antibiotics for GNR VAPs. However, ultimately duration of therapy depends on the attending physician. We sought to review our patients with GNR VAPs and assess if we are using a prolonged antibiotics course, and if patients with GNR VAPs have worse outcomes. We hope that this can inform future therapy in our patient population.

## Methods

### *Study design*

This retrospective chart review analyzed data from the trauma registry of a Level 1 Trauma Center between February 2019 and May 2022. This registry captures all trauma patients evaluated at our institution. We then further reviewed all patients who developed a VAP, in particular a GNR VAP. We identified patient demographics, injury characteristics, and outcomes as well as information about the diagnosis of pneumonia, the organisms identified on culture, and the possible effect of antibiotic course. The protocol was reviewed and deemed to be exempt by the institutional review board.

### *Patient population*

The study included all trauma patients admitted to the ICU who received mechanical ventilation for at least 48 h, and met the following criteria: (1) were older than 18 years; (2) had suspicion of VAP; and (3) had positive quantitative culture results of pulmonary secretions obtained by bronchoalveolar lavage (BAL) (threshold for significant culture was $\geq 10^5$ colony-forming units/mL) or positive sputum cultures for those few patients who did not have quantitative cultures.

### *Data collection*

We included baseline data on demographics, injury characteristics, and outcomes from the trauma registry. These included age, sex, race, BMI, mechanism of injury, injury severity scoring, and clinical details about chest trauma (presence of a flail chest, pulmonary contusions, pneumothorax, hemothorax, etc.).

In addition, electronic medical records were reviewed to collect additional data for each VAP episode including duration of mechanical ventilation, Sequential Organ Failure Assessment (SOFA) score on date of diagnosis, leukocyte count, procalcitonin (when available), temperature, ratio of the partial pressure of inspired oxygen to the fraction of inspired oxygen (PaO2/FiO2), a qualitative measure of the pulmonary infiltrate density, and presence of a concurrent infections (bacteremia, UTI, wound infection, etc.). Microbiology was also collected as the quantity and strains of pathogens cultured at a significant concentration from a distal pulmonary fluid sample and the possibility of a recurrent VAP. Patients were considered to have a recurrent VAP if at least one of the causative bacterial strains from the index VAP grew at a significant concentration on a second BAL culture. Both the dose and duration of empiric and species-specific antibiotics used for each VAP episode were collected. Discharge dispositions were measured.

### *Data analysis*

Patient background information, admission characteristics, and microbiology and antibiotic use per VAP episode were compared between patients who were infected by a GNR and those who were not. The patients infected by a GNR were further segregated by those who had complex infections defined as the presence of a recurrent VAP, and those who had a simple infection defined as a single VAP episode. The recurrence and nonrecurrence groups were compared to evaluate for any differences in background or clinical characteristics, as well as the microbiology and dose/duration of antibiotics for the index VAP episode. We used descriptive statistics to compare these groups using Fisher's exact test to compare categorical variables (due to small numbers) and Student's *t*-test to compare continuous variables.

## Results

### *Patient characteristics*

We identified 50 trauma patients with subsequent VAP admitted to the ICU between February 2019 and May 2022. Eleven of these patients had GNR VAPs while the other thirty-nine had VAPs due to non-GNR organisms. These two groups had similar demographics (86 % male, average age 50). They also had similar injury characteristics (Table 1). Microorganisms cultured from each VAP were recorded (Supplemental Table 1). While injury severity score was similar between the two groups, patients with GNR pneumonia had prolonged ventilator days (22 vs 11 days, $p = 0.001$), increased tracheostomy placement (91 vs 49 %, $p = 0.02$), and higher length of stay (48 vs 30 days, $p = 0.003$) (Table 1).

Within the 11 patients in the GNR VAP group, six experienced a recurrent infection. None of the thirty-nine patients with a VAP caused by a non-GNR microbe experienced a recurrent infection. When comparing the six patients who experienced a recurrent GNR VAP and the five who did not to assess for risk factors for recurrence, both groups had similar demographics and injury characteristics (Table 2). However, the six patients who experienced recurrences had a prolonged length of stay (51 vs 20 days, $p = 0.01$), while other outcomes were similar.

### *Index VAP*

Among the six patients who experienced a recurrence, four were

**Table 1**
Patient demographics, admission characteristics, and hospital stay details for GNR and non-GNR VAP groups.

| | VAP causative organism | | |
|---|---|---|---|
| | GNR | Non-GNR | p-Value |
| Total, n | 11 | 39 | |
| Age, mean ± SD | 55 ± 16 | 49 ± 19 | 0.35 |
| Sex | | | |
| Male, n (%) | 10 (91) | 33 (85) | 1.0 |
| Race | | | 0.84 |
| Black or African American | 5 (45) | 14 (36) | |
| White | 3 (27) | 12 (31) | |
| Other | 3 (27) | 13 (33) | |
| Comorbidities | | | |
| COPD | 4 (36) | 4 (10) | 0.06 |
| CHF | 1 (9) | 2 (5) | 0.53 |
| Mechanism of injury, n (%) | | | |
| Assault | 0 (0) | 2(5) | 1.0 |
| Bicycle | 0 (0) | 3 (8) | 1.0 |
| Fall | 5 (45) | 12 (31) | 0.48 |
| MVC | 1 (9) | 6 (15) | 1.0 |
| MVC with pedestrian struck | 1 (9) | 7 (18) | 0.67 |
| Motorcycle | 0 (0) | 4 (10) | 0.56 |
| Gunshot wound | 2 (18) | 2 (5) | 0.21 |
| Other | 2 (18) | 3 (8) | 0.30 |
| Admission characteristics | | | |
| ISS, median | 23 | 26 | |
| ISS, IQR | 8 | 16 | |
| SOFA score, mean ± SD | 9 ± 3 | 8 ± 2 | 0.25 |
| Hospital stay | | | |
| Length of stay, median | 48 | 30 | 0.003 |
| Ventilator days, mean ± SD | 22 ± 10 | 11 ± 8 | 0.001 |
| Chest tube placement, n (%) | 3 (27) | 8 (21) | 0.69 |
| Flail chest, n (%) | 0 (0) | 1 (3) | 1.0 |
| Pneumothorax, n (%) | 2 (18) | 10 (26) | 1.0 |
| Tracheostomy, n (%) | 10 (91) | 19 (49) | 0.02 |

VAP = ventilator-associated pneumonia; GNR = gram-negative rod; MVC = motor vehicle collision; ISS = injury severity score; SOFA = sequential organ failure assessment.

**Table 2**
Admission characteristics for recurrent and nonrecurrent GNR VAPs groups.

| | Ventilator-associated pneumonia | | |
|---|---|---|---|
| | Multi GNR VAP Episodes | Single GNR VAP Episode | p-Value |
| Total, n | 6 | 5 | |
| Age, mean ± SD | 58 ± 19 | 51 ± 14 | 0.50 |
| Sex | | | |
| Male, n (%) | 6 (100) | 4 (80) | 0.45 |
| Race, n (%) | | | 0.18 |
| Black or African American | 2 (33) | 3 (60) | |
| White | 3 (50) | 0 (0) | |
| Other | 1 (17) | 2 (40) | |
| Comorbidities, n (%) | | | |
| COPD | 2 (33) | 2 (40) | 1.0 |
| CHF | 0 (0) | 1 (20) | 0.45 |
| Mechanism of injury, n (%) | | | 0.44 |
| Penetrating | 2 (33) | 0 (0) | |
| Blunt | 3 (50) | 5 (100) | |
| Admission characteristics, mean ± SD | | | |
| ISS | 21 ± 6 | 23 ± 4 | 0.54 |
| SOFA score | 10 ± 2 | 9 ± 3 | 0.52 |
| Hospital stay | | | |
| Length of stay, mean ± SD | 51 ± 19 | 20 ± 11 | 0.01 |
| Ventilator days, mean ± SD | 24 ± 8 | 19 ± 12 | 0.25 |
| Chest tube placement, n (%) | 2 (33) | 1 (20) | 1.0 |
| Flail chest, n (%) | 0 (0) | 0 (0) | 1.0 |
| Pneumothorax, n (%) | 1 (16) | 0 (0) | 1.0 |
| Tracheostomy, n (%) | 6 (100) | 4 (80) | 0.45 |

GNR = gram-negative rod; VAP = ventilator-associated pneumonia; ISS = injury severity score; SOFA = sequential organ failure assessment.

caused by *Pseudomonas aeruginosa* and two were caused by *Enterobacter* spp. Two patients who had a recurrent VAP caused by *Pseudomonas aeruginosa* were administered ten days of antibiotics treatment for their index infection, while the other two patients received seven days. Both patients who suffered an *Enterobacter* spp. recurrence had a seven day antibiotic course for their index VAP infections. Among the five patients who did not experience a recurrence, two received antibiotic therapy for ten days, one patient for seven days, and two patients for less than seven days. The two patients who received less than seven days of treatment had antibiotic therapy stopped according to provider judgement.

Characteristics of the index VAP were compared between the GNR and non-GNR patients (Table 3). Diagnostic criteria for the index VAP and infection characteristics including WBC count, procalcitonin, temperature, and P/F ratio were similar between both groups. The SOFA score within 24 h of the day of index VAP diagnosis was higher in the group that had a GNR infection ($p = 0.01$).

Antibiotics used for the index VAPs in the recurrent and nonrecurrent GNR VAP groups were compared and there was no statistically significant difference between the antibiotics for the index VAP between these groups (Table 3).

### *Outcomes*

Discharge dispositions including hospice, short-term nursing facility, long-term acute care, acute rehabilitation, home, or death were compared. There was no significant difference in these outcomes between the GNR and non-GNR groups or the GNR VAP recurrent and nonrecurrent groups.

## Discussion

Trauma patients with GNR VAPs have a prolonged hospital course requiring extended ventilator support. Much of this is related to the high rate of recurrent pneumonias in this group, despite our already prolonged use of antibiotics. In this retrospective chart review, we observed

**Table 3**
Characteristics of index VAP for recurrent and nonrecurrent GNR VAPs.

| | Ventilator-associated pneumonia | | |
|---|---|---|---|
| | Multi GNR VAP Episodes | Single GNR VAP Episode | p-Value |
| Total, n | 6 | 5 | |
| Index VAP diagnostic criteria[a] | | | |
| Clinical criteria | 2 (33) | 1 (20) | 1.0 |
| BAL | 4 (67) | 2 (40) | 0.57 |
| Sputum | 2 (33) | 2 (40) | 1.0 |
| Radiography | 3 (50) | 3 (60) | 1.0 |
| Index VAP | | | |
| Leukocyte count ($\times 10^3$), mean ± SD | 10 ± 3 | 13 ± 5 | 0.25 |
| Procalcitonin, median | 0.22 | 2.33 | |
| Temperature, n (%) | | | 0.32 |
| 36.5–38.4 | 1 (17) | 3 (60) | |
| 38.5–38.9 | 3 (50) | 1 (20) | |
| ≥39.0 or ≤36.0 | 2 (33) | 1 (20) | |
| $P_aO_2/F_iO_2$, n (%) | | | 0.68 |
| >240 | 4 (67) | 2 (40) | |
| ≤240 | 2 (33) | 3 (60) | |
| SOFA score, mean ± SD[b] | 10 ± 2 | 9 ± 3 | |
| Concurrent infection, n (%) | | | |
| Bacteremia | 2 (33) | 1 (20) | |
| COVID-19 | 0 (0) | 1 (20) | |
| Antibiotics used for index infection | | | |
| Cefepime | 5 | 5 | 1.0 |
| Piperacillin tazobactam | 3 | 0 | 0.18 |
| Ceftriaxone | 1 | 0 | 1.0 |
| Meropenem | 0 | 3 | 0.21 |
| Levofloxacin | 0 | 1 | 0.45 |
| Ciprofloxacin | 0 | 1 | 0.45 |
| Cefazolin | 2 | 3 | 0.57 |
| Ampicillin sulbactam | 1 | 0 | 1.0 |
| Tobramycin | 1 | 0 | 1.0 |
| Nafcillin | 1 | 0 | 1.0 |
| Antibiotic duration, n (%)[c] | | | |
| 10 days | 2 (33) | 2 (40) | 1.0 |
| 7–9 days | 4 (67) | 1 (20) | 0.24 |
| <7 days | 0 (0) | 2 (40) | 0.18 |

GNR = gram-negative rod; VAP = ventilator-associated pneumonia; BAL = bronchoalveolar lavage; SOFA = sequential organ failure assessment.
[a] Multiple diagnostic criteria could be used to diagnosis a VAP episode.
[b] Not all patients had SOFA recorded.
[c] Counted as days of appropriate antibiotic therapy (not including broad spectrum antibiotics used).

that ten days of appropriate antibiotic therapy for GNR VAPs did not prevent VAP recurrence in six out of eleven patients with a GNR VAP.

While most of our patients with VAP had non-GNR sources, and no recurrences, six out of eleven of the patients with VAP related to GNR bacteria suffered at least one recurrence. One of these patients experienced three recurrences over a five-month period and died in the ICU. These recurrent GNR VAP infections are accompanied by lengthy ICU stays.

We also found that VAPs caused by the GNR *Enterobacter aerogenes* accounted for a third of the patients who suffered a GNR VAP recurrence between February 2019 and May 2022. Both patients had seven days of appropriate antibiotic therapy for their respective index VAPs. While the remainder of recurrences was attributed to *Pseudomonas aeruginosa* infections, this is a pertinent finding in considering which GNR strains may require a prolonged antibiotic course. In comparing the GNR and non-GNR index VAPs, we also noted that the SOFA score was higher in the GNR group. This indicates that higher SOFA scores for admitted trauma patients may be a herald sign that the patient is at increased risk of a GNR VAP.

Optimizing antibiotic duration for VAPs has been the subject of multiple past studies, yet it remains a challenge [7–9]. Since the PneumA Trial Group compared eight and fifteen days of antibiotic

therapy for VAPs, it has been widely accepted that certain pernicious GNRs are especially notorious for causing difficult to treat VAPs with an increased risk of recurrence [6]. Chastre et al. concluded that non-fermenting gram-negative bacilli (NFGNB) VAPs may require prolonged treatment for adequate coverage. They noted a higher recurrence rate in NFGNB VAPs treated for eight days (40.6 % versus 25.4 %). However, since then, studies have demonstrated conflicting results. In 2007, Hedrick et al. compared recurrence rates in patients who received a three to eight day and nine or more day course of antibiotics for a NFGNB VAP [10]. Surprisingly, a lower recurrence rate was seen in the patients who received the shorter antibiotic treatment. Chastre et al. results were supported by Bouglé et al. in 2022, which did not demonstrate non-inferiority of eight days of antibiotic treatment compared to fifteen days but was met with criticism [11–13].

This study has several limitations. It is a retrospective study, so many clinical criteria may not be well-documented or easy to abstract from the charts. This was limited to a single trauma center and the demographics and injury characteristics of our patients are unique so the results may not be generalizable to other patient populations. We also were limited by a small sample size. Given the relative rarity of VAP due to GNR, a larger multicenter study may help shed more light on this important problem. We also rely on microbiological data to define VAP. However, many settings may use a more inclusive definition that is clinically based. The precise definition of recurrent VAP is also debatable. Are these recurrent infections or persistent infections that were incompletely treated? Regardless of the specifics, it is evident that this is a very high-risk group that merits further study to identify methods to optimize management.

## Conclusion

For patients suffering from a VAP caused by certain GNRs, we found seven to ten days of appropriate antibiotic treatment insufficient in preventing recurrences in six of the eleven patients. Patients receiving mechanical ventilation, especially those presenting with high SOFA scores, should be monitored carefully and early identification of patients in this group should be pursued. The optimal therapy remains unclear, but by continuing to assess our own practice and outcomes, we hope we will impact outcomes in our patient population. Further study to identify optimal treatment regimens for GNR VAP is essential to prevent morbidity and mortality in this high-risk group.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sopen.2023.09.014.

## CRediT authorship contribution statement

The study design was developed by RM, HH, SB, ZS, and NG. Data collection was completed by RM, HH, and NG. Data analysis, data interpretation, writing, and revisions were performed by all authors.

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## Ethical approval

IRB Exemption obtained.

## Declaration of competing interest

The authors have no relevant conflicts of interest to report.

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