I, __Erika J. Lu______________________________________,
hereby submit this work as part of the requirements for the degree of:

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in:

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It is entitled:

Factors associated with ventilator-associated pneumonia recurrence in the surgical intensive care unit

This work and its defense approved by:

Chair: Dr. Paul Succop______________
       Dr. Erin Haynes______________
Factors associated with ventilator-associated pneumonia
recurrence in the surgical intensive care unit

A thesis submitted to the Graduate School
of the University of Cincinnati
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In the Department of Epidemiology
College of Environmental Health
by
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Committee Members:
Dr. Paul Succop (Committee Chair)
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Abstract:

Objective:
To determine predisposing factors and outcomes for recurrent ventilator associated pneumonia (VAP).

Design:
Retrospective review.

Patients:
All adult surgical patients mechanically ventilated > 48 hours between January 2000 and December 2004 were evaluated. VAP was defined as \( \geq 10^4 \) colony forming units/mL in a bronchoalveolar lavage or protected catheter lavage, and recurrence as a positive quantitative culture \( \geq 4 \) days after initiation of antibiotics.

Main Outcome Measures:
We analyzed potential risk factors for recurrence, including initial pathogen, APACHE II scores, age, white blood cell count, presence of trauma, and duration of hospital stay before diagnosis.

Results:
Eighty four of 177 patients (48%) with confirmed VAP developed recurrence, with 68% involving methicillin-resistant *S. aureus* or nonfermenting gram-negative bacilli. APACHE II score, duration of hospital stay, and age were associated with recurrence (OR 1.06, p=0.04; OR 1.03, p=0.04; OR 1.02, p=0.03).

Conclusions:
There is a high rate of VAP recurrence in the surgical population with the majority involving drug-resistant organisms. Treatment should include coverage for these pathogens.
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Introduction:

Ventilator-associated pneumonia (VAP) is a significant problem in the management of trauma and general surgical patients in the surgical intensive care unit (SICU), with an incidence as high as 42%\(^1\). Its association with increased mortality in trauma patients has been a subject of considerable debate\(^2,3\). Because of its frequency and severity, nosocomial pneumonia in patients on prolonged mechanical ventilation represents one of the main reasons for antibiotic use in the SICU\(^3\), with each episode estimated to cost more than $40,000\(^4,5\).

Other outcome variables have not been well studied. Recurrent VAP may be an important factor affecting morbidity, mortality, or cost of care, but relatively little is known about this complication. Assessment of the efficacy of preventive measures has not been possible. Of the studies of recurrent VAP, most have focused on medical ICU patients, and there are conflicting data on factors contributing to recurrence\(^6-8\). Specifically, it is unclear whether initial infecting pathogen or underlying disease severity impacts pulmonary infection recurrence. Given the paucity of data regarding etiology and antibiotic resistance patterns of recurrent VAP in the surgical population, this study had four specific aims: to define the incidence of recurrent VAP in the SICU, to describe the bacteriology of recurrent cases, to determine patient characteristics predisposing to recurrent disease, and to determine whether recurrence is associated with excess mortality in a surgical population.
Materials and Methods:

Clinical and biologic data were collected from a four year retrospective database which included all non-transplant patients admitted to the SICU at the University of Cincinnati Hospital with clinically suspected VAP from January 2000 to December 2004. The following data were recorded for each patient: culture densities, initial causal pathogen(s), recurrent pathogen(s), age, white blood cell count (WBC), presence of trauma, duration of hospital stay prior to diagnosis, and hospital survival. Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were obtained on trauma patients from our University of Cincinnati Trauma Registry. APACHE II scores for nontrauma patients were calculated from data on the day of primary VAP diagnosis. By our SICU protocol, each patient with suspected VAP underwent fiberoptic bronchoalveolar lavage (BAL) or protected catheter lavage (PCL). During the period of this study most samples were obtained by PCL. VAP was defined as $\geq 10^4$ colony-forming units/mL in a BAL or PCL specimen$^9$. Early onset VAP occurred at 5 or less days in the hospital and late onset VAP occurred after 5 days of hospitalization$^4$.

Empiric therapy was guided by gram stain, with ceftriaxone being given to patients with early onset VAP ($\leq$ 5 days) and a combination of cefipime and tobramycin for late onset VAP ($> 5$ days). Vancomycin was added for late VAP if gram positive organisms were seen on gram stain. Antibiotics were tailored to sensitivities of microorganisms identified in lavage cultures.

Outcome Measures

Recurrence was defined as a positive quantitative culture $\geq 4$ days after initiation of antibiotics for the primary episode. These episodes were further classified into relapse and superinfection. Relapse was defined as a recurrence with the same organism as the first VAP. Superinfection was defined as a recurrence with an organism different from those encountered in the initial episode of VAP. Patients with polymicrobial infection recurrence were classified as
having a relapse if at least one of the initial causative bacterial strains grew at a significant concentration from a distal bronchial sample. Multi-drug resistant organisms were defined as those resistant to 3 or more classes of antibiotics. Mortality from any cause was recorded during hospitalization.

Statistical Analyses

Categorical variables were compared with chi-square tests and continuous variables with Student’s t-test. Univariate associations of patients’ clinical characteristics with outcome variables were examined by logistic regression. Each clinical characteristic with a \( p \leq 0.15 \) was entered into a multiple logistic regression model. Backward stepwise variable elimination (exit threshold set at one tailed \( p > 0.05 \)) was used. All potential explanatory variables included in the multivariable analysis were put into a correlation matrix to rule out collinearity. Statistical significance was defined as \( p < 0.05 \). Analyses were performed using SAS 9.0 (SAS Institute, Cary, NC) software.
Results:

Primary VAP episode

There were 177 patients with confirmed VAP, of whom 63% were trauma patients and 69% were male with an average age of 50 years. The first episode of VAP occurred 8.8 ± 9.1 days after hospital admission.

There were a total of 20 different organisms isolated in primary VAP episodes (Figure 1). *Hemophilus influenzae* represented the greatest proportion of early infections, but was only involved in 9% of late VAP. Twenty eight percent of early infections were attributable to nonfermenting gram negative bacilli (NF-GNB) and methicillin-resistant *Staphylococcus aureus* (MRSA). The incidence of these potentially multidrug resistant organisms increased to 52% in late VAP. When examining the frequency of specific drug resistant pathogens in the early versus late VAP groups, we found that MRSA nearly quadrupled, Stenotrophomonas more than doubled, and Pseudomonas nearly tripled.

Recurrent VAP episode

Eighty-four patients (48%) had recurrent VAP. Sixty eight percent of recurrent episodes involved NF-GNB or MRSA. *Stenotrophomonas* comprised the largest proportion of recurrent episodes at 31%, followed by *Pseudomonas* (16%), *Acinetobacter* (14%), and MRSA (7%). The median time to recurrence was 9 days.

Clinical characteristics of patients with and without VAP recurrence are given in Table 1. APACHE II scores, days in hospital prior to diagnosis, and patient age were correlated with recurrent infection by multivariable analysis (one tailed \( p=0.02 \), \( p=0.04 \) and \( p=0.04 \), respectively). The WBC demonstrated a trend toward association, but did not achieve statistical significance. The initial infecting organism was not associated with recurrence. Overall hospital mortality was 21%. There was no correlation between VAP recurrence and excess hospital
mortality (p=0.30).

Relapse and Superinfections

The overall infection relapse and superinfection rates were 33 (39%) and 51 (61%), respectively. The majority of recurrences were due to superinfections, regardless of the organism isolated from the first episode (Figure 2). Figure 3 demonstrates a rolling average of time elapsed from primary VAP episode to the first recurrence of VAP. There are two peaks of recurrence, first at 7 days following the first episode, and again 15 days after the primary VAP. The bulk of these peaks are due to superinfections. The mortality rates of patients with relapse was not significantly different from that in patients with superinfections (27% vs 22%, p=0.61)
Discussion:

This study uses data from a large retrospective database to assess clinical characteristics contributing to VAP recurrence in the SICU and to evaluate the bacteriology of primary and recurrent disease. These characteristics included demographic variables such as patient age and gender, disease severity at onset of primary VAP, and the presence of drug-resistant organisms (NF-GNB and MRSA) in the initial VAP.

This study is the first to analyze pulmonary infection recurrence in a mechanically ventilated surgical patient population. VAP recurrence rates have been reported by several authors in medical intensive care unit (ICU) settings\textsuperscript{6-8,10}. Rello and colleagues found nine patients with 10 superinfections among 58 patients with VAP\textsuperscript{11} and Combes’ group reported a recurrence rate of 23%\textsuperscript{7}. In our population of 177 patients with primary VAP, we found a significantly higher rate of 48% recurrence. This may in part be due to our high percentage of trauma patients, their accompanying lung injuries, and their need for more prolonged mechanical ventilation. Posttraumatic immunosuppression has been demonstrated in studies showing dysfunction of macrophages, splenocytes, and monocytes in mice following pulmonary contusion\textsuperscript{12}. Antonelli et al showed there was an increased risk of developing pneumonia in the presence of pulmonary contusion and an abbreviated injury scale (AIS) score of greater than 4 for the thorax and 9 for the abdomen\textsuperscript{13}.

In this population, patients who had recurrent VAP were older, had been in the hospital longer, and had more severe underlying illness as reflected by higher APACHE II scores. This finding is similar to that found in Combes’ study which demonstrated a correlation between Simplified Acute Physiology Score (SAPS) II at ICU admission and recurrence\textsuperscript{6}. However, an earlier study by the same group failed to demonstrate association between disease severity scores
and recurrence\textsuperscript{7}. This disparity may be due to differences in sample sizes and the earlier study being underpowered to detect a difference. Larger studies are needed to in surgical populations are needed to corroborate these findings.

The relationship between high-risk pathogens and recurrence remains difficult to clarify. Recurrent disease may occur through colonization, persistence of the initial causative strain, or weakening of host defenses in the respiratory tract\textsuperscript{8,14}. \textit{Pseudomonas aeruginosa} enters airway epithelial cells during infection, creating a hydrated polymeric matrix that forms a biofilm in the airway tissue, making the organism resistant to killing by antibiotics\textsuperscript{15}. In addition, release of endotoxin activates mediators that in turn lead to organ dysfunction and septic shock\textsuperscript{16}.

\textit{Acinetobacter baumannii} grows in moist, aerobic environments such as around the cuff of endotracheal tubing. Adherence factors present on this organism make it difficult to eradicate completely\textsuperscript{17,18} despite adequate antimicrobials. \textit{Stenotrophomonas maltophilia} shares a tendency to colonize the respiratory tract and is uniformly resistant to carbapenems\textsuperscript{4}.

Fibronectin-mediated adhesin is a glycoprotein present on the cell membrane of MRSA that aids the pathogen in adhesion to host tissue\textsuperscript{19,20}. These unique virulence factors enable chronic infection and may contribute to recurrence\textsuperscript{21,22}.

Attempts to describe the association between initial infection with a drug-resistant organism and recurrence have yielded conflicting results. A 2003 study of 124 patients with primary VAP suggested that the presence of NF-GNB or MRSA during the primary infection was not associated with recurrence\textsuperscript{7}. However, a later study of a larger cohort of patients demonstrated that the presence of NF-GNB in the primary episode was associated with a 2.83 greater odds of recurrence\textsuperscript{6}. Several studies have examined factors associated specifically with \textit{Pseudomonas} pneumonia recurrence. Adult respiratory distress syndrome\textsuperscript{14}, chronic lung disease, higher APACHE II scores at the end of the first episode, longer duration of hospital stay,
and longer duration of mechanical ventilation\textsuperscript{23} have been associated with clinical recurrence of \textit{P. aeruginosa}. One study also suggests that, based on chromosomal fingerprinting of strains isolated from distal secretions, most recurrent episodes of \textit{P. aeruginosa} VAP are relapses\textsuperscript{14}.

One important result from this study was that the microbiology of the first episode was not associated with recurrence. Univariate analyses of \textit{Acinetobacter}, \textit{Pseudomonas}, and \textit{Stenotrophomonas} in the primary VAP failed to independently demonstrate any association with pulmonary infection recurrence and thus could not be considered as a single group of NF-GNB. Similarly, there was no association between the presence of MRSA in the initial culture and recurrent disease. However, over two-thirds of recurrent cases were due to NF-GNB or MRSA, and the majority (61\%) were due to superinfection. Therefore, regardless of the initial infecting pathogen, patients who recurred were likely to have an infection with a different, drug-resistant organism. This finding suggests that the initial infecting isolate is not a valid guide for therapy of recurrence. Furthermore, treatment of pulmonary infection recurrence in mechanically ventilated patients should consider coverage for multi-drug resistant pathogens.

The higher rate of NF-GNB and MRSA found in our late onset primary VAP group is consistent with studies that have shown that the risk of multi-drug resistant organisms is increased after 5 days of hospitalization and by prior antimicrobial therapy\textsuperscript{24,25}. In a study of 135 consecutive episodes of VAP, Trouillet and coworkers\textsuperscript{21} found that 57\% of cases were caused by potentially resistant pathogens. They attributed their high rate of drug resistance, in part, to the volume of patients in their hospital and to their large referral population. The SICU patient population in this study has a similar profile, putting it at risk for higher rates of infection with potentially drug resistant pathogens. Furthermore, there is a high background use of broad-spectrum antibiotics for our critically ill patients, which is a predictor of drug-resistant VAP\textsuperscript{4}.

Several limitations to this study should be noted. First, the frequency of specific drug
resistant organisms causing VAP may vary by patient population, hospital, exposure to antibiotics, changes over time, and type of ICU patient. Given the heterogeneity of this patient group and the variations in hospital-specific nosocomial pathogens, our results may not be generalizable to other surgical populations. Second, the duration of antibiotic treatment was determined by the treating surgeon, and prolonged use of antibiotics may contribute to the emergence of bacterial resistance. Prospective studies controlling for the duration of antimicrobial therapy for VAP are needed to examine the impact of length of treatment on recurrence in the surgical population. Third, the use of $\geq 10^4$ CFU/mL as the diagnostic threshold may have overestimated the incidence of VAP. However, this is less likely given that only patients with clinically suspected VAP underwent BAL or PCL.

In summary, VAP recurrence is common in the surgical population. The majority of recurrences involve superinfection with a different organism from the primary episode, so surgeons should be careful in using the primary pathogen to guide empiric therapy for recurrent disease. Given that over two-thirds of the recurrent VAP in this study involved nonfermenting gram negative bacilli or MRSA, treatment of these episodes should consider coverage for drug-resistant pathogens. With the differences in antibiotic resistance profiles amongst hospitals, the results of this study may not be applicable to other surgical ICUs. However, these data suggest that it may be useful for other clinicians to examine local nosocomial organism patterns to help guide empiric therapy for recurrent VAP. Studies of resource utilization in VAP in the surgical ICU should consider the impact of recurring episodes of VAP in the cost of the first episode.
References:


### Appendix

Table 1. Univariate analyses of clinical characteristics on day of bronchoscopy for primary VAP

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>VAP recurrence</th>
<th>No VAP recurrence</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>APACHE II score*</td>
<td>15 ±6</td>
<td>13 ± 6</td>
<td>1.06 (1.01 - 1.68)</td>
<td>0.04</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>61 (34)</td>
<td>62 (35)</td>
<td>1.33 (0.70 – 2.53)</td>
<td>0.39</td>
</tr>
<tr>
<td>Age</td>
<td>54 ± 19</td>
<td>47 ± 19</td>
<td>1.02 (1.02 – 1.41)</td>
<td>0.03</td>
</tr>
<tr>
<td>Days in Hospital Prior to primary VAP</td>
<td>10 ± 11</td>
<td>8 ± 7</td>
<td>1.03 (0.99 – 1.07)</td>
<td>0.04</td>
</tr>
<tr>
<td>WBC at Diagnosis (x10³/µL)</td>
<td>17 ± 15</td>
<td>13 ± 7</td>
<td>1.04 (0.99 - 1.09)</td>
<td>0.08</td>
</tr>
<tr>
<td>Days in ICU Prior to primary VAP</td>
<td>8 ± 9</td>
<td>7 ± 6</td>
<td>1.03 (0.98 – 1.07)</td>
<td>0.19</td>
</tr>
<tr>
<td>Presence of Trauma, n (%)</td>
<td>55 (31)</td>
<td>58 (33)</td>
<td>1.14 (0.62 – 2.12)</td>
<td>0.67</td>
</tr>
<tr>
<td>Acinetobacter, n (%)</td>
<td>8(5)</td>
<td>18 (10)</td>
<td>0.44 (0.18 – 1.07)</td>
<td>0.07</td>
</tr>
<tr>
<td>Stenotrophomonas, n (%)</td>
<td>21 (12)</td>
<td>22 (12)</td>
<td>1.08 (0.54 – 2.14)</td>
<td>0.84</td>
</tr>
<tr>
<td>Pseudomonas, n (%)</td>
<td>10 (6)</td>
<td>9 (5)</td>
<td>1.26 (0.49 - 3.27)</td>
<td>0.63</td>
</tr>
<tr>
<td>MRSA,n (%)</td>
<td>11 (6)</td>
<td>8(5)</td>
<td>1.60 (0.61 – 4.19)</td>
<td>0.34</td>
</tr>
</tbody>
</table>

*Collected on day of admission for trauma patients from the Trauma Registry
Figure 1
Organisms isolated in primary VAP episode

[Bar chart showing the number of patients infected with different organisms, with labels for each category and a legend indicating 'Late VAP' and 'Early VAP']
Figure 2

Percentage of recurrences due to superinfection vs relapse

<table>
<thead>
<tr>
<th>Organism</th>
<th>Relapse</th>
<th>Superinfection</th>
<th>% of all recurrences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudomonas</td>
<td>40</td>
<td>68</td>
<td>59</td>
</tr>
<tr>
<td>Acinetobacter</td>
<td>41</td>
<td>59</td>
<td>65</td>
</tr>
<tr>
<td>Stenotrophomonas</td>
<td>35</td>
<td>56</td>
<td>65</td>
</tr>
<tr>
<td>MRSA</td>
<td>44</td>
<td>51</td>
<td>65</td>
</tr>
<tr>
<td>MSSA</td>
<td>17</td>
<td>83</td>
<td>83</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>83</td>
<td>83</td>
<td>83</td>
</tr>
<tr>
<td>Serratia</td>
<td>17</td>
<td>83</td>
<td>83</td>
</tr>
<tr>
<td>E.coli</td>
<td>17</td>
<td>83</td>
<td>83</td>
</tr>
</tbody>
</table>
Figure 3
Time from primary VAP to first recurrence

![Graph showing time from primary VAP to first recurrence with three curves: Relapse (red), Superinfection (yellow), and Recurrence (green).]