Comparison of the Bacterial Etiology of Early-Onset and Late-Onset Ventilator-Associated Pneumonia in Subjects Enrolled in 2 Large Clinical Studies

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BACKGROUND: Ventilator-associated pneumonia (VAP) is classified as early-onset or late-onset, in part, to identify subjects at risk for infection with resistant pathogens. We assessed differences in the bacterial etiology of early-onset versus late-onset VAP. METHODS: Subjects enrolled in 2004–2006 in 2 clinical studies of doripenem versus imipenem or piperacillin/tazobactam, with a diagnosis of VAP ($n = 500$) were included in the analysis. Subjects were classified by ventilator status: early-onset VAP (< 5 d of ventilation) or late-onset VAP (≥ 5 d of ventilation). Baseline demographics and bacterial etiology were analyzed by VAP status. RESULTS: Late-onset VAP subjects had higher Acute Physiology and Chronic Health Evaluation (APACHE II) scores (mean 16.6 versus 15.5, $P = .008$). There were no significant differences in Clinical Pulmonary Infection Score, sex, age, or presence of bacteremia between the groups. A total of 496 subjects had a baseline pathogen, and 50% of subjects in each group had ≥ 2 pathogens. With the exception of *Staphylococcus aureus*, which was common in early-onset VAP, the pathogens (including potentially multidrug-resistant (MDR) pathogens) isolated from early-onset versus late-onset VAP were not significantly different between groups. *Acinetobacter baumannii* or *Pseudomonas aeruginosa* with decreased susceptibility to any study drug was observed in early-onset and late-onset VAP subjects. CONCLUSIONS: There were no significant differences in the prevalence of potential MDR pathogens associated with early-onset or late-onset VAP, even in subjects with prior antibiotics. Empiric therapy for early-onset VAP should also include agents likely to be effective for potential MDR pathogens. Further prospective studies should evaluate microbiology trends in subjects with VAP.
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Introduction

Ventilator-associated pneumonia (VAP), defined as pneumonia occurring more than 48–72 hours after endotracheal intubation,[1,2] is a common complication in subjects on mechanical ventilation. The risk of this complication ranges between 8% to 25% in the ICU.[3,4] VAP is associated with increased hospital stay (by ~9 d), healthcare costs (~$12,000–40,000), high mortality (20–50%), and infection with multidrug-resistant (MDR) pathogens.[2,3,5-8] During the past few years the rates of VAP have declined; however, despite the implementation of multiple prevention strategies, VAP continues to occur.[9,10] VAP is classified as early-onset or late-onset, in part, to identify subjects at risk for infection with resistant pathogens. Early-onset VAP (< 5 d of hospitalization) has been commonly associated with a better prognosis and bacteria that are more susceptible to antibiotic therapy.[5,11] On the other hand, late-onset VAP presents ≥ 5 days from hospital admission, and is associated with higher morbidity, mortality, and MDR pathogens.[11]

Several studies have identified the association of MDR pathogens and late-onset of VAP,[12,13] which has been linked in part to previous antibiotic administration, time on mechanical ventilation, and local factors, which are institution specific.[3,12,14,15] The most commonly described MDR pathogens are methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, *Acinetobacter* species, and extended-spectrum beta-lactamase-producing Gram-negative bacilli.[6,16] Inadequate antimicrobial therapy, such as inappropriate antimicrobial coverage, or delayed initiation of antimicrobials, has been associated with higher hospital mortality in subjects with hospital-acquired pneumonia or VAP.[17-21] Therefore, the microbiological differentiation between early-onset and late-onset VAP has been implicated in the selection of broad-spectrum antimicrobial coverage for MDR pathogens.

The current practice guidelines recommend that subjects with early-onset VAP and no other risk factors for MDR pathogens should be treated with limited spectrum antimicrobial coverage. However, during the past decade, multiple epidemiological and microbiological risk factors have changed, suggesting that the distinction between early-onset and late-onset VAP should be reassessed and redefined. Therefore, our aim was to assess potential differences in bacterial etiology of subjects with early-onset versus late-onset VAP, using the original data from 2 prospective, multicenter, parallel, randomized, active controlled, open-label studies.

QUICK LOOK

Current knowledge

Ventilator-associated pneumonia (VAP) is defined as pneumonia occurring 48–72 hours after endotracheal intubation. VAP occurs at a rate of 8% to 25% in the ICU. VAP is associated with longer stay, higher costs, higher mortality, and more frequent infection with multidrug-resistant (MDR) pathogens. MDR pathogens occur more often in late-onset VAP.

What this paper contributes to our knowledge

There were no microbiological differences in the prevalence of potential MDR pathogens between early-onset and late-onset VAP in subjects previously treated with antibiotics. Clinicians should consider antibiotics that are active against MDR pathogens in patients with early-onset VAP.

Methods

This was a retrospective cohort study from 2 previously published randomized controlled trials[22,23] in subjects with VAP (DORI-09 and DORI-10). The 2 studies were conducted in nosocomial pneumonia/VAP (DORI-09) and VAP (DORI-10). DORI-09 was an open-label study comparing doripenem 500 mg every 8 hours, administered as a 1-hour infusion, versus piperacillin-tazobactam 4.5 g every 6 hours, conducted between June 2004 and October 2006, in 531 subjects with nosocomial pneumonia and early-onset VAP. DORI-10 was an open-label study that compared doripenem 500 mg every 8 hours, administered as a 4-hour infusion, with imipenem 500 mg every 6 hours or 1,000 mg every 8 hours, as a 30-min or 60-min infusion, respectively, conducted between June 2004 and October 2006, in 448 subjects with early-onset and late-onset VAP.

Both studies were conducted in accordance with the ethical principles of the Declaration of Helsinki and in compliance with the Guideline for Good Clinical Practice and applicable regulatory requirements. The protocol and informed consent form for each study were reviewed and approved by an institutional review board or ethics committee before subjects were enrolled.

Group Definitions

Subjects were distributed into 2 groups according to the number of intubation days: early-onset VAP (< 5 d) or late-onset VAP (≥ 5 d). Two complementary protocols, DORI-09 and DORI-10, were used to assess the aim of this study.

DORI-09 Subject Characteristics

DORI-09 included hospitalized male or female subjects, 18 years or older, with a clinical diagnosis of nosocomial

pneumonia or early-onset VAP, based on: the presence of a new or progressive infiltrate on chest radiograph; either fever, hypothermia, or changes in peripheral white blood cell count attributable to infection; an Acute Physiology And Chronic Health Evaluation (APACHE) II score between 8 and 25; and, for intubated subjects, a Clinical Pulmonary Infection Score (CPIS) ≥ 5.[22] In addition, subjects had either respiratory failure requiring mechanical ventilation or at least 2 of the following signs and symptoms: cough; new onset of purulent sputum production or other respiratory secretions (eg, tracheal secretions), or a change in the character of sputum; auscultatory findings on pulmonary examination of rales and/or evidence of pulmonary consolidation; dyspnea, tachypnea, or breathing frequency ≥ 30 breaths/min, particularly if any or all of these were progressive in nature; and/or hypoxemia.

Subjects were excluded if they were on mechanical ventilation for ≥ 5 days, unlikely to survive the 5-week to 7-week study period, or had known nosocomial pneumonia (prior study) caused by pathogen(s) resistant to meropenem or piperacillin/tazobactam. Subjects with MRSA were not excluded, as adjunctive therapy with vancomycin was allowed. Subjects were also excluded if they required concomitant systemic antimicrobial therapy (other than vancomycin or amikacin) in addition to the study drug, or had received systemic antibiotic therapy for ≥ 24 hours in the 72-hour period before randomization to the study drug (unless they had failed prior therapy for nosocomial pneumonia or developed symptoms of pneumonia with a new pulmonary infiltrate while receiving the prior antibiotic regimen).

Other exclusion criteria were: subjects with ARDS, known bronchial obstruction, or a history of post-obstructive pneumonia; cavitary lung disease based on chest x-ray findings; primary lung cancer or another malignancy metastatic to the lungs; and cystic fibrosis. In addition, patients were excluded from the study if they had known or suspected *Pneumocystis jiroveci* pneumonia, *Legionella*, active tuberculosis, or any rapidly progressing disease or immediately life-threatening illness, including acute hepatic failure or septic shock, requiring peritoneal dialysis, hemodialysis, or hemofiltration, or substantial clinical laboratory abnormalities or immunocompromising illness. Subjects with COPD were allowed.

DORI-10 Subject Characteristics

DORI-10 included hospitalized adult male or female subjects who met clinical and radiologic criteria for VAP and were mechanically ventilated for at least 24 hours or weaned from the ventilator in the previous 72 hours and had a CPIS ≥ 5. Subjects were required to have a new or progressive infiltrate on chest x-ray and, based on the CPIS criteria, at least one of: fever (> 38.5°C) or hypothermia (< 36°C); elevated total peripheral white blood cell count (> 11 g/L) or leukopenia (< 4 g/L) indicative of infection and an APACHE II score between 8 and 29.[24] Vancomycin and/or amikacin (or another aminoglycoside) were added at the discretion of the investigator in cases where infection with MRSA or *P. aeruginosa*, respectively, were suspected.

Patients were excluded if they were unlikely to survive the study period or had an order of "no cardiopulmonary resuscitation" in case of cardiac arrest; an infection or a complication that required non-study systemic antibacterial therapy (other than per-protocol adjunctive therapy for *Pseudomonas* species or MRSA coverage) or prolonged (ie, more than 14 d) antimicrobial treatment; or had received systemic antibiotic therapy for ≥ 24 hours in the 48 hours before randomization (unless they had failed prior therapy for VAP). Also excluded were patients with cavitary lung disease (based on radiographic findings), primary lung cancer or other malignancy metastatic to the lungs, cystic fibrosis, known or suspected *Pneumocystis jiroveci* pneumonia, empyema, structural lung disease (eg, bronchiectasis), ARDS, any rapidly progressing disease or immediately life-threatening illness (eg, acute hepatic failure or septic shock), needed drotrecogin alfa, peritoneal dialysis, hemodialysis, or hemofiltration, or had clinically important laboratory abnormalities or immunocompromising illness.

Subjects were withdrawn from the study if the culture was negative and the patient had not received antibiotic therapy for 72 hours before collection, or if MRSA was the only pathogen identified. Vancomycin and/or amikacin were also to be withdrawn within 48 hours if the baseline culture failed to confirm MRSA or *P. aeruginosa*, respectively.

Data Abstraction

Chart review data included demographics, comorbid conditions, physical examination findings, laboratory and microbiology data, chest radiograph reports, and CPIS variables. We extracted these parameters at the time of enrollment in the studies.

Cultures

The microbiology evaluation was similar for both studies, and is described elsewhere, but it is summarized below.[22,23] For intubated subjects, a lower respiratory tract specimen was obtained by endotracheal suctioning or bronchoalveolar lavage/protected-specimen brush when available, prior to initiating study drug therapy. Bacteriostatic saline was not permitted for the bronchoscopy. Blood cultures were also obtained at study entry. The susceptibility testing was performed to each participating center's labo-

Table 1. Baseline Demographic and Clinical Characteristics of Early-Onset Versus Late-Onset Ventilator-Associated Pneumonia

Characteristics	Early-Onset VAP $n = 248$	Late-Onset VAP $n = 248$	P*
Male, no. (%)	192 (77.4)	182 (73.4)	.35
Age, mean ± SD y	49.4 ± 20.1	52.5 ± 19.2	.08
Age ≥ 65 y, no. (%)	70 (28.2)	76 (30.6)	.62
Age ≥ 75 y, no. (%)	35 (14.1)	38 (15.3)	.80
Weight, mean ± SD kg	80.1 ± 18.9	82.3 ± 18.5	.02
APACHE II score, mean ± SD	15.5 ± 4.6	16.6 ± 4.6	.01
APACHE II score > 15, no. (%)	111 (44.8)	147 (59.3)	< .01
CPIS, mean ± SD	6.9 ± 1.5	7.0 ± 1.4	.66
Comorbid conditions, no. (%)			
Congestive heart failure	16 (6.5)	14 (5.6)	.85
Cerebrovascular disease	53 (21.4)	41 (16.5)	.21
Chronic renal disease	4 (1.6)	5 (2.0)	.99
Bacteremia	37 (14.9)	25 (10.1)	.13
Anti-MRSA coverage, no. (%)	85 (34.3)	78 (31.5)	.57
Anti-pseudomonal double coverage, no. (%)	117 (47.2)	64 (25.8)	< .01
Antibiotic therapy in the prior month, no. (%)	170 (68.5)	212 (85.5)	< .01

* Via Fisher exact test for categorical variables and *t* test for continuous variables, or Wilcoxon-Mann-Whitney test for ordinal variables.
VAP = ventilator-associated pneumonia
APACHE = Acute Physiology and Chronic Health Evaluation
CPIS = Clinical Pulmonary Infection Score
MRSA = methicillin-resistant *Staphylococcus aureus*

ratory standard. Decreased susceptibility to either study drug was defined as a 4-fold or greater increase of minimum inhibitory concentration from baseline as well as a minimum inhibitory concentration ≥ 8 μg/mL.

Clinical Outcome

The primary outcome was the rate of VAP due to potential MDR pathogens in early-onset and late-onset VAP. Potential MDR pathogens were defined according to the microbiological identification of MRSA, *P. aeruginosa*, *Acinetobacter* species, and extended-spectrum beta-lactamase pathogens such as *Klebsiella, Enterobacter*, and *Serratia* species.[11]

Statistical Analyses

Demographic variables and the presence of specific pathogens at baseline were performed to compare the subjects between groups of early-onset and late-onset VAP. The statistical methods performed were Fisher exact test for dichotomous variables, the 2-sample *t* test for continuous variables, and the Wilcoxon-Mann-Whitney test for ordinal variables.

Results

A total of 496 subjects who met the criteria for VAP in the DORI-09 and DORI-10 studies with confirmed microbiology results were included in the current analysis (Table 1). Subjects were stratified into early-onset ($n = 248$) and late-onset VAP ($n = 248$). Both groups had similar rates of males, age, and weight. The late-onset VAP subjects had similar rates of comorbid conditions, including congestive heart failure, cerebrovascular disease, and chronic renal disease, when compared to the early-onset VAP subjects. In addition, there were no significant differences in CPIS or bacteremia between the early-onset and late-onset VAP subjects. The late-onset VAP subjects had higher APACHE II scores (mean 16.6 versus 15.5, $P = .008$), compared to early-onset VAP. In addition, a higher proportion of late-onset VAP subjects had an APACHE II score above 15. The late-onset VAP subjects had similar rates of anti-MRSA coverage, but lower anti-pseudomonal coverage and higher prior antibiotic therapy within 1 month of developing VAP, when compared to early-onset VAP. There was a significant difference in the number of antibiotic therapies in the prior month between groups ($P < .01$).

Microbiology Results

Baseline pathogens were found in 496 subjects, and 298 subjects had ≥ 2 pathogens. The most frequent group of isolated pathogens were Gram-negative bacilli, followed by Gram-positive cocci (Table 2). The predominant Gram-negative bacilli were *Haemophilus influenzae*, *P. aeruginosa*, and *Klebsiella pneumoniae*. In addition, the 2 most

Table 2. Microbiology Results for Early-Onset Versus Late-Onset Ventilator-Associated Pneumonia

Pathogen	Early-Onset VAP $n = 248$	Late-Onset VAP $n = 248$	P*
Gram-positive	139 (56.0)	124 (5.0)	.21
Staphylococcus aureus	109 (44.0)	83 (33.5)	.02
MRSA†	18 (16.5)	21 (25.3)	.15
S. pneumoniae	26 (1.5)	15 (6.0)	.10
Gram-negative	187 (75.4)	209 (84.3)	.02
Haemophilus influenzae	66 (26.6)	50 (2.2)	.11
Pseudomonas aeruginosa	36 (14.5)	37 (14.9)	.99
Klebsiella pneumoniae	28 (11.3)	29 (11.7)	.99
Escherichia coli	22 (8.9)	33 (13.3)	.15
E. cloacae	21 (8.5)	28 (11.3)	.37
Acinetobacter baumannii	15 (6.0)	22 (8.9)	.30
Multidrug-resistant pathogens‡	69 (27.8)	80 (32.3)	.33

Values are number and percent.
* Via Fisher exact test.
† Percent and *P* for methicillin-resistant *S. aureus* (MRSA) was based on total number of *S. aureus*.
‡ Percent and *P* for multidrug-resistant pathogens (MRSA, *P. aeruginosa*, *Acinetobacter* species, and extended-spectrum beta-lactamases).

frequently isolated Gram-positive cocci were *S. aureus*, and *Streptococcus pneumoniae*. *S. aureus* was more frequently isolated among subjects with early-onset VAP, when compared to late-onset VAP (44.0% vs 33.5% $P = .02$). In contrast, MRSA was numerically higher among late-onset VAP subjects, as compared to early-onset VAP subjects (25.3% vs 18%, $P = .15$). However, the difference was not statistically significant. In addition subjects with late-onset VAP were more likely to be infected with Gram-negative bacilli, as compared to early-onset VAP subjects (84.3% vs 75.4%, $P = .02$). However, there were no significant differences for specific pathogens, including *P. aeruginosa* or *A. baumannii* between early-onset and late-onset VAP. No extended-spectrum beta-lactamases were identified in this study. Finally, there were no statistically significant differences in VAP caused by potential MDR pathogens when comparing early-onset versus late-onset VAP.

Discussion

Our results suggest no differences in the rate of potential MDR pathogens between early-onset and late-onset VAP. In addition, the presence of *A. baumannii* or *P. aeruginosa* with decreased susceptibility to any study drug (minimum inhibitory concentration ≥ 8 μg/mL) was almost similar in both early-onset and late-onset VAP. Despite higher APACHE II scores in the late-onset VAP group, no significant difference was present in CPIS, sex, age, or bacteremia between groups.

Previous studies have shown a higher association between MDR pathogens and late-onset VAP.[6,16] This association is in part due to previous antibiotic therapy, time on mechanical ventilation, and local factors, which are institution specific.[3,12,14,15]

Currently, in patients with late-onset VAP the Infectious Diseases Society of America/American Thoracic Society clinical practice guidelines recommend broad-spectrum antibiotic therapy to cover MDR pathogens. Moreover, in patients with early-onset VAP in whom prior administration of antibiotic therapy or hospitalization within the past 90 days have been present, a risk of infection and colonization with MDR pathogens should be considered and thus treated similarly to patients with late-onset VAP.[12] To support these recommendations, Ibrahim and colleagues have reported MDR pathogens to be common in both early-onset and late-onset VAP.[21] One proposed explanation for these results was the presence of previous hospitalization or antibiotic administration in those patients developing early-onset VAP before being transferred to the ICU.[3,21] Interestingly, this is similar to those factors linked with MDR in late-onset VAP. However, limited additional data are available about the similarities in MDR pathogens in VAP.[21] Our data show that a change in epidemiology and microbiology suggests that potential MDR pathogens are present in both early-onset and late-onset VAP, even in subjects with prior antimicrobial therapy, and, thus, broad-spectrum antibiotics should be considered as an early therapeutic approach in both types of VAP. Prior studies suggest that the presence of MDR pathogens is associated with inappropriate antibiotic regimen selection for the treatment of hospital-acquired pneumonia and VAP.[17-21]

Our study has limitations that are important to acknowledge. First, this study had an open label design that could allow for selection bias. We excluded subjects who received systemic antibiotic therapy for $\geq$ 24 hours in the 48 hours before randomization (unless they had failed prior therapy for VAP), making the possible presence of MDR pathogens due to prior antibiotic administration less likely. Second, the proportion of male subjects enrolled in the study was not different among groups. However, due to the low proportion of women enrolled in this study, the conclusions may not be generalizable to women. Third, potential risk factors that may influence the bacterial etiology of VAP, such as previous infections, colonization, or intubation, were not collected as part of the study. Future studies should consider these confounders when assessing the association of resistant pathogens and the presentation of VAP. To minimize bias, in-house handling and data analysis were blinded in the original studies. Although the number of bronchoalveolar lavage, tracheal suctioning specimen, sputum culture, or protected-specimen brush for the diagnosis of VAP was not available, the best approach to the diagnosis of VAP is still a

matter of controversy (microbiological vs clinical approach). In these studies, objective criteria were used to establish clinical outcomes.

Conclusions

In conclusion, there were no microbiological differences in the prevalence of potential MDR pathogens associated with early-onset or late-onset VAP in subjects who have received previous antibiotic therapy. VAP is classified as early-onset or late-onset, in part, to identify subjects at risk for infection with resistant pathogens. Therefore, clinical practice guidelines should reevaluate the definition of VAP and recommend antimicrobial agents active against potential MDR pathogens, even for patients with early-onset VAP. Further prospective studies should evaluate microbiology trends in subjects with VAP in order to address the findings of our study.

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