RESPIRATORY CARE Paper in Press. Published on January 08, 2013 as DOI: 10.4187/respcare.02173

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

Marcos I. Restrepo, MD, MSc; Janet Peterson, PhD; Juan F. Fernandez, MD; Zhihai Qin, PhD; Alan C. Fisher, PhD; and Susan C. Nicholson, MD.

Affiliation: VERDICT (MIR), South Texas Veterans Health Care System Audie L Murphy Division (MIR); the University of Texas Health Science Center at San Antonio, Department of Medicine, Division of Pulmonary and Critical Care Medicine (MIR, JFF); Janssen Scientific Affairs, (JP, ZQ, ACF, SCN)

Janssen Scientific Affairs LLC, 1000 Rt 202s Raritan, NJ 08869.

Author emails:

Janet Peterson, PhD; JPeter13@its.jnj.com

Juan F. Fernandez, MD; Jfelipefernandez@hotmail.com

Zhihai Qin, PhD; Zqin@its.jnj.com

Alan C. Fisher, PhD; acf900@gmail.com

Susan C. Nicholson, MD; Snicho10@its.jnj.com.

Word count: 2237

Corresponding author: Marcos I. Restrepo, MD, MSc; VERDICT (11C6) – South Texas Veterans Health Care System ALMD - 7400 Merton Minter Boulevard - San

Antonio Texas, 78229; Phone: (210)-617-5300 ext. 15413 - Fax: (210) 567-4423; Email: restrepom@uthscsa.edu

Conflicts of interest

Dr. Marcos I. Restrepo participated in advisory boards for Ortho-McNeil-Janssen, Theravance, Forest Laboratories, Johnson & Johnson, Trius and Novartis. Consultant for Theravance, Trius and Pfizer (Wyeth).

No conflicts of interest were reported by Drs. Juan F. Fernandez

Support: Dr. Restrepo time is partially protected by Award Number K23HL096054 from the National Heart, Lung, And Blood Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Heart, Lung, And Blood Institute or the National Institutes of Health."

The funding agencies had no role in the preparation, review, or approval of the manuscript. The views expressed in this article are those of the author and do not necessarily represent the views of the Department of Veterans Affairs, nor the University of Texas Health Science Center at San Antonio.

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ABSTRACT

Purpose: To assess potential differences in bacterial etiology of subjects with early-onset vs. late-onset ventilator associated pneumonia (VAP).

Methods: Subjects enrolled in 2004-2006 in 2 clinical studies of doripenem vs. 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 days of ventilation) or late-onset VAP (≥5 days of ventilation)]. Baseline demographics and bacterial etiology were analyzed by VAP status.

Results: Late-onset VAP subjects had higher APACHE II scores [mean 16.6 vs. 15.5 (p=0.008)]. There were no significant differences in CPIS, gender, age, or presence of bacteremia between 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, pathogens, including potentially MDR, isolated from early vs. late-onset VAP was not significantly different between groups. *Acinetobacter baumannii* or *Pseudomonas aeruginosa* with decreased susceptibility to any study drug was observed in early and late onset VAP subjects.

Conclusion: There were no significant differences in the prevalence of potential MDR pathogens associated with early or late-onset VAP, even in subjects with prior antibiotics.

Clinical Implications: VAP is classified as early-onset or late-onset, in part, to identify subjects at risk for infection with resistant pathogens. 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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KEY WORDS

- Ventilator associated pneumonia
- Intensive care unit
- Outcome and process assessment
- Critical care
- Microbiology
- Early onset
- Late onset
- Mechanical ventilation

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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 intensive care unit (ICU).[3, 4] VAP is associated with increase hospital length of stay (~ by 9 days), health care cost (~$12,000 to 40,000), high mortality (20-50%) and infection with multidrug resistant pathogens (MDR).[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] [Kollef 2012, Dudeck MA, AJIC 2011] 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 days of hospitalization) has been commonly associated with a better prognosis and more susceptible bacteria to antibiotic therapy.[5,11] On the other hand, late-onset VAP presents ≥ 5 days from hospital admission is associated with a higher morbidity, mortality and multidrug-resistant pathogens.[11] Several studies had 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*, *Pseudomonas aeruginosa*, *Acinetobacter* spp. and extended spectrum betalactamase 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 (HAP) or VAP.[17-21] Therefore, the microbiological differentiation between early-onset

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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 vs. late-onset VAP, using the original data from two prospective, multicenter, parallel, randomized, active controlled, open-label studies.

METHODS

This is a retrospective cohort study from two randomized controlled trials done in subjects with VAP previously published (DORI-09 and DORI-10). The two studies were conducted in nosocomial pneumonia (NP)/VAP **(DORI-09)** and VAP **(DORI-10)**. [22, 23] DORI-09 was an open-label study comparing doripenem 500 mg q8h administered as a 1-hour infusion versus piperacillin-tazobactam 4.5 g q6h conducted between June 2004 and October 2006 in 531 subjects with NP and early-onset VAP. DORI-10 was an open-label study that compared doripenem 500 mg qh8 administered as a 4-hour infusion with imipenem 500 mg q6h or 1000 mg q8h as a 30 or 60 minutes infusion respectively, conducted between June 2004 and October 2006 in 448 subjects with early- 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

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and applicable regulatory requirements. Each study protocol and informed consent form were reviewed and approved by an institutional review board (IRB) or ethics committee (IEC) before subjects were enrolled.

Group definitions

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

DORI-09 Subject Characteristics

Hospitalized males or female subjects aged 18 years or older with a clinical diagnosis of NP 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 were included in DORI-09.[22] In addition, subjects had either respiratory failure requiring mechanical ventilation or at least two of the following signs and symptoms: cough; new onset of purulent sputum production or other respiratory secretions (e.g., 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 respiratory rate ≥ 30 per minute, particularly if any or all of these were progressive in nature and/or hypoxemia.

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Subjects were excluded if they were on mechanical ventilation for greater than or equal to 5 days, unlikely to survive the 5- to 7-week study period; known NP (prior study) to be 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 study drug, or had received systemic antibiotic therapy for ≥ 24 hrs in the 72 hrs period before randomization to study drug (unless failed prior therapy for NP or developed symptoms of pneumonia with a new pulmonary infiltrate while receiving the prior antibiotic regimen).

Other exclusion criteria were: subjects with Adult Respiratory Distress Syndrome (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, subjects were excluded from the study if it was known or suspected *Pneumocystis jiroveci* pneumonia, *Legionella* or active tuberculosis, any rapidly progressing disease or immediately life-threatening illness including acute hepatic failure or septic shock; requiring peritoneal dialysis, hemodialysis or hemofiltration or significant clinical laboratory abnormalities or immunocompromising illness. Subjects with chronic obstructive pulmonary disease (COPD) were allowed.

DORI-10 Subject Characteristics:

Hospitalized adult male or female subjects that met clinical and radiologic criteria for VAP were included in the study if mechanically ventilated for at least 24 hours or

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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 1 of the following: fever (>38.5°C), or hypothermia (<36°C); elevated total peripheral white blood cell (WBC) count (>11G/L) or leukopenia (<4G/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. Subjects were excluded if they were unlikely to survive the study period or with an order of "no cardiopulmonary resuscitation" in case of cardiac arrest; with an infection or a complication that required non-study systemic antibacterial therapy (other than per protocol adjunctive therapy for *Pseudomonas* spp. or MRSA coverage) or prolonged (i.e., more than 14 days) antimicrobial treatment, or if subjects had received systemic antibiotic therapy for ≥ 24 hrs in the 48 hrs before randomization (unless they had failed prior therapy for VAP) . In addition, subjects with a cavitary lung disease based on radiographic findings, primary lung cancer or another malignancy metastatic to the lungs, cystic fibrosis, known or suspected *Pneumocystis jiroveci* pneumonia; empyema, structural lung disease (e.g. bronchiectasis) or ARDS; any rapidly progressing disease or immediately life-threatening illness, including acute hepatic failure or septic shock; the need for Xigris® (drotrecogin alfa); requirement for peritoneal dialysis, hemodialysis or hemofiltration; clinically significant laboratory abnormalities; immunocompromising illness.

Patients were withdrawn from the study if the culture was negative and the patient had not received antibiotic therapy for 72 hrs before collection or if MRSA was the only

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pathogen identified. Vancomycin and or amikacin were also to be withdrawn within 48 hrs if the base line 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 clinical pulmonary infection score (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 (LRT) specimen was obtained by endotracheal aspiration or bronchial alveolar lavage (BAL)/protected-specimen brush (PSB) 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 at each participating center laboratory standard. Decreased susceptibility to either study drug was defined as four-fold or greater increase of MIC from baseline as well as MIC $\geq$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

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microbiological identification of MRSA, *P. aeruginosa*, *Acinetobacter* spp. and extended spectrum beta-lactamases (ESBL) pathogens such as *Klebsiella, Enterobacter* and *Serratia* spp. [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's exact test for dichotomous variables, the two-sample t-test for continuous variables, and the Wilcoxon-Mann-Whitney test for ordinal variables.

RESULTS

A total of 496 subjects that met the criteria for VAP in DORI-09 and DORI-10 studies with confirmed microbiology results were included in the current analysis (Table 1). Subjects were stratified in early-onset (n=248) and late-onset VAP (n=248). Both groups had similar rates of males, age, and weight. Late-onset VAP subjects had similar rates of comorbid conditions, including congestive heart failure, cerebrovascular disease, and chronic renal disease when compared to early-onset VAP subjects. In addition, there were not significant differences in CPIS or bacteremia between early-onset and late-onset VAP subjects. Late-onset VAP subjects had higher APACHE II scores [mean 16.6 vs. 15.5 (p=0.008)] compared to early-onset VAP. In addition, a higher proportion of late-onset VAP had an APACHE II score above 15. Late-onset VAP subjects had similar rates of anti-MRSA coverage, but lower anti-pseudomonal coverage and higher prior antibiotic

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therapy within 1 month of developing VAP when compared to early-onset VAP. There was a significant difference in the number of antibiotic therapy in the prior month between groups ($p<0.01$).

Microbiology results

Base line 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 two most 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=0.02). In contrast, MRSA was numerically higher among late-onset VAP subjects as compared to early-onset VAP subjects (25.3% vs 18%; p = 0.15). 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 = 0.02). However, there were no significant differences for specific pathogens, including *P. aeruginosa* or *A. baumannii* between early- and late- onset VAP. No ESBLs were identified in this study. Finally, there were no statistically significant differences among VAP caused by potential MDR pathogens when comparing early-onset vs. late-onset VAP.

DISCUSSION

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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. baumanni* or *P. aeruginosa* with decreased susceptibility to any study drug (MIC ≥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, gender, age or bacteremia between groups.

Previous studies have shown a higher association between MDR pathogens with 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 IDSA/ATS clinical practice guidelines recommends 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 showed that a change in epidemiology and microbiology suggest that potential MDR pathogens are present in both early-onset and late-onset VAP even in subjects with prior antimicrobial therapy,

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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 (HAP) and VAP. [17-21]

Our study has limitations that are important to acknowledge. First, this study was an open label design that could allow for selection bias. We excluded subjects who received systemic antibiotic therapy for ≥ 24 hrs in the 48 hrs 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 BAL, tracheal aspirate, sputum culture or PSB 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.

In conclusion, there were no microbiological differences in the prevalence of potential MDR pathogens associated with early or late-onset VAP in subjects who have received previous antibiotic therapy. VAP is classified as early-onset or late-onset, in

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part, to identify subjects at risk for infection with resistant pathogens. Therefore, clinical practice guidelines should re-evaluate 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.

Acknowledgements

Special acknowledgment and appreciation to Dr Stephanie M. Levine for her editorial assistance.

Drs. Restrepo and Peterson were the primary persons involved in the design, data analysis, interpretation, and manuscript preparation.

Drs. Fernandez, Qin, Fisher; and Nicholson participated in design, interpretation, and manuscript revision.

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Table 1. Baseline demographic and clinical characteristics among Early-onset vs. Late-onset VAP.

Characteristics	Early-onset VAP (n=248) N (%)	Late-onset VAP (n=248) N (%)	P-value*
Gender, Male	192 (77.4)	182 (73.4)	0.35
Age, mean (SD)	49.4 (20.1)	52.5 (19.2)	0.08
Age > or = 65 years	70 (28.2)	76 (30.6)	0.62
Age > or = 75 years	35 (14.1)	38 (15.3)	0.80
Weight (kg), mean (SD)	80.1 (18.9)	82.3 (18.5)	0.02
APACHE II score, mean (SD)	15.5 (4.6)	16.6 (4.6)	0.01
APACHE II score >15	111 (44.8)	147 (59.3)	<0.01
CPIS score, mean (SD)	6.9 (1.5)	7.0 (1.4)	0.66
Comorbid conditions			
Congestive heart failure	16 (6.5)	14 (5.6)	0.85
Cerebrovascular disease	53 (21.4)	41 (16.5)	0.21
Chronic renal disease	4 (1.6)	5 (2.0)	0.99
Bacteremia	37 (14.9)	25 (10.1)	0.13
Anti-MRSA coverage	85 (34.3)	78 (31.5)	0.57
Anti-Pseudomonal double coverage	117 (47.2)	64 (25.8)	<0.01
Antibiotic therapy in the prior month	170 (68.5)	212 (85.5)	<0.01

* p value was calculated based on Fisher's exact test for categorical variables and t-test for continuous variables and Wilcoxon-Mann-Whitney test for ordinal variables.

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Table 2. Microbiology results among Early-onset vs. Late-onset VAP.

Pathogen	Early-onset VAP (n=248) N (%)	Late-onset VAP (n=248) N (%)	P-value*
All Gram positive	139 (56.0)	124 (50.0)	0.21
S. aureus	109 (44.0)	83 (33.5)	0.02
• MRSA**	18 (16.5)	21 (25.3)	0.15
S. pneumoniae	26 (10.5)	15 (6.0)	0.10
All Gram negative	187 (75.4)	209 (84.3)	0.02
H. influenzae	66 (26.6)	50 (20.2)	0.11
P. aeruginosa	36 (14.5)	37 (14.9)	0.99
K. pneumoniae	28 (11.3)	29 (11.7)	0.99
E. coli	22 (8.9)	33 (13.3)	0.15
E. cloacae	21 (8.5)	28 (11.3)	0.37
A. baumannii	15 (6.0)	22 (8.9)	0.30
MDR pathogens* **	69 (27.8)	80 (32.3)	0.33

* p value was calculated based on Fisher's exact test.
** Percent and p-value for MRSA was based on total number of *S. aureus*.
*** Percent and p-value for MDR pathogens (MRSA, *P. aeruginosa*, *Acinetobacter* spp. and extended spectrum beta-lactamases (ESBL).