MAJOR ARTICLE

Severity of Disease and Clinical Outcomes in Patients With Hospital-Acquired Pneumonia Due to Methicillin-Resistant *Staphylococcus aureus* Strains Not Influenced by the Presence of the Panton-Valentine Leukocidin Gene

Paula Peyrani,[1] Marty Allen,[1] Timothy L. Wiemken,[1] Nadia Z. Haque,[2] Marcus J. Zervos,[2] Kimbal D. Ford,[3] Ernesto G. Scerpella,[3] Julie E. Mangino,[4] Daniel H. Kett,[5] Julio A. Ramirez,[1] and the IMPACT-HAP Study Group

[1]Division of Infectious Diseases, University of Louisville, Kentucky; [2]Division of Infectious Diseases, Henry Ford Health System, Detroit, Michigan; [3]Pfizer, Inc, Collegeville, Pennsylvania; [4]Division of Infectious Diseases, Ohio State University, Columbus; and [5]Division of Pulmonary and Critical Care Medicine, Miller School of Medicine at the University of Miami, Florida

(See the article by Hota et al, on pages 757–65.)

Background. Patients with community-acquired pneumonia (CAP) infected with methicillin-resistant *Staphylococcus aureus* (MRSA) strains carrying the Panton-Valentine leukocidin (PVL) gene have severe clinical presentation and poor clinical outcomes. Antibiotics that suppress toxin production have been suggested for the management of these patients. The objective of this study was to compare the severity of disease and clinical outcomes of patients with hospital-acquired pneumonia/ventilator-associated pneumonia (HAP/VAP) infected with MRSA carrying the PVL gene with those patients infected with MRSA strains that do not carry the PVL gene.

Methods. This was a multicenter observational study of patients with HAP and VAP. MRSA isolates were subjected to genetic analysis to define the presence of the PVL gene, the USA type and the staphylococcal cassette chromosome *mec* type. Severity of disease was evaluated with the Acute Physiology and Chronic Health Evaluation II (APACHE II) score. The primary clinical outcome was mortality at hospital discharge.

Results. A total of 109 cases of MRSA HAP/VAP were evaluated. The incidence of PVL^+ MRSA was 27%. APACHE II score at diagnosis of HAP/VAP was 21 ± 8 for PVL^+ MRSA and 20 ± 6 for PVL^- MRSA ($P = .67$). Mortality was 10% (3/29) for patients with PVL^+ MRSA versus 10% (8/80) for patients with PVL^- MRSA ($P > .99$).

Conclusions. In patients with HAP or VAP due to MRSA, severity of disease and clinical outcomes are not influenced by the presence of the PVL gene. Therapeutic strategies directed to block PVL exotoxin may not impact outcomes in these patients.

Panton-Valentine leukocidin (PVL) is a pore-forming toxin secreted by strains of methicillin-resistant *Staphylococcus aureus* (MRSA) that are epidemiologically associated with the current outbreak of community-associated MRSA (CA-MRSA) infections [1, 2]. In the United States, the primary MRSA circulating clone in the community corresponds to the genetic background USA300 [3]. One of the most serious infections produced by these strains of MRSA carrying the PVL gene is community-acquired pneumonia (CAP). Patients with CAP due to MRSA carrying the PVL gene may present with extensive lung necrosis, multilobar infiltrates, leukopenia, hemoptysis, and, often, severe sepsis [4, 5]. Although these patients are not immunocompromised, CAP due to MRSA strains carrying the PVL gene is usually associated with poor clinical outcomes [4, 5].

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Correspondence: Julio Ramirez, MD, FACP, Division of Infectious Diseases, University of Louisville and VA Medical Center, 501 E Broadway, MedCenter One, Ste 380, Louisville, KY 40202 (j.ramirez@louisville.edu).

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Even though a clear association between CAP due to MRSA strains carrying the PVL gene and poor patient outcomes has been documented, controversy still exists regarding the actual role of PVL in the pathogenesis of pneumonia [6, 7]. In one of these rodent models, the presence of PVL was sufficient to cause necrotizing pneumonia and also favored the transcription of other staphylococcal virulence factors [6]. It is unclear what the best antimicrobial therapy is for patients with CAP due to MRSA strains carrying the PVL gene. Laboratory studies indicate that antibiotics that block protein synthesis decrease production of PVL exotoxin by MRSA [8]. Because the pathogenesis of CA-MRSA CAP seems to be toxin mediated, investigators have suggested that antibiotics that suppress toxin production, such as clindamycin or linezolid, may improve clinical outcomes in patients with CAP infected with MRSA strains carrying the PVL gene [9].

Recent literature indicates that these community-associated strains of MRSA have taken up residence in US hospitals and are now being reported as etiologic agents of nosocomial infections [10, 11]. In our institutions, we have recently identified patients with hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) produced by MRSA strains carrying the PVL gene. We hypothesize that patients with HAP/VAP due to MRSA strains carrying the PVL gene will have more severe disease and worse clinical outcomes when compared with patients with HAP/VAP due to MRSA without the PVL gene. If the presence of the PVL gene in patients with HAP/VAP were to be associated with poor clinical outcomes, as in the case of CAP, consideration may be given for antibiotics that inhibit protein synthesis. To test our hypothesis, we designed a study with the objective of comparing the severity of disease and clinical outcomes of patients with HAP/VAP infected with MRSA carrying the PVL gene with those of patients infected with MRSA not carrying the PVL gene.

MATERIALS AND METHODS

Study Design and Study Population

This was a retrospective, observational study of intensive care unit (ICU) patients with a diagnosis of HAP/VAP in 4 academic medical centers in the United States: the University of Louisville (Louisville, Kentucky), the Ohio State University Medical Center (Columbus, Ohio), the Henry Ford Health System (Detroit, Michigan), and the University of Miami/Jackson Memorial Hospital (Miami, Florida). Patients included in this study were treated during the period from November 2008 through July 2010. Local institutional review board review was obtained in each participating hospital. Data were collected on a case report form, entered into a Web-based database, and transferred electronically to the Improving Medicine through Pathway Assessment of Critical Therapy in Hospital-Acquired Pneumonia (IMPACT-HAP) Data and Statistical Coordinating Center at the University of Louisville (www.impact-hap.net). The Center validated the quality of data by checking for discrepancies and inconsistencies. Upon validation, the case was accepted for analysis.

MRSA Genetic Studies

MRSA isolates were tested by means of polymerase chain reaction (PCR) to detect the PVL gene [12]. According to the results of PCR, the etiology of HAP/VAP was characterized as MRSA PVL positive in isolates carrying the PVL gene or MRSA PVL negative in isolates not carrying the PVL gene. MRSA isolates were further characterized by USA type by means of pulse-field gel electrophoresis [12]. Staphylococcal cassette chromosome (SCC) *mec* type was defined by PCR methodology [12].

Study Definitions

The following 3 criteria had to be present for the patient to be included in the study:

1. Meeting the Centers for Disease Control and Prevention (CDC) definition for HAP or VAP [13].
2. Respiratory culture positive for MRSA.
3. Genetic analysis performed for the isolated MRSA strains.

There were no exclusion criteria. Severity of disease was assessed by calculating the Acute Physiology and Chronic Health Evaluation II (APACHE II) score at the time of diagnosis of HAP/VAP [14]. Duration of mechanical ventilation in days was calculated by subtracting the date of pneumonia diagnosis from the date of extubation. Length of stay in the ICU was calculated by subtracting the date of pneumonia diagnosis from the date of discharge from the ICU. Length of stay in the hospital was calculated by subtracting the date of pneumonia diagnosis from the date of discharge from the hospital. Mortality was defined as all-cause mortality at hospital discharge.

Study Variables

The predictor variable was the presence or absence of the PVL gene. The primary outcome variables were APACHE II score to define severity of illness at time of diagnosis and mortality to define clinical outcome at hospital discharge. The secondary clinical outcome variables were 28-day mortality, length of stay in the hospital, length of stay in the ICU, and duration of mechanical ventilation. The following confounding variables were utilized during the evaluation of clinical outcomes: age, sex, diabetes mellitus, AIDS, cancer, chemotherapy, chronic obstructive pulmonary disease, steroid use, end-stage renal disease, end-stage liver disease, APACHE II score, multilobar infiltrates in chest radiograph, evidence of severe sepsis on the day of pneumonia diagnosis, and blood cultures positive for MRSA.

Statistical Analysis

Baseline characteristics of patients with MRSA HAP/VAP carrying the PVL gene and of patients with MRSA HAP/VAP without the

PVL gene were compared. The χ^2 or Fisher exact test was used to compare categorical variables, and the Mann–Whitney *U* test was used to compare continuous variables. Kaplan–Meier survival curves were constructed to examine the length of hospital stay and length of ICU stay after HAP/VAP diagnosis for all patients. A survival curve for duration of mechanical ventilation was constructed for patients with VAP. Log-rank tests were used to assess statistical differences between the survival curves.

Traditional methods for the adjustment of multiple confounding variables in multivariate analysis were not appropriate because of the small number of outcomes and risk of overfitting the regression models. To circumvent this statistical limitation, a propensity score approach was used [15]. A logistic regression model was used to condense all variables in Table 1 into the propensity score. A linear regression model was used to examine the effect of PVL status on APACHE II score while adjusting for the propensity score. A modified Poisson regression model with robust error variance was then used to determine the effect of PVL status on mortality while adjusting for the propensity score [16]. The propensity score was also used to adjust for confounding effects in the relationship between PVL status and the secondary outcomes. A similar Poisson model was used for 28-day mortality, whereas Cox proportional hazards regression models were constructed for each of the 3 time-to-event outcomes. *P* values of $\leq$.05 were considered to reveal a statistically significant difference in all analyses. SAS, version 9.2 (SAS), and MedCalc, version 11 (MedCalc Software), were used for all analyses.

Table 1. Characteristics of Patients With Hospital-Acquired Pneumonia/Ventilator-Associated Pneumonia (HAP/VAP) by Panton-Valentine Leukocidin (PVL) Status

Variable	PVL positive (n = 29)	PVL negative (n = 80)	*P*
Age, mean years ± SD	53 ± 15.2	62 ± 16.6	.008
Age ≥65 years	6 (20.7)	38 (47.5)	.01
Male sex	19 (65.5)	58 (72.5)	.48
Diabetes mellitus	5 (17.2)	28 (35)	.075
AIDS	0 (0)	1 (1.3)	.55
Cancer	3 (10.3)	14 (17.5)	.36
Chemotherapy	1 (3.4)	2 (2.5)	.79
COPD	6 (20.7)	12 (15)	.48
Steroid use, proportion (%)	4/28 (14.3)	9 (11.3)	.67
End-stage liver disease	2 (6.9)	1 (1.3)	.11
End-stage renal disease	1 (3.4)	7 (8.8)	.35
APACHE II score, mean ± SD	21 ± 7.5	20 ± 6.2	.67
Multilobar involvement	10 (34.5)	24/76 (31.6)	.78
Severe sepsis	21 (72.4)	59 (73.8)	.89
Blood cultures positive for MRSA	5/25 (20)	7/77 (9.1)	.14

Data are no. (%) of patients, unless otherwise indicated.

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; COPD, chronic obstructive pulmonary disease; MRSA, methicillin-resistant *Staphylococcus aureus*; SD, standard deviation.

RESULTS

Patient Characteristics

A total of 109 cases of MRSA HAP/VAP were identified. Of those, 29 (27%) carried the PVL gene. Table 1 compares the baseline patient characteristics of patients with MRSA HAP/VAP carrying the PVL gene and those of patients with MRSA HAP/VAP not carrying the PVL gene. Patients with PVL^+ MRSA were younger than their PVL^- counterparts, and this difference was statistically significant. All patients were treated with anti-MRSA therapy on the day of diagnosis of HAP/VAP. Empiric therapy, defined as treatment during the first 48 hours, was performed with vancomycin in 92% of patients. MRSA was isolated from sputum specimens in 37% of patients, from tracheal aspirate specimens in 28% patients, and from bronchoalveolar lavage specimens in 35% patients.

Severity of Disease

Mean APACHE II scores were similar in patients with HAP/VAP due to MRSA regardless of PVL status (21 ± 8 for MRSA carrying the PVL gene vs 20 ± 6 for MRSA not carrying the PVL gene; $P = .67$). The presence of the PVL gene did not predict APACHE II scores in patients with HAP/VAP ($\beta = 1.95$; standard error = 1.7; $t = 1.2$; $P = .24$).

Methicillin-Resistant *Staphylococcus aureus* Characteristics

Table 2 describes selected characteristics of the MRSA strains. Of those strains carrying the PVL gene, 100% were SCC*mec* type IV, whereas only 25% of those strains not carrying the PVL gene had this SCC*mec* type ($P < .001$). Very few of the strains carrying the PVL gene were resistant to clindamycin (7%), whereas 79% of the strains not carrying the PVL gene were resistant to clindamycin ($P < .001$).

Clinical Outcomes

Table 3 compares the outcomes of patients with MRSA HAP/VAP carrying the PVL gene with those of patients with MRSA HAP/VAP without the PVL gene. For the primary study outcome of mortality at hospital discharge, there was no statistically significant difference ($P > .99$) between patients with MRSA HAP/VAP carrying the PVL gene (10%) and patients with MRSA HAP/VAP not carrying the PVL gene (10%). For the secondary outcome of 28-day mortality, there was no statistically significant difference ($P = .59$) between patients with MRSA HAP/VAP carrying the PVL gene (32%) and patients with MRSA HAP/VAP not carrying the PVL gene (38%). Length of hospital stay, length of ICU stay, and duration of mechanical ventilation were similar between patients with MRSA HAP/VAP carrying the PVL gene and patients with MRSA HAP/VAP without the PVL gene.

Table 2. Characteristics of Methicillin-Resistant *Staphylococcus aureus* Strains Causing Hospital-Acquired Pneumonia/Ventilator-Associated Pneumonia by Panton-Valentine Leukocidin (PVL) Status

Variable	PVL positive (n = 29)	PVL negative (n = 80)	*P*
SCC*mec* type			<.001
I	0 (0.0)	0 (0.0)	
II	0 (0.0)	58 (72.5)	
III	0 (0.0)	2 (2.5)	
IV	27 (100.0)	20 (25.0)	
USA-300	29 (100)	7 (8.8)	<.001
Clindamycin resistant	2 (6.9)	63 (78.8)	<.001
Erythromycin resistant	27 (93.1)	74 (92.5)	>.99

Data are no. (%) of patients, unless otherwise indicated.

Abbreviation: SCC, staphylococcal cassette chromosome.

Figures 1 and 2 depict the Kaplan–Meier survival curves for length of hospital stay and length of ICU stay, respectively, for patients with MRSA HAP/VAP carrying the PVL gene, compared with patients with MRSA HAP/VAP not carrying the PVL gene. Figure 3 represents the Kaplan–Meier survival curve for duration of mechanical ventilation for patients with VAP due to MRSA carrying the PVL gene, compared with patients with VAP not carrying the PVL gene.

Results of the multivariate analyses for clinical outcomes can be found in Table 4. The presence of the PVL gene was not associated with any of the 5 clinical outcomes examined.

DISCUSSION

This study indicates that almost one-third of the patients with HAP/VAP due to MRSA are infected with strains carrying the PVL gene. PVL status does not influence severity of disease at time of HAP/VAP diagnosis. Patients with HAP/VAP infected with MRSA strains carrying the PVL gene are not at increased risk of mortality when compared with patients with MRSA HAP/VAP not carrying the PVL gene. Length of stay in the hospital and ICU, as well as duration of mechanical ventilation, are not different in patients with MRSA HAP/VAP infected with PVL-positive versus PVL-negative strains.

The literature indicates that MRSA strains carrying the PVL gene are now producing a substantial number of healthcare-associated infections [10, 11]. Our study supports the concept that MRSA carrying the PVL gene is now an emerging nosocomial pathogen.

Our findings seem to indicate that PVL exotoxin does not play a role in the pathogenesis of MRSA HAP or VAP. One possible explanation for our findings is that in hospitalized

Table 3. Clinical Outcomes of Patients With Methicillin-Resistant *Staphylococcus aureus* Hospital-Acquired Pneumonia/Ventilator-Associated Pneumonia by Panton-Valentine Leukocidin (PVL) Status

Outcome	PVL positive	PVL negative	*P*
In-hospital mortality, proportion (%)	3/29 (10.3)	8/80 (10)	>.99
28-day mortality, proportion (%)	8/25 (32)	24/63 (38.1)	.59
Length of hospital stay, mean days ± SD	20.4 ± 8.1	21.0 ± 7.6	.74
Length of stay in the ICU, mean days ± SD	17.7 ± 9.6	17.1 ± 9.7	.68
Time receiving mechanical ventilation, mean days ± SD	16.1 ± 11.2	15.5 ± 10.5	.78

Data are no. (%) of patients, unless otherwise indicated.

Abbreviations: ICU, intensive care unit; SD, standard deviation.

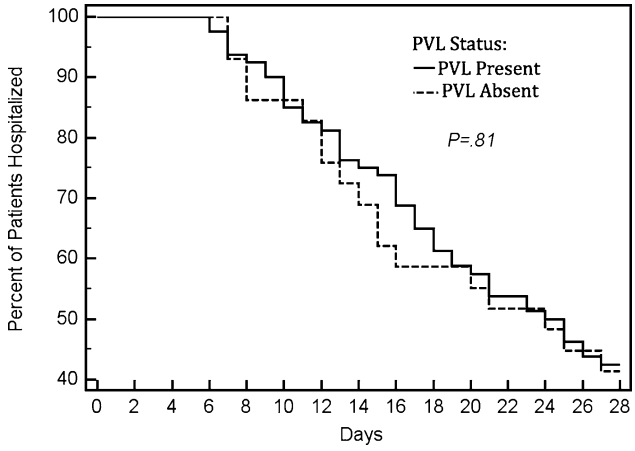

Figure 1. Kaplan–Meier survival curve for patients with hospital-acquired pneumonia/ventilator-associated pneumonia indicating length of hospital stay by Panton-Valentine leukocidin (PVL) status.

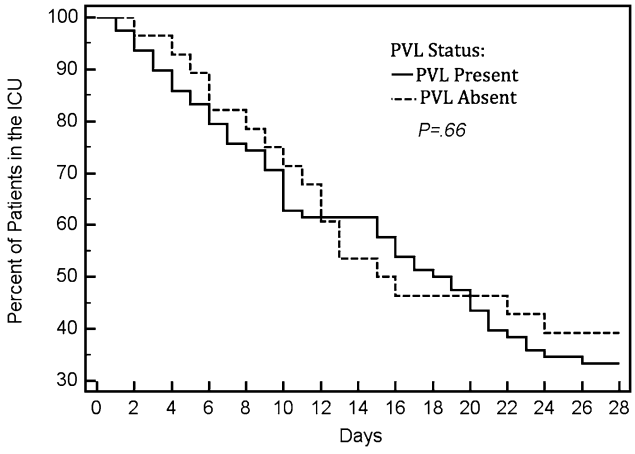

Figure 2. Kaplan–Meier survival curve for patients with hospital-acquired pneumonia/ventilator-associated pneumonia indicating length of intensive care unit stay by Panton-Valentine leukocidin (PVL) status.

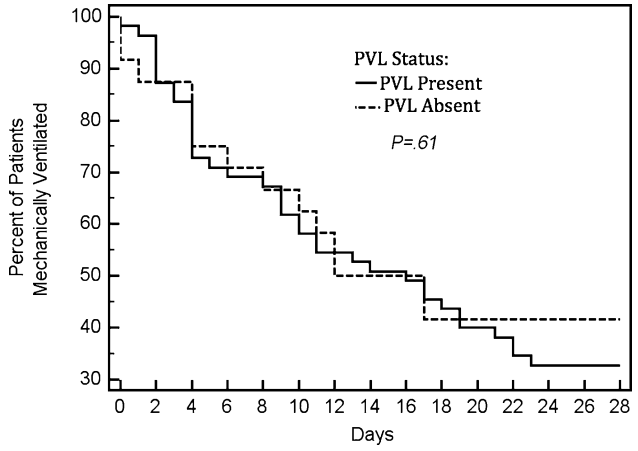

Figure 3. Kaplan–Meier survival curve for patients with ventilator-associated pneumonia indicating duration of mechanical ventilation by Panton-Valentine leukocidin (PVL) status.

patients with HAP/VAP, MRSA strains carrying the PVL gene are not expressing the potent PVL exotoxin. Phylogenetically, MRSA USA300 strains that carry the PVL gene originated in the community, and it can be speculated that these strains need to express more virulence factors in order to infect healthy hosts in the community. On the other hand, as these species move into healthcare facilities, MRSA strains may not need to express these virulence factors in order to infect immunocompromised, hospitalized hosts.

Rapid institution of appropriate antibiotic therapy is the first, and perhaps the most important, aspect of treatment for MRSA pneumonia [9]. Initiation of treatment for patients with CAP is usually delayed for several days from the onset of symptoms until the time patients present to the hospital. Onset of treatment in hospitalized ICU patients often occurs within 24 hours after the development of signs of symptoms compatible with the diagnosis of HAP/VAP. Early institution of antimicrobial treatment in patients with HAP/VAP may substantially reduce the capability of MRSA to produce the PVL exotoxin regardless of the initial anti-MRSA antibiotic selection. Because empiric therapy was performed with vancomycin in 92% of the population, in this study we were unable to evaluate the role of linezolid on clinical outcomes.

Table 4. Results of Multivariate Analyses

Outcome	RR/HR (95% CI)[a]	*P*
In-hospital mortality	0.98 (.16–6.15)	.99
28-day mortality	1.07 (.45–2.51)	.88
Length of stay in the hospital	0.86 (.47–1.68)	.71
Length of stay in the ICU	0.74 (.40–1.38)	.34
Time receiving mechanical ventilation	0.88 (.28–1.19)	.14

Abbreviations: CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; RR, risk ratio.

[a] RR calculated for in-hospital and 28-day mortality; HR calculated for length of stay in the hospital, length of stay in the ICU, and time receiving mechanical ventilation.

Community-acquired pneumonia due to MRSA carrying the PVL gene is considered a toxin-mediated disease, and the use of antibiotics that suppress toxin production has been suggested in these patients [8, 9]. It should be emphasized that this recommendation is currently based only on expert opinion without supporting clinical data. Given our study findings that the presence of the PVL gene was not associated with any of the 5 clinical outcomes examined, therapies that inhibit PVL production may not offer advantages in the management of patients with HAP/VAP caused by MRSA strains carrying the PVL gene. The possible impact of the host immune status on MRSA phenotype requires further investigation. Future research is also necessary to clearly define the role of toxins or exotoxins in the pathogenesis of MRSA infections in the community and in hospitals. If other staphylococcal toxins are involved in the pathogenesis of HAP/VAP, specific therapies that suppress toxin production or activity may warrant testing.

Our study has several limitations. First, the diagnosis of pneumonia was based on CDC criteria and not on quantitative bronchoalveolar lavage cultures. Using clinical criteria for diagnosis of HAP/VAP may produce overdiagnosis. Second, the etiologic diagnosis of MRSA HAP/VAP was based on respiratory samples including sputum and tracheal aspirates. Using samples other than bronchoalveolar lavage to characterize the etiology of HAP/VAP may include patients colonized but not infected with MRSA.

A strength of our data includes enrollment of patients representing different geographic areas in the United States, making our results more generalizable.

In conclusion, the results of this study provide evidence that the increased severity of disease and poor patient outcomes reported in patients with CAP due to MRSA strains carrying the PVL gene are not evident in patients with HAP/VAP infected with MRSA strains carrying the PVL gene. Although there is an epidemiologic correlation between PVL, MRSA, and poor outcomes in patients with CAP, additional studies evaluating the role of other virulence determinants are needed for patients with MRSA HAP/VAP.

Notes

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Potential conflicts of interest. K. D. F. and E. G. S. are employed by Pfizer Inc. M. A. has received research support from Ortho-McNeil and also honoraria from lectures for Pfizer. J. E. M. has received honoraria from

Madcat Healthcare, Pfizer, Astellas, and Merck for participation in advisory boards, and educational grants from Fallon Medica LLC. D. H. K. has received research support and served as a consultant to and is on the speakers' bureau of Pfizer. J. A. R. has received research support from Pfizer, is a consultant for Pfizer, and has received honoraria from Pfizer, Merck, and Wyeth for lectures. M. J. Z. has received research support from Astellas, Cubist, Pfizer, and Johnson & Johnson and is on the speakers' bureaus of Astellas and Cubist. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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