Risk Factors Associated with Potentially Antibiotic-Resistant Pathogens in Community-Acquired Pneumonia

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Abstract

Rationale: To identify pathogens that require different treatments in community-acquired pneumonia (CAP), we propose an acronym, "PES" (*Pseudomonas aeruginosa*, *Enterobacteriaceae* extended-spectrum β-lactamase–positive, and methicillin-resistant *Staphylococcus aureus*).

Objectives: To compare the clinical characteristics and outcomes between patients with CAP caused by PES versus other pathogens, and to identify the risk factors associated with infection caused by PES.

Methods: We conducted an observational prospective study evaluating only immunocompetent patients with CAP and an established etiological diagnosis. We included patients from nursing homes. We computed a score to identify patients at risk of PES pathogens.

Measurement and Main Results: Of the 4,549 patients evaluated, we analyzed 1,597 who presented an etiological diagnosis. Pneumonia caused by PES was identified in 94 (6%) patients, with 108 PES pathogens isolated ($n = 72$ *P. aeruginosa*, $n = 15$ *Enterobacteriaceae* extended-spectrum β-lactamase positive, and $n = 21$ methicillin-resistant *Staphylococcus aureus*). These patients were older ($P = 0.001$), had received prior antibiotic treatment more frequently ($P < 0.001$), and frequently presented with acute renal failure ($P = 0.004$). PES pathogens were independently associated with increased risk of 30-day mortality (adjusted odds ratio = 2.51; 95% confidence interval = 1.20–5.25; $P = 0.015$). The area under the curve for the score we computed was 0.759 (95% confidence interval, 0.713–0.806; $P < 0.001$).

Conclusions: PES pathogens are responsible for a small proportion of CAP, resulting in high mortality. These pathogens require a different antibiotic treatment, and identification of specific risk factors could help to identify these microbial etiologies.

Keywords: community-acquired pneumonia; antibiotic therapy; infection

(Received in original form July 8, 2014; accepted in final form December 18, 2014)

Supported by a European Respiratory Society long-term fellowship (E.P.).

Author Contributions: conception and design—E. Prina, O.T.R., and A.T.; analysis and interpretation of the data—E. Prina, O.T.R., and A.T.; recruitment of patients and data collection—E. Polverino and C.C.; drafting the manuscript—E. Prina, O.T.R., and A.T.; review of the manuscript for important intellectual content—R.M., J.P.d.l.B., M.F., L F. and J.M.

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This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Ann Am Thorac Soc Vol 12, No 2, pp 153–160, Feb 2015

DOI: 10.1513/AnnalsATS.201407-305OC
Internet address: www.atsjournals.org

In recent years, concern has arisen regarding pathogens in community-acquired pneumonia (CAP) because of the recognition of some problematic pathogens (1, 2). These pathogens require different antibiotics than those used in the initial empiric treatment recommended by the CAP guidelines. To overcome this problem, the guideline proposed by the Infectious Disease Society of America/American Thoracic Society (3) suggested health care–associated pneumonia (HCAP) as a new definition of pneumonia occurring in patients in contact with health care systems, and, for this reason, with higher risk of infections due to resistant pathogens. However, the definition of HCAP has presented many limitations, including the following: it could lead to overtreatment in some patients; it does not consider some important risk factors associated with

nosocomial pathogens; and the data on the microbial spectrum were conflicting (4). Nursing home–acquired pneumonia represents a subgroup of HCAP, and conflicting data exist regarding its microbiology. Indeed, a recent case–control study demonstrated that nursing home–acquired pneumonia presented an etiology similar to that of CAP (5).

The acronym, "ESKAPE" (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella species*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter species*) was proposed to identify the pathogens responsible for nosocomial infections that could evade antibiotic treatment (6). ESKAPE pathogens are potentially multiresistant, and they require different antibiotic treatment and are associated with high mortality. In lung infections, this concept has been explored in ventilator-associated pneumonia; however, it has never been explored in CAP (7, 8). To translate and customize this approach for patients with CAP, and to identify pathogens that are not correctly covered by initial empiric treatment, we propose the acronym, "PES" (*P. aeruginosa*, *Enterobacteriaceae* extended-spectrum β-lactamase positive [$ESBL^+$], and methicillin-resistant *Staphylococcus aureus* [MRSA]).

The aim of our study was to compare the clinical characteristics and outcomes of immunocompetent patients with CAP resulting from PES pathogens versus CAP from other pathogens and, secondarily, to identify the risk factors associated with infection with PES.

Methods

Study Population and Data Collection

We prospectively assessed patients aged 16 years and over with a diagnosis of CAP at the Hospital Clinic, Barcelona, Spain from November 1996 to December 2011. The Ethics Committee of the hospital approved the study (registration no. 2,009/5,251).

Pneumonia was defined as a new pulmonary infiltrate observed on a chest radiograph at admission with symptoms and signs of a lower respiratory tract infection. We excluded patients with previous use of oral corticosteroids (≥10 mg prednisone-equivalent/d for at least 2 wk), other immunosuppressive therapy, active neoplasms, human immunodeficiency virus infection, or active tuberculosis. We included patients from nursing homes.

The following parameters were recorded upon admission: age; sex; tobacco and alcohol consumption; inhaled corticosteroid treatment; nursing home; comorbidities; previous antibiotics taken in the last month; previous pneumonia; vaccination status; clinical symptoms and signs; arterial blood gases; chest radiograph; laboratory parameters; and therapy.

We calculated the pneumonia severity index (PSI) (9) on admission. Data on the length of stay, 30-day mortality, and complications were collected. We followed up the patients until hospital discharge, and all survivors were re-examined or at least contacted by telephone 30 days after discharge from the hospital.

The patients were divided into two groups: the PES group, comprised of patients affected by PES; and the no-PES group, comprised of the patients with the remaining etiologies.

Empirical antibiotic treatment was considered adherent when it followed the Spanish CAP guidelines (10). In this study, we defined chronic respiratory disease as the presence of chronic obstructive pulmonary disease or bronchiectasis. Chronic obstructive pulmonary disease was defined according to the American Thoracic Society/European Respiratory Society criteria (11). Altered mental status was defined as a Glasgow coma scale <15. Chronic kidney disease was defined by a history of decreased kidney function (defined as a glomerular filtration rate <60 ml/min/1.73 m^2) for 3 or more months. According to the site-of-care decision, patients could be admitted to the hospital (to general ward or intensive care settings) or evaluated in an emergency department for up to 24 hours (observation status), and then treated outside the hospital (12).

Microbiological Evaluation

The criteria for the microbiological diagnosis are described in the online supplement.

To define the PES group, we considered all the *P. aeruginosa* cases, because they are missed by the usual empirical antibiotic coverage suggested by the guidelines. MRSA was defined as *Staphylococcus* with *in vitro* resistance to oxacillin, corresponding to a minimum inhibitory concentration ≥4 μg/ml. *Enterobacteriaceae* was defined as $ESBL^+$ by observation of resistance to oxyimino-β-lactam substrates that confer resistance to most β-lactam antibiotics, including penicillin, cephalosporin, and aztreonam.

Statistical Analysis

The categorical and continuous data are presented as the number (percentage) and as the mean (±SD) (or the median and interquartile range), respectively. The categorical variables were compared with the Chi-square or Fisher's exact tests. The quantitative continuous variables were compared using the unpaired Student's *t* test or the Mann-Whitney test for the normally and nonnormally distributed variables, respectively.

The risk factors associated with the PES pathogens were fit through a logistic regression model. To construct this multivariate analysis, all the candidate variables with *P* less than 0.25 (13) in the univariate analysis were included in the initial model. A parsimonious model was automatically selected using a likelihood ratio backward elimination method (14). We constructed other multivariate models to identify the independent risk factors associated only with *P. aeruginosa*, and all the steps described previously here were performed. To evaluate the role of the PES pathogens on 30-day mortality, the multivariate logistic regression included the selection of candidate variables with *P* less than 0.25 in the univariate analysis related to the PES pathogens or 30-day mortality.

All the multivariate models had the continuous variables assessed for the assumption of linearity in the logit. Single colinearity was evaluated using Pearson's correlation among the independent variables, and the multicolinearity was evaluated with the variance inflation factor. The odds ratio and corresponding 95% confidence interval (95% CI) for each variable were computed. The discriminative ability of the models to predict the outcome of the patients was assessed by the area under the receiver operating characteristic (ROC) curve. The calibration ability of the model was evaluated using the Hosmer-Lemeshow goodness-of-fit statistic. The ROC curves were used to identify the optimal cutoff values for the outcome associations.

Based on the final multivariate model with risk factors for PES, a predictive additive scoring tool was derived. The data were managed throughout the steps suggested by Steyerberg (14). First, we

ran an internal validation of the model generating 1,000 datasets of the same sample size using bootstrap sample with replacement. The difference between the coefficients in the original sample and bootstrap samples is a surrogate of the overfitting/"optimism" of the model. Subsequently, we multiplied the original coefficients by the slope index generated from the bootstrapping to correct for optimism. Therefore, the final coefficients were rounded and converted to integers. Risk classes were defined by the quartiles of the created score.

A two-sided *P* values of 0.05 or less were considered statistically significant. The statistical analyses were performed using SPSS 19.0 software (SPSS Statistics for Windows, Version 19.0; IBM, Armonk, NY) and the R free source statistical package version 2.15.2 and comprehensive-R archive network-specific libraries (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient Characteristics

During the study period, 4,549 patients were evaluated for CAP, and we analyzed 1,597 patients who presented an etiological diagnosis. The number of positive samples was 1,784 (Figure 1). A total of 80% of the patients ($n = 1,278$) was admitted, whereas 20% ($n = 319$) of the patients were treated outside the hospital.

The patients with pneumonia resulting from PES pathogens were older, had more frequently received antibiotics in the previous 30 days, and had a higher prevalence of comorbidities (chronic kidney disease, chronic respiratory disease, diabetes mellitus, and chronic heart failure; Table 1).

The PES group more frequently manifested dyspnea and altered mental status at diagnosis than did the other patients. Fewer patients in the PES group presented with fever and lower C-reactive protein levels. Regarding the severity, the PES group showed higher pneumonia severity by the PSI scores (Table 1).

Microbiologic Assessment

The most frequent pathogens were *Streptococcus pneumoniae*, respiratory viruses, and atypical bacteria (Table 2). Polymicrobial etiology was detected in 193 patients (12%). A total of 94 patients (6%) presented with pneumonia caused by PES pathogens, and 108 PES pathogens were isolated ($n = 72$ *P. aeruginosa*, $n = 15$ $ESBL^+$, and $n = 21$ MRSA); 12 patients presented with more than one PES pathogen (eight patients, *P. aeruginosa* + *Enterobacteraceae*; two patients, *P. aeruginosa* + MRSA; two patients with the three pathogens). Among the PES group, 52% of patients presented a presumptive diagnosis (detected by sputum examination) and 48% of the patients with definitive diagnosis (detected by other samples). The source for each PES pathogen is specified in Table E1 in the online supplement. PES pathogens were detected in 15 of 327 patients (5%) treated outside the hospital after Emergency Department visit: 14 patients infected by *P. aeruginosa* (one of them with coinfection with MRSA and another one coinfected with $ESBL^+$), and one patient infected by MRSA.

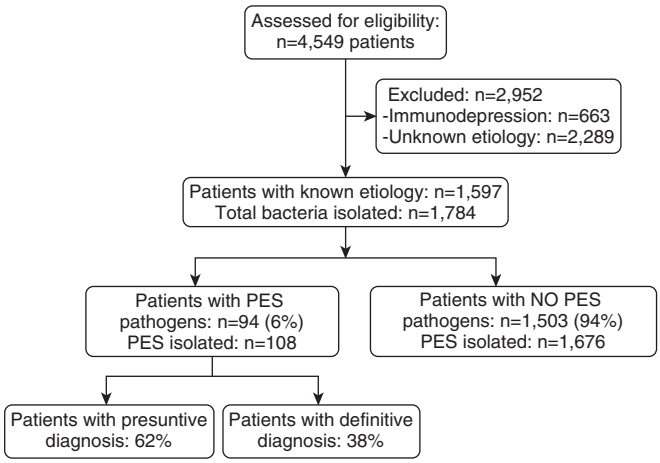

Figure 1. The study flowchart. PES = *Pseudomonas aeruginosa*, *Enterobacteriaceae* extended spectrum β-lactamase, and methicillin-resistant *Staphylococcus aureus*.

Antibiotic Treatment

In the overall population, 78% (1,243/1,597) of the entire cohort received an empirical antibiotic treatment compliant with the Spanish guideline. Among the PES group, 73% (69/94) received compliant empiric antibiotic coverage, without differences between the PES and no-PES groups ($P = 0.287$). According to culture results, adequate antibiotic coverage was observed only in 17% (16/94) of patients with PES pathogens (Table E2). Patients with PES who received adequate empiric antibiotic treatment regarding culture results had similar mortality rates than patients who received inadequate empiric antibiotic (18% versus 15% [$P = 0.738$], respectively).

Risk Factors for PES Pathogens

We identified the following seven independent predictors of PES pathogens at the time of diagnosis (Table 3): age 65 years or older; male sex; previous antibiotic use; chronic respiratory disease; chronic kidney disease; altered mental status; and temperature over 37.8°C on arrival at the first evaluation. The model had a discrimination based on the area under the curve of 0.759 (95% CI, 0.713–0.806; $P < 0.001$) and good calibration by the Hosmer-Lemeshow test (Chi-square = 9.862; $P = 0.275$).

Based on the model, we constructed the PES score depicted in Table 4. In our sample ($n = 1,597$), the score ranged from 0 to 12 points, with a median of 3 (2–5) points. Its performance in identifying patients with PES pathogens was an area under the curve–ROC of 0.754 (0.708–0.801), and it was calibrated (Chi-square = 6.591; $P = 0.360$). Clustering the patients with PES ($n = 94$) according to the score, we found 70% of patients in the high-risk group (score, ⩾5), 29% of patients with PES in the moderate-risk group (score, 2–5), and 1% of patients in the low-risk group (score, ⩽1) (Figure 2). The best cutoff was 5 points, with a sensitivity of 70%, a specificity of 71%, and an accuracy of 71%. According to our score, if we intend to treat high-risk patients (PES score, ⩾5), 28% of the entire cohort should be treated with a broad-spectrum antibiotic.

Table 1. General characteristics of study population at initial evaluation: *Pseudomonas aeruginosa*, *Enterobacteriaceae* extended-spectrum β-lactamase, methicilline-resistant *Staphylococcus aureus* versus the No–*Pseudomonas aeruginosa*, *Enterobacteriaceae* extended-spectrum β-lactamase, methicilline-resistant *Staphylococcus aureus* group

	PES (*n* = 94)	NO PES (*n* = 1,503)	*P* Value
Demographic data			
Age, yr, mean ± SD	69 ± 15	63 ± 18	0.001
Male sex	77 (82)	951 (63)	<0.001
Previous antibiotics in the last month	36 (36)	319 (22)	<0.001
Smokers	64 (68)	893 (59)	0.096
Active alcohol abuse	9 (10)	99 (7)	0.224
Inhaled corticosteroid	39 (42)	254 (17)	<0.001
Nursing Home	8 (9)	49 (3)	0.015
Comorbidities			
Chronic respiratory disease	44 (47)	315 (21)	<0.001
COPD	33 (35)	279 (19)	<0.001
Bronchiectasis	11 (11)	36 (2)	<0.001
Chronic heart failure	24 (26)	222 (15)	0.004
Diabetes mellitus	22 (23)	218 (15)	0.026
Chronic liver disease	8 (8)	87 (6)	0.281
Chronic kidney disease*	15 (16)	81 (5)	<0.001
Neurologic disease	18 (19)	214 (14)	0.199
Characteristics at pneumonia diagnosis			
Dyspnea, n (%)	83 (89)	980 (66)	<0.001
Cough, *n* (%)	77 (83)	1242 (83)	0.932
Fever, *n* (%)	64 (68)	1249 (84)	<0.001
Altered mental status, *n* (%)	35 (37)	365 (24)	0.003
Respiratory rate, per min	30 ± 7	27 ± 7	<0.001
Systolic blood pressure, mm Hg	130 ± 27	130 ± 26	0.958
Temperature, °C	37.1 ± 1.2	37.6 ± 1.1	<0.001
Laboratory findings			
Leukocyte, cells/mm^3	14,512 ± 6,263	14,706 ± 8,261	0.823
C-reactive protein, mg/dl	16 ± 12	21 ± 12	0.006
Creatinine, mg/dl	1.3 ± 0.9	1.2 ± 0.8	0.302
Pa_{O_2}/Fi_{O_2} ratio	257 ± 72	283 ± 71	0.002
Pneumonia severity index			
Risk class IV–V, *n* (%)	65 (71)	731 (49)	<0.001

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; PES = *Pseudomonas aeruginosa*, *Enterobacteriaceae* extended-spectrum β-lactamase, methicilline-resistant *Staphylococcus aureus*.
Values are given as number (%) unless otherwise stated.
*Regarding ambulatory hemodyalisis, there were only four patients in the no-PES group.

Therefore, it will be possible to increase the coverage of PES pathogens from 17 to 70% considering our score. However, 24% (381/1,597) of patients from the entire cohort classified in the high-risk group would receive a broad-spectrum antibiotic and, thus, these 381 patients could receive an inadequate treatment or be overtreated.

Pathogen-Specific Risk Factors

Within the PES group, the univariate analysis showed that infections from *Enterobacteriaceae* ESBL$^+$ were related to previous antibiotic use, whereas MRSA infections were associated with diabetes mellitus, chronic kidney disease, and altered mental status at diagnosis. Both pathogens were frequently diagnosed in nursing home patients (Tables 5 and 6). Regarding *P. aeruginosa*, previous antibiotic use, chronic respiratory disease, and a Po_2/Fi_{O_2} ratio less than 200 were independent risk factors in the multivariate model, whereas acute flu symptoms and fever were protective factors (Table 7).

Complications and Outcomes

In comparison with the other group, the patients with PES had a longer hospital length of stay and 30-day mortality (both $P < 0.001$; Table E4), and presented higher rates of acute renal failure at admission ($P = 0.004$).

The PES pathogens were an independent variable associated with an increased risk of 30-day mortality (odds ratio = 2.51; 95% confidence interval = 1.20–5.25; $P = 0.015$), adjusted for PSI, altered mental status, septic shock, and adherence to the antibiotic guidelines (Table E5).

Discussion

In a large population of immunocompetent patients with CAP and a defined etiology, we found that the PES pathogens were an independent risk factor for 30-day mortality. We proposed a new acronym and risk factors associated with these pathogens to assist attending physicians in disregarding or suspecting these pathogens, and, thus, to select a more individualized antibiotic treatment and a more aggressive diagnostic etiological approach.

In CAP, prescribing effective empirical antibiotics has been challenging. The problem posed is the balance between selecting the correct initial antibiotic, leading to the excessive use of broader

Table 2. All etiologic isolation

	n (%)
Etiologic diagnosis	1,784
Streptococcus pneumoniae	792 (44)
Respiratory viruses*	287 (16)
Atypical	198 (10)†
Chlamydia pneumoniae	76
Coxiella burnetii	42
Mycoplasma pneumoniae	86
Legionella pneumophila	143 (8)
Haemophilus influenzae	119 (6)
Pseudomonas aeruginosa‡	72 (4)
Enterobacteriaceae	49 (3)§
Escherichia coli	16
Escherichia coli ESBL^{+}‡	10
Klebsiella pneumoniae	9
Klebsiella pneumonia ESBL^{+}‡	3
Enterobacter ESBL^{+}‡	2
Providencia	2
Morganella	1
Proteus	0
Others	9
Staphylococcus aureus	47 (3)
MSSA	26
MRSA‡	21
Other	77 (4)

Definition of abbreviations: ESBL = *Enterobacteriaceae* extended-spectrum β-lactamase; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*.
*Respiratory viruses included: influenza A; influenza B; parainfluenza virus; respiratory syncytial virus; and adenovirus.
†Six cases presented a coinfection of two atypical bacteria.
‡PES pathogens.
§Three cases presented a coinfection of two *Enterobacteriaceae*.

Table 3. Multivariate logistic regression to predict the presence of *Pseudomonas aeruginosa*, *Enterobacteriaceae* extended-spectrum β-lactamase, methicillin-resistant *Staphylococcus aureus* pathogens

	β	OR	95% CI	*P* Value
Age >65 yr	0.596	1.82	1.08-3.05	0.024
Male	0.723	2.06	1.18-3.59	0.011
Previous antibiotic use in the last month	0.909	2.48	1.56-3.94	<0.001
Chronic respiratory disease*	0.790	2.20	1.36-3.57	0.001
Chronic kidney disease	0.958	2.61	1.35-5.02	0.004
Altered mental status	0.696	2.01	1.26-3.19	0.003
Temperature >37.8°C	−0.571	0.57	0.36-0.89	0.014

Definition of abbreviations: CI = confidence interval; OR = odds ratio.
Area under the curve = 0.759 (0.713-0.806), $P < 0.001$; Hosmer-Lemeshow test (Chi-square = 9.862), $P = 0.275$.
*Chronic obstructive pulmonary disease plus bronchiectasis.

spectrum drugs, instead of selecting narrow-spectrum antibiotics and increasing the risk of error in the empirical coverage. In our study, PES micro-organisms accounted for 6% of CAP, representing a small percentage of patients with a higher risk of death compared with other patients. Our incidence rate was in contrast to recent studies, which have reported higher incidences for *P. aeruginosa* (7–19%), $ESBL^+$ (5%), and MRSA (9–22%) (15–18). The observed incidence could be attributed to case-mix differences, because we included only immunocompetent patients, and 20% of our patients were not admitted to the hospital upon CAP diagnosis. The selection of these patients enhances our target and avoids bias in the selection. Moreover, treatment of patients with CAP outside the hospital is quite frequent, and does not exclude their risk of being infected with pathogens that should be treated differently, as was demonstrated in our population (5% of patients who stayed in observational status in the emergency department and were discharged were infected by PES pathogens).

In recent years, the HCAP concept has been subject to criticism in Europe. In particular, this definition could lead to excessive antibiotic treatment in many patients who do not need it, with the risk of increasing resistance, and inadequate treatment of others (19, 20). Recent studies have confirmed that, in Europe, there is no difference in etiology between HCAP and CAP; however, HCAP is a more severe pneumonia, with a poor outcome that is not influenced by the selection of antibiotic treatment, but is most likely related to the comorbidities of patients (5, 21, 22). In 2010, the European Respiratory Society, in collaboration with the European Society for Clinical Microbiology and Infectious Diseases, proposed an updated revision to the guidelines. They declared that the definition of HCAP is not clinically relevant in Europe, and recommended looking for risk factors for multidrug resistant (MDR) micro-organisms to better individualize antibiotic treatment (23).

Previous studies reported scores that aimed to identify patients with a higher risk of resistant pathogens in hospitalized patients with CAP and HCAP, including immunosuppressed patients (16, 18). The scale proposed by Aliberti presented better accuracy in an external validation study (24), and included, within the strongest weighted factors, hospitalization in the preceding 90 days and chronic renal failure (16). Shorr and colleagues (18) published a retrospective study that analyzed patients admitted for a bacterial pneumonia, including immunosuppressed patients. Those authors compared a new score (defined as: 4, recent hospitalization; 3, nursing home; 2, chronic hemodialysis; 1, critically ill) for HCAP criteria to identify patients with resistant pathogens (MRSA, *P. aeruginosa*, *Acinetobacter baumannii*, and extended-spectrum β-lactamase gram-negative bacteria). The new score presented better accuracy than the HCAP definition. Shindo and colleagues (17), in a recent study performed in Asia, analyzed 1,143 hospitalized patients from 10 centers. Although MDR pathogens were more frequently isolated in HCAP (26.6%), they were also detected in CAP (8.6%). The following six independent factors were described for MDR pathogens: prior hospitalization; immunosuppression; previous antibiotic use; use of gastric acid–suppressive agents; tube feeding; and nonambulatory status. Moreover, they defined some additional risk factors for MRSA (including chronic dialysis during the preceding 30 days, positive MRSA history within the previous 90 days, and congestive heart failure). The risk factors were similar in patients with CAP and HCAP (17). Based on their results, the authors proposed the use of broad antibiotic treatment only in those patients with three or more risk factors (but to consider MRSA coverage in the case of two or more risk factors). All of these studies included immunosuppressed patients, who should be considered a special population that requires different diagnostic procedures and initial antibiotic treatment (25). Moreover, they used the term "MDR" pathogens, a nonspecific and confused term used in the current literature (26). As such, a direct comparison between their study and ours would be unreliable.

According to the PES score, patients with a score of 5 points or higher had a high risk of presenting a PES pathogen. If we seek to treat high-risk patients (PES score, ⩾5), 28% of the entire cohort should be treated with a broad-spectrum antibiotic.

Table 4. Score to assess the risk of pneumonia due to *Pseudomonas aeruginosa*, *Enterobacteriaceae* extended-spectrum β-lactamase, methicillin-resistant *Staphylococcus aureus* pathogens

Score to PES Pathogen	Points
Age, yr	
<40	0
40–65	1
>65	2
Male	1
Previous antibiotic use	2
Chronic respiratory disorder*	2
Chronic renal disease	3
At emergency	
Consciousness impairment	2
Fever	−1

Definition of abbreviation: PES = *Pseudomonas aeruginosa*, *Enterobacteriaceae* extended-spectrum β-lactamase, methicilline-resistant *Staphylococcus aureus*.
Area under the curve = 0.754 (0.708–0.801), $P < 0.001$; Hosmer-Lemeshow test (Chi-square = 6.591), $P = 0.360$.
*Chronic obstructive pulmonary disease plus bronchiectasis.

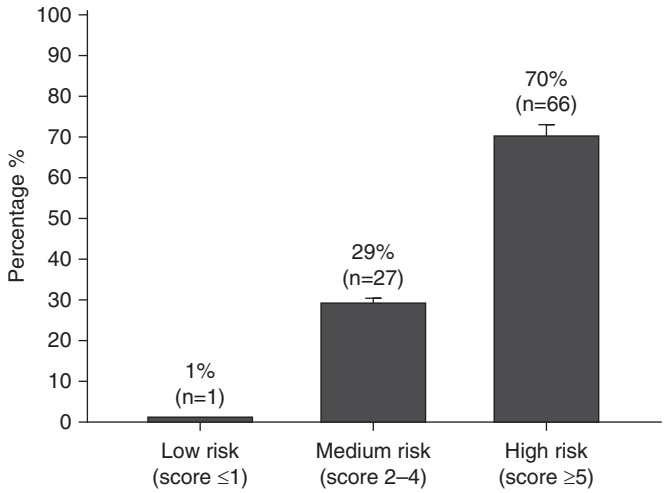

Figure 2. Distribution of patients with *Pseudomonas aeruginosa*, *Enterobacteriaceae* extended-spectrum β-lactamase, methicilline-resistant *Staphylococcus aureus* (PES) pathogens according PES score groups.

Therefore, with the use of our scoring scale, it might be reasonable to observe an increase in the coverage of PES pathogens from 17%, based on the current approach and culture results, to 70% (based in our model). On the other hand, the patients with 1 or 0 point presented a low probability of presenting PES, helping the clinician to consider no antibiotic coverage for potentially resistant pathogens. However, our score needs an external validation and further studies. Our analysis raised another important point that should be evaluated when new scores are introduced in clinical practice. Using our score to treat high-risk patients, 24% of CAP cases would receive a broad-spectrum antibiotic inadvertently, which could be harmful, as it may be inadequate or overtreatment. The association of macrolides with the initial broad-spectrum treatment and a policy of de-escalation after culture results could be a solution when managing patients at high risk of potentially resistant pathogens.

PES pathogens were an independent risk factor for 30-day mortality, which confirms the importance of early diagnosis of these pathogens in CAP. Although their association with poor outcomes needs to be better understood, such as approaching causal inference, some factors could be highlighted as follows: an increased risk of receiving inadequate empirical antibiotic treatment; the particular virulence of pathogens; and the baseline characteristics of the affected patients. The current literature is consistent in reports that patients with HCAP and CAP are affected by similar pathogens (5, 17, 27), and that differences in mortality between these two types of pneumonia might be attributable to individual risk factors rather than to antibiotic treatment (21). The role of status performance and comorbidities in the poor prognosis of patients with PES should be studied further.

Antibiotic treatment for PES must be different from the standard empirical treatment proposed by the CAP guidelines (28). Supporting the findings currently reported in the literature (28, 29), we observed that patients with chronic respiratory disease or severe hypoxemia presented an increased risk of *P. aeruginosa*. In agreement with a recent study (30), the main risk factors associated with MRSA were diabetes mellitus and nursing home residency. Patients at risk of $ESBL^+$ are more likely to be from nursing homes, have had previous antibiotic use, and have had a higher rate of intensive care unit admission.

The first strength of our study is the prospective large cohort of patients with CAP studied. The second strength is the use of the PES concept, which appears here for the first time in the literature. This acronym has some advantages over the confusing term, "MDR" (26) used in previous studies, such as: (*1*) the MDR definition includes a myriad of mixed pathogens, with a widespread range of different resistant patterns; (*2*) the MDR definition varies across the current literature, and could be

Table 5. Baseline differences between *Enterobacteriaceae* extended-spectrum β-lactamase–positive and other pathogens

	ESBL (*n = 15*)	Others (*n = 1,582*)	*P* Value
Demographic data			
Age, yr, mean ± SD	65 ± 12	63 ± 18	0.529
Male sex	12 (80)	1,016 (64)	0.204
Nursing home	3 (20)	54 (3)	0.015
Previous antibiotic	7 (50)	348 (23)	0.024
Comorbidities			
Chronic respiratory disease	9 (60)	712 (45)	0.261
Chronic heart failure	4 (27)	242 (15)	0.270
Diabetes mellitus	2 (13)	238 (15)	>0.99
Chronic liver disease	1 (6)	94 (6)	0.604
Chronic kidney disease	1 (7)	95 (6)	0.608
Neurologic disease	4 (27)	228 (14)	0.257
Symptoms and signs, *n* (%)			
Dyspnea	12 (80)	1,051 (67)	0.410
Fever	13 (87)	1,300 (83)	>0.99
Altered mental status	6 (40)	391 (25)	0.226
Outcome			
Hospital stay, d, mean ± SD	15 ± 8	9 ± 11	0.057
ICU admission	4 (27)	140 (9)	0.040
30-d mortality	3 (20)	93 (6)	0.057
Complication			
Pleural effusion	2 (13)	257 (16)	>0.99
Multilobar pneumonia	3 (20)	418 (26)	0.771
Bacteremia	3 (20)	354 (22)	>0.99
Septic shock	2 (13)	146 (9)	0.644

Definition of abbreviations: ESBL = *Enterobacteriaceae* extended-spectrum β-lactamase; ICU = intensive care unit.
Values are given as *n* (%) unless otherwise stated.

Table 6. Baseline differences between methicillin-resistant *Staphylococcus aureus* and other pathogens

	MRSA (*n* = 21)	Others (*n* = 1,576)	*P* Value
Demographic data			
Age, yr, mean ± SD	70 ± 14	63 ± 18	0.077
Male sex	6 (29)	563 (36)	0.597
Nursing home	3 (14)	54 (3)	0.037
Previous antibiotic	9 (43)	346 (23)	0.036
Comorbidities			
Chronic respiratory disease	9 (43)	712 (46)	0.799
Chronic heart failure	6 (29)	240 (15)	0.120
Diabetes mellitus	9 (43)	231 (15)	0.002
Chronic liver disease	0	95 (6)	—
Chronic kidney disease	4 (19)	92 (6)	0.034
Neurologic disease	5 (24)	227 (14)	0.217
Symptoms and signs, *n* (%)			
Dyspnea	19 (90)	1,044 (67)	0.023
Fever	13 (65)	1,300 (83)	0.065
Altered mental status	10 (48)	387 (25)	0.015
Outcome			
Hospital stay, d, mean ± SD	17 ± 16	9 ± 11	0.040
ICU admission	4 (21)	140 (9)	0.086
30-d mortality	2 (9)	94 (6)	0.363
Complication			
Pleural effusion	2 (9)	257 (16)	0.558
Multilobar pneumonia	6 (29)	415 (26)	0.170
Bacteremia	6 (29)	351 (22)	0.441
Septic shock	3 (15)	145 (9)	0.424

Definition of abbreviations: ICU = intensive care unit; MRSA = methicillin-resistant *Staphylococcus aureus*.
Values are given as *n* (%) unless otherwise stated.

a source of misunderstanding, preventing comparison among reports, and presenting barriers to the clinical decision-making process; (*3*) taking in to account immunocompetent patients with CAP, who are most commonly observed, the available definitions of MDR are not suitable, as some pathogens without MDR patterns also require different antibiotics (i.e., *Pseudomonas*). In contrast, the PES acronym includes the most common "different to treat pathogens" in CAP, helping the clinician to first identify high-risk immunocompetent patients. Identifying them, the attending physician could consider covering these pathogens with two broad-spectrum antibiotics or adding (or not) antibiotics to cover MRSA, although we were not able to definitively identify these patients in our study. The third strength of our study is that it included only immunocompetent patients, which enhanced our inclusion criteria and our generalizability. Indeed, a considerable percentage of patients with CAP is attended at the Emergency Department and treated outside, which does not decrease their risk for PES pathogens. Furthermore, we believe that immunocompromised patients require different management by the clinician, from diagnostic approach and stratification of risk to antibiotic and adjunctive treatments (25). In fact, previous studies looking for MDR pathogens in CAP found immunocompromised status as a major risk factor for MDR pathogens (16, 17).

Table 7. Multivariate logistic regression to predict *Pseudomonas aeruginosa* pathogen

	OR	95% CI	*P* Value
Previous antibiotic use	2.13	1.26–3.60	0.005
Chronic respiratory disease*	3.47	1.97–6.09	<0.001
Po_2/FI_{O_2} <200 mm Hg	2.36	1.28–4.36	0.006
Acute flu symptoms	0.39	0.21–0.72	0.003
Temperature >37.8°C	0.49	0.28–0.85	0.011

Definition of abbreviations: CI = confidence interval; OR = odds ratio.
Area under the curve = 0.745 (0.685–0.804), $P < 0.001$; Hosmer-Lemeshow test (Chi-square = 3.573), $P = 0.827$.
*Mainly for users of inhaled corticosteroid.

The following limitations of the study should be highlighted. First, this is a single-center study, and these results require external validation and a prospective, multicenter trial of the impact on patient outcome to become part of clinical practice. Indeed, an external validation is a fundamental step to testing the generalizability of our findings and to plan an interventional trial. Second, the limited sample regarding MRSA and *Enterobacteriaceae* $ESBL^+$ did not permit us to perform a multivariate analysis for the identification of exclusive risk factors. Third, we lack information regarding any previous colonization of PES pathogens before the CAP episode. Fourth, we do not have data on the time of the first antibiotic dose; however, it is a standard rule in our emergency department to administer the first dose of antibiotics in patients with CAP while the patient is still in the emergency department. Fifth, our cohort had few cases of patients receiving chronic hemodialysis (only four patients), which could be a limitation to identifying this variable as a risk factor for PES pathogens in our study. Finally, although we applied recommended procedures in the development of our model and score, we could not run an external validation, a fundamental step to validating our study.

In conclusion, PES could be a useful acronym for identifying the pathogens that cause CAP and require different antibiotic treatment. Attending physicians should be concerned with obtaining a microbial diagnosis and empirically treating PES pathogens in patients at higher risk (older patients with chronic respiratory disease, chronic kidney disease, and those with altered mental status at presentation). Further studies are needed, and the PES concept must be validated in other populations. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank all of the clinicians who took part in the preparation of this article.

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