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Original Article

Risk factors for drug-resistant pathogens in immunocompetent patients with pneumonia: Evaluation of PES pathogens☆

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ABSTRACT

Rationale: The new acronym, PES pathogens (*Pseudomonas aeruginosa*, *Enterobacteriaceae* extended-spectrum beta-lactamase-positive, and methicillin-resistant *Staphylococcus aureus*), was recently proposed to identify drug-resistant pathogens associated with community-acquired pneumonia.
Objectives: To evaluate the risk factors for antimicrobial-resistant pathogens in immunocompetent patients with pneumonia and to validate the role of PES pathogens.
Methods: A retrospective analysis of a prospective observational study of immunocompetent patients with pneumonia between March 2009 and June 2015 was conducted. We clarified the risk factors for PES pathogens.
Results: Of the total 1559 patients, an etiological diagnosis was made in 705 (45.2%) patients. PES pathogens were identified in 51 (7.2%) patients, with 53 PES pathogens (*P. aeruginosa*, 34; ESBL-positive *Enterobacteriaceae*, 6; and MRSA, 13). Patients with PES pathogens had tendencies toward initial treatment failure, readmission within 30 days, and a prolonged hospital stay. Using multivariate analysis, female sex (adjusted odds ratio [AOR] 1.998, 95% confidence interval [CI] 1.047–3.810), admission within 90 days (AOR 2.827, 95% CI 1.250–6.397), poor performance status (AOR 2.380, 95% CI 1.047–5.413), and enteral feeding (AOR 5.808, 95% CI 1.813–18.613) were independent risk factors for infection with PES pathogens. The area under the receiver operating characteristics curve for the risk factors was 0.66 (95% CI 0.577–0.744).
Conclusions: We believe the definition of PES pathogens is an appropriate description of drug-resistant pathogens associated with pneumonia in immunocompetent patients. The frequency of PES pathogens is quite low. However, recognition is critical because they can cause refractory pneumonia and different antimicrobial treatment is required.

1. Introduction

Pneumonia caused by drug-resistant pathogens (DRPs) has traditionally been confined to hospital-acquired pneumonia. In recent years, resistant pathogens have extended into the community because of developed healthcare delivery and treatment. In 2005, in the joint guidelines proposed by the American Thoracic Society (ATS) and the Infectious Disease Society of America (IDSA), a new category of pneumonia, healthcare-associated pneumonia (HCAP) was defined [1]. The original ATS/IDSA guidelines stated that all patients with HCAP should receive empiric antimicrobial treatment directed at DRPs. However, some limitations have arisen regarding the definition of HCAP, including the following: some of the variables differ between countries; variables predict different multidrug-resistant pathogens (MDRs); and the concept of HCAP could lead to overtreatment in some cases [2,3].

Recently, Prima and colleagues have proposed the acronym PES (*Pseudomonas aeruginosa*, *Enterobacteriaceae* extended-spectrum beta-lactamase-positive, and methicillin resistant *Staphylococcus aureus*) which require different treatments when identified in community-acquired pneumonia (CAP), including nursing

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home–acquired pneumonia [4]. They also defined risk factors for PES pathogens.

The aim of this study was to evaluate PES pathogens in immunocompetent patients with pneumonia by comparing clinical characteristics and outcomes with immunocompetent patients who had no PES pathogens and to subsequently identify the risk factors for PES pathogens in our patients.

2. Materials and methods

2.1. Study population and data collection

We conducted a retrospective analysis of a prospective observational study of immunocompetent patients over 16 years of age with pneumonia who were admitted to the Kurashiki Central Hospital (1150-bed-community hospital) between March 2009 and June 2015. The study was approved by the Kurashiki Central Hospital ethics committee. Informed consent was obtained from all of the patients at the time of admission.

Pneumonia was diagnosed by the presence of new infiltrative shadows on chest x-rays and symptoms such as acute respiratory infection including cough, fever, purulent sputum, dyspnea, and chest pain. We excluded patients with hospital-acquired pneumonia; those who had previously used corticosteroids ($\geq$10 mg prednisolone-equivalent/day); those who had undergone immunosuppressive therapy; and those who had active neoplasms, human immunodeficiency virus infection, or active tuberculosis. Residents of nursing homes or extended-care facilities were included when they were thought to be immunocompetent.

Baseline demographic and clinical data was obtained from all patients upon admission. Data included patient characteristics (age, sex, smoking history, alcohol consumption, nursing home residency, comorbid diseases, previously used antimicrobials, enteral feeding, and performance status by the Eastern Cooperative Oncology Group criteria [5]) in addition to vital signs, pneumonia severity, laboratory data, percutaneous oxygen saturation or arterial blood gases, chest roentgenograms, microbiological examinations, previously used antimicrobials, and clinical outcomes.

The outcome measures were 30-day survival or hospital discharge within 30 days. Initial treatment failure was defined as death during initial treatment or a change in antimicrobial treatment due to poor response to initial therapy. Recurrence was defined as emergence of pneumonia after remission of a prior case. The pneumonia severity index system [6] was used to evaluate pneumonia severity.

All of the variables were compared between patients with PES pathogens and those with non-PES pathogens.

2.2. Microbiological examination

Blood cultures were performed on all patients upon admission. If sputum was available, Gram staining and quantitative cultures were performed. Sputum data was evaluated when Gram staining revealed numerous leukocytes (>25 in a 100X microscopic field) but few epithelial cells. An organism exhibiting heavy growth ($\geq 10^7$ colony forming units [CFU]/mL) on a sputum culture was considered a presumptive pathogen. Moderate growth (10^5 or 10^6 CFU/mL) on the sputum culture was also considered a presumptive pathogen if the Gram staining was compatible with the culture results. *Streptococcus pneumoniae* and *Legionella pneumophila* serogroup 1 were detected using the Binax NOW® rapid immunochromatographic assay (Binax Inc., Portland, ME, U.S.A.). *Mycoplasma pneumoniae* was detected by culturing sputum samples or pharyngeal swabs in a pleuropneumonia-like organism medium and/or by the protective antigen method. *Chlamydophila pneumoniae* was detected by enzyme-linked immunosorbent assay. Standard serological methods using single or paired sera were applied to determine whether there was elevation of antibodies against *M. pneumoniae* (a single increase $\geq$ 320 or a fourfold increase in paired sera) and *C. pneumoniae* (a single increase up to $\geq$ 3.0 as the cut-off index or a $\geq$1.3 cut-off index increase in paired sera). When multiple pathogens satisfied the above criteria in one patient, the pneumonia was defined as polymicrobial. MRSA was defined with a minimum inhibitory concentration $\geq$4 μg/mL to oxacillin. ESBL-positive *Enterobacteriaceae* was defined by observation of resistance to oxymino-β-lactam substances and inhibition by clavulanic acid.

2.3. Statistical analysis

The data were analyzed using the Statistical Analysis System® software program version 9.3 (SAS institute Inc., Cary, NC, U.S.A.). The chi-square test was used to compare categorical data, and Fisher's exact test was used when there were less than 10 data points for any parameter. The unpaired Student's t-test or the Mann–Whitney U test was used for continuous data to compare the two groups. A P value < 0.05 was considered statistically significant.

The risk factors for infection with PES pathogens were analyzed using a logistic regression model. All of the variables with $P < 0.25$ in the univariate analysis were included to construct the multivariate analysis. Odds ratios and 95% CIs were calculated.

We determined the area under the receiver-operating characteristic (ROC) curve for the risk factors defined by the multivariate logistic regression to predict PES pathogens.

3. Results

3.1. Patient characteristics

During the study period, 1559 patients were assessed, and an etiological diagnosis was determined in 705 patients. Of those, 170 patients met the criteria for healthcare-associated pneumonia (HCAP). The baseline patient characteristics of the PES pathogen group and the non-PES pathogen group are shown in Table 1. The patients with PES pathogens were older than the non-PES patients and had a lower frequency of male sex and smoking history but a higher frequency of hospital discharge within 30 days, bronchiectasis, enteral feeding, and poor performance status (PS3 or 4).

Baseline clinical findings at admission are shown in Table 2. The rates of orientation disturbance, low blood pressure, and hypoxemia were not significantly different between the two groups. Laboratory findings showed a high frequency of anemia in the PES patients. Bacteremia was recognized in 6 PES patients and in 56 non-PES patients, revealing no significant difference in frequency.

3.2. Pathogen distribution

The organisms isolated in 705 patients are shown in Table 3. *Streptococcus pneumoniae* was the most common pathogen. A polymicrobial etiology was detected in 108 patients (15.3%). A total of 51 patients (7.2%) presented with pneumonia due to PES pathogens, and 53 PES pathogens were isolated (*P. aeruginosa*: 34; ESBL-positive *Klebsiella pneumoniae*: 3; ESBL-positive *Escherichia coli*: 3; and MRSA: 13). Two patients presented with dual PES pathogens (*P. aeruginosa* + MRSA; *K. pneumoniae* + MRSA). In the PES group, 27 patients (52.9%) met the criteria for HCAP.

Table 1
Baseline characteristics of patients with PES vs. non-PES pathogens.

Variables	PES (n = 51)	Non-PES (n = 654)	*P* value
Age	78.8 ± 13.4	74.5 ± 14.7	0.165
Gender, male, n%	26 (51.0%)	437 (66.8%)	0.021
Smoking history	21 (41.2%)	383 (58.6%)	0.015
Alcohol abuse	0 (0%)	22 (3.4%)	0.183
Nursing home resident	7 (13.7%)	61 (9.3%)	0.305
Hospital discharge within 30 days	18 (35.3%)	113 (17.3)	0.001
Matched with HCAP criteria	27 (52.9%)	143 (21.9%)	0.188
Previous antibiotic treatment, n%	16 (31.4%)	134 (20.5%)	0.067
Comorbidity			
Congestive heart failure, n%	21 (32.1%)	211 (32.3%)	0.192
Chronic obstructive pulmonary disease, n%	11 (21.6%)	153 (23.4%)	0.766
Bronchiectasis, n%	8 (15.7%)	21 (3.2%)	<0.001
Chronic liver disease, n%	4 (7.8%)	31 (4.7%)	0.326
Chronic kidney disease, n%	6 (11.8%)	61 (9.3%)	0.568
Cerebrovascular disease, n%	15 (22.9%)	145 (22.2%)	0.234
Diabetes, n%	7 (13.7%)	118 (18.0%)	0.437
Enteral feeding	10 (19.6%)	15 (2.3%)	<0.001
Poor performance status (3–4), n%	25 (49.0%)	123 (18.8%)	<0.001

Table 2
Clinical findings of patients with PES pathogens vs. non-PES pathogens at admission.

Variables	PES (n = 51)	Non-PES (n = 654)	*P* value
Orientation disturbance, n %	14 (27.5%)	142 (21.7%)	0.342
Systolic BP < 90, n %	5 (9.8%)	34 (5.2%)	0.166
PaO_2/FiO_2 ratio < 250, n %	17 (33.3%)	270 (41.2%)	0.266
Laboratory findings			
BUN ≥ 21 mg/dL, n%	20 (39.2%)	320 (48.9%)	0.181
Na < 130 mEq/dL, n%	6 (11.8%)	43 (6.6%)	0.160
Glucose ≥ 250 mg/dL, n%	3 (5.9%)	51 (7.8%)	0.620
Hematocrit < 30%, n%	13 (19.6%)	71 (10.9%)	0.002
Bacteremia	6 (11.8%)	56 (8.6%)	0.437
PSI (pneumonia severity index)	117 ± 34.9	110 ± 39.4	0.102

3.3. Antimicrobial treatment

All of the patients underwent empirical antimicrobial treatment at the time of admission in accordance with the pneumonia guidelines of the Japanese Respiratory Society [7,8]. Among the PES patients, penicillin with a beta-lactamase inhibitor was most often used, in 36 patients (70.6%). Combination therapy was used in 8 patients (15.7%). Seventeen patients (33.3%) received antimicrobials that covered PES pathogens. Second-line antimicrobials were changed or added to the first-line choices based upon culture results or clinical efficacy in 23 PES patients (45.1%). The mortality rates of patients who received adequate therapy and those who did not receive such treatment were 5.9% and 8.8%, respectively, which revealed no significant difference ($P = 0.854$).

Table 3
Microbiological results.

Organism	n (%)
Streptococcus pneumoniae	319 (45.2%)
Streptococcus anginosus group	41 (5.8%)
Other *streptococcus*	29 (4.1%)
MSSA[a]	50 (7.1%)
MRSA[b]	13 (1.8%)
Moraxella catarrhalis	41 (5.8%)
Haemophilus influenzae	88 (12.5%)
Klebsiella pneumoniae	40 (5.7%)
ESBL+	3
Escherichia coli	16 (2.3%)
ESBL+	3
Pseudomonas aeruginosa	34 (4.8%)
Other *Enterobacteriaceae*	9 (1.3%)
Mycoplasma pneumoniae	18 (2.6%)
Chlamydophila pneumoniae	52 (7.4%)
Chlamydophila psittaci	3 (0.4%)
Legionella spp.	20 (2.8%)
Anaerobes	24 (3.4%)
Influenza virus	6 (0.9%)
Other organisms	12 (1.7%)
Polymicrobial	108 (15.3%)

[a] Methicillin-susceptible *Staphylococcus aureus*.
[b] Methicillin-resistant *Staphylococcus aureus*.

3.4. Clinical outcomes

Table 4 details the clinical outcomes in both groups. The rate of initial treatment failure was higher in the PES group ($P = 0.010$), but 30-day mortality was not significantly different ($P = 0.487$). The PES group had a higher rate of re-admission within 30 days ($P = 0.009$) and a longer hospital stay ($P < 0.001$).

3.5. Risk factors for PES pathogens

By univariate analysis, 10 variables revealed a *P* value < 0.25 and were included to construct the multivariate analysis. The following four variables were thought to be independent predictors of infection with PES pathogens (Table 5): female sex (AOR 1.998, 95% CI 1.047–3.810, $P = 0.036$); admission within 90 days (AOR 2.827, 95%CI 1.250–6.397, $P = 0.013$); poor performance status (PS 3 or 4) (AOR 2.380, 95%CI 1.047–5.413, $P = 0.039$); and enteral feeding (AOR 5.808, 95%CI 1.813–18.613, $P = 0.003$).

Fig. 1 shows the ROC curves for counting numbers of the four risk factors and for the PES scores of our patients as proposed by Prina and colleagues, based on the following seven risk factors for PES pathogens: age 65 years or older, male sex, previous antibiotic use, chronic respiratory disease, kidney disease, altered mental status, or temperature over 37.8 °C. The areas under the curve (AUC) for our variables were 0.660 (95% CI 0.577–0.744) and 0.606 (95% CI 0.524–0.678) which reflects the PES score.

4. Discussion

Recently, many investigations have been undertaken to explore the risk factors for pneumonia due to drug-resistant pathogens. However, each study has pointed to different pathogens as being drug resistant. For example, Shorr and colleagues defined MRSA, *P. aeruginosa*, and ESBL-producing *Enterobacteriaceae* as resistant pathogens and developed a scoring system using the following

Table 4
Clinical outcomes in patients with PES pathogens and non-PES pathogens.

Variables	PES (n = 51)	Non-PES (n = 654)	*P* value
ICU admission, n (%)	3 (5.9%)	51 (7.8%)	0.620
Initial treatment failure[a], n (%)	12 (23.5%)	74 (11.3%)	0.010
30 days mortality, n (%)	4 (5.7%)	36 (5.5%)	0.487
Re-admission within 30 days, n (%)	5 (9.8%)	19 (2.9%)	0.009
Length of hospital stay, days	15.0 ± 9.9	12.8 ± 3.5	<0.001

[a] Death during the initial treatment or a change to other antimicrobials due to a lack of response to the initial ones.

Table 5
Multivariate logistic regression for risk factors for infection with PES pathogens.

variables	Adjusted odds ratio	95% confidential interval	*P* value
Female sex	1.998	1.047–3.810	0.036
Previous antimicrobial use	1.689	0.829–3.438	0.149
Fever < 37.8 °C	0.642	0.335–1.230	0.181
Admission within 90 days	2.827	1.250–6.397	0.013
Hemodialysis	1.736	0.200–15.102	0.617
Poor performance status (3, 4)	2.380	1.047–5.413	0.039
Presence of aspiration	0.896	0.412–1.949	0.782
Chronic heart disease	1.248	0.641–2.427	0.514
Cerebrovascular disease	0.661	0.278–1.568	0.347
Tube feeding	5.808	1.813–18.613	0.003

factors: recent hospitalization, long-term facility residency, ICU admission, and hemodialysis [9]. Aliberti and colleagues defined MRSA, multidrug-resistant *P. aeruginosa*, *Stenotrophomonas maltophilia*, vancomycin-resistant *Enterococcus*, *Acinetobacter baumannii*, and ESBL-producing *Enterobacteriaceae* as multidrug-resistant organisms, and created another scoring system using the following risk factors: chronic renal failure, recent hospitalization, nursing home residency, cerebrovascular disease, diabetes, chronic obstructive pulmonary disease, recent antimicrobial therapy, immunosuppression, home wound care, and home infusion therapy [10,11]. Shindo and colleagues defined MRSA, *P. aeruginosa*, and ESBL-producing *Enterobacteriaceae* as CAP resistant pathogens, and listed six risk factors: prior hospitalization, immunosuppression, previous antibiotic use, use of gastric acid-suppressive agents, enteral feeding, and non-ambulatory status and showed that a counting method of these factors was more sensitive in the detection of MDR pathogens than the two scores describe above [12]. Maruyama and colleagues defined MRSA, *P. aeruginosa*, *A. baumannii*, ESBL-producing *Enterobacteriaceae* as drug resistant and analyzed patients with healthcare-associated pneumonia using the following risk factors based on the definition of Brito and colleagues [13]: recent antibiotics, recent hospitalization, poor functional status, and immunosuppression [14]. However, the subjects of these studies also included HCAP patients with an immunocompromised status.

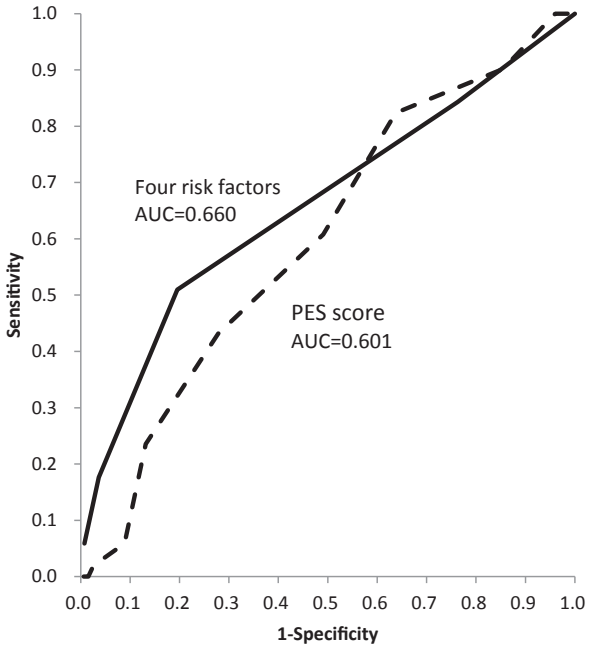

Fig. 1. Receiver operating characteristics (ROC) curve for prediction of PES pathogens. Four risk factors were as follows: female sex, admission within 90 days, poor performance status (3 and 4), and enteral feeding. PES score was calculated as the sum of the following score: age 40–65, 1; >65, 2; male sex, 1; previous antibiotic use, 2; chronic respiratory disorder, 2; chronic renal disease, 3; consciousness impairment, 2; and fever > 37.8 °C, -1.

Recently, there have been many opinions criticizing the concept of HCAP in Europe. They include the following: the definition of HCAP could lead to overtreatment; the concept of HCAP cannot define resistant pathogens accurately; and the definition includes immunocompromised patients [2,3,15,16]. On the other hand, it has been reported that the poor outcomes in HCAP patients were not influenced by resistant pathogens or by selection of antimicrobials, but rather, were related to the general status of the patients including their comorbidities [17–20]. Thus, it is thought to be necessary to analyze risks for drug-resistant pathogens in immunocompetent patients. There have been few studies examining risk factors in only CAP patients. Recently, Torres and colleagues studied CAP cases with bacteremia and listed the risk factors for antibiotic-resistant pathogens (multidrug-resistant *Streptococcus pneumoniae*, MRSA, *P. aeruginosa*, and ESBL-producing *Enterobacteriaceae*) as follows: prior antibiotic treatment, C-reactive protein <22.2 mg/dL, and absence of pleuritic pain [21]. Recent studies have reported that there was no difference in etiology between HCAP and CAP [19,22,23] when subjects were immunocompetent. Therefore, CAP patients and HCAP patients who were thought to be immunocompetent were enrolled into our study. We regarded PES pathogens as drug-resistant pathogens in this population.

In our study, the frequency of PES pathogens in immunocompetent patients with pneumonia was not very high (7.5%), and the

frequency of each PES pathogen was similar to those in Prina's study. Specifically, we detected only a few cases of pneumonia due to ESBL-producing *Enterobacteriaceae*. However, drug-resistant pathogens other than PES were seldom recognized in this study. Thus, it might be appropriate in immunocompetent patients to define PES pathogens as drug-resistant organisms for which common antimicrobials for CAP are ineffective.

Prina and colleagues reported that PES pathogens were independently associated with 30-day mortality. On the other hand, there was no difference with regard to the severity of pneumonia or 30-day mortality between the PES group and the non-PES group in our population. However, the increases in initial treatment failures, re-admission rates, and prolongation of hospital stays were recognized in PES patients, indicate that pneumonia due to PES pathogens is thought to be refractory.

Risk factors for PES pathogens analyzed in our multivariate analysis showed considerable differences compared with those in Prina's previous study. Female sex was dominant, while age was not a significant factor in our patients. Comorbidities and previous use of antimicrobials were also not significant, while recent hospitalization was a risk factor. It is worthy of note that, in our results, poor performance status was an independent risk factor. More than half of our PES patients satisfied the criteria for HCAP. Patients who are immunocompetent but who have poor general status, along with patients undergoing enteral feeding, are thought to be susceptible to PES infection. It is known that aspiration is highly associated with HCAP, especially in patients with poor performance status [24,25]. Many patients with aspiration pneumonia experience recurrent pneumonia and undergo repeated antimicrobial treatments, which leads to infection due to PES pathogens. When we previously investigated the clinical findings of pneumonia in bedridden patients (PS 3 and 4), 6.9% of the cases were due to PES pathogens [26]. These findings seemed to depend on the differences between targeted subjects in both studies. Our study and Prina's are both single-center cohorts, which might reflect the characteristics of the individual institutions. We experienced many elderly patients (average age: 74.8 years), reflecting the aging society in Japan, who exhibited poor performance status. However, the AUCs of both our study and the PES score are quite low. So, we have to do further analysis about the risk factors of drug-resistant pathogens.

Our study had several limitations. First, as mentioned above, this was a single-center study and may have a population bias. Second, there is a possibility that patients were colonized with PES pathogens and that they might not have been the causative agents of pneumonia, even though they were detected in large quantities. We defined strict microbiological criteria in deciding the etiology. However, we often found it difficult to conclude that the detected pathogens were the causative agents in HCAP patients [27]. It was reported that recurrent airway infections led to colonization with *P. aeruginosa* or MRSA in the lower respiratory tract [28]. Third, the frequency of PES pathogens, especially ESBL-producing *Enterobacteriaceae* was relatively low in immunocompetent populations, thus we could not analyze the risks for each pathogen separately. Fourth, we could not analyze the influence of previously prescribed antimicrobials because we did not have details of the exact medications prescribed by previous doctors.

In conclusion, we believe it is appropriate to define PES pathogens as drug resistant in immunocompetent patients. Pneumonia due to PES pathogens is refractory, though the frequency is low. Caution is required in the treatment of pneumonia caused by PES pathogens, especially in patients with poor performance status or enteral feeding.

Conflict of interest

Tadashi Ishida has received honoraria from Pfizer Japan Inc. The other authors have no conflicts of interest.

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