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Early View

Research letter

Difficult to Treat Microorganisms in Patients Over 80 Years with Community-Acquired Pneumonia: The Prevalence of PES Pathogens

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Difficult to Treat Microorganisms in Patients Over 80 Years with Community-Acquired Pneumonia: The Prevalence of PES Pathogens

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To the Editor

In 2015, in a cohort of immunocompetent adults, we reported PES pathogens (*Pseudomonas aeruginosa*, extended spectrum ß-lactamase-producing *Enterobacteriaceae,* and MRSA) in 6% of patients with community-acquired pneumonia (CAP) and microbiological diagnosis. We proposed the use of the PES score, as described previously [1], to assess the risk of pneumonia due to PES pathogens. The score was shown to have good accuracy, with an area under the receiver operating characteristic curve (AUC) of 0.754 (0.708 to 0.801). We therefore decided to investigate the frequency and characteristics of CAP caused by PES pathogens in late elderly (≥80 years old) patients with CAP.

We performed a retrospective observational analysis of data prospectively collected from–patients with CAP admitted to Hospital Clinic of Barcelona, Spain between November 1996 and January 2020. We included late elderly patients with a microbiological diagnosis of CAP, and clustered data into two groups (non-PES and PES) according to isolated PES microorganisms. Adherence to empirical antibiotic treatment was considered in accordance with Spanish CAP guidelines [2].

During the study period, 6,130 patients with CAP diagnosis were hospitalised. We analysed 647 (9%) late elderly patients with CAP and an aetiological diagnosis (572 [88%] non-PES and 75 [12%] PES [PES pathogen isolated (n=24 *P. aeruginosa*, n=17 *Enterobacteriaceae*, n= 12 MRSA, n=22 more than one PES pathogen)]). When compared to the non-PES group, the PES group was more likely to be male, former smoker, nursing home resident; present with higher rates of pneumonia episodes in the last year, prior hospitalisation and antibiotic use in the last 90 days, prior recovery of PES pathogens, chronic respiratory diseases, specifically COPD; and receive inhaled

corticosteroids more frequently. Upon admission, the PES group presented higher CRP levels, PSI score, rate of severe CAP and percentage of polymicrobial aetiology, and had received inadequate antibiotic therapy more frequently. After excluding patients with a do-not-resuscitate order, no differences were found between groups with respect to ICU admission, mechanical ventilation, and in-hospital and 30-day mortality. The length of hospital stay and 1-year mortality were, however, higher in the PES group (Table 1). In the multivariable logistic regression analysis, male sex (odds ratio [OR] 2.49, 95% confidence interval [CI] 1.41 to 4.40, p=0.002), prior antibiotic use in the last 90 days (OR 1.74, 95% CI 1.02 to 2.98, p=0.042), a previous episode of pneumonia in the last year (OR 2.82, 95% CI 1.61 to 4.97, p<0.001), and prior recovery of PES pathogens (OR 23.69, 95% CI 1.87 to 300.84, p=0.015) were risk factors for CAP caused by PES pathogens. Chronic cardiovascular disease was the only factor related with a lower risk of CAP caused by PES pathogens (OR 0.44, 95% CI 0.21 to 0.92, p=0.032).

Based on the scores of the previously published model[1], we constructed the PES score for each individual in the cohort. The median (interquartile range) score was 4 (3; 6) in the overall cohort, with a higher score recorded for patients with PES isolation (median 4 [3; 7]) than for those without PES isolation (median 4 [3; 5]) (p<0.001). Its performance in identifying patients with PES pathogens was an AUC of 0.64 (95% CI 0.58 to 0.71). Interestingly, we observed that a cut-off PES score of 5 points obtained a sensitivity of 49% (95% CI 37% to 61%), specificity of 64% (95% CI 60% to 68%), positive predictive value (PPV) of 15% (95% CI 10% to 20%), negative predictive value (NPV) of 91% (95% CI 88% to 94%), positive likelihood ratio (LR+) of 1.36 (95% CI 1.05 to 1.75), negative likelihood ratio (LR-) of 0.80 (95% CI 0.63 to 1.00), positive post-test

probability of 15% (95% CI 12% to 19%), and negative post-test probability of 9% (95% CI 8% to 12%). Using Youden's index, we calculated that the best cut-off in late elderly CAP patients was 3 points: this cut-off obtained a sensitivity of 95% (95% CI 89% to 100%), specificity of 24% (95% CI 20% to 27%), PPV of 14% (95% CI 11% to 17%), NPV of 97% (95% CI 94% to 100%), LR+ of 1.24 (95% CI 1.16 to 1.33), LR- of 0.22 (95% CI 0.09 to 0.59), positive post-test probability of 14% (95% CI 13% to 15%), and negative post-test probability of 3% (95% CI 1% to 7%).

After excluding patients with a do-not-resuscitate order (11%), the multivariable Cox hazards regression analysis revealed that PES pathogens were not associated with in-hospital mortality. However, multilobar pneumonia (HR 1.79, 95% CI 1.03 to 3.11, p=0.041), partial (HR 3.33, 95% CI 1.80 to 6.18, p=0.001) or not living independently (HR 3.39, 95% CI 1.59 to 7.22, p=0.002), acute renal failure (HR 2.47, 95% CI 1.39 to 4.39, p=0.002), and septic shock (HR 6.22, 95% CI 3.35 to 11.52, p=0.001) were independently associated with in-hospital mortality. Prior influenza vaccination (HR 0.55; 95% CI 0.32 to 0.96, p=0.035) was the only protective factor against in-hospital mortality in our population.

To the best of our knowledge, this is the first study to report the prevalence of PES pathogens in late elderly patients hospitalized with CAP. In this population we found a prevalence of 12%, higher than that observed in three previous studies reporting data in the general population (6%, 6.9% and 7.5%, respectively)[1, 3, 4]. These results reflect differences in clinical characteristics of late elderly patients [5] who are more susceptible to infections, recurrent pneumonia[6] and sepsis[7], and have a higher likelihood of receiving recurrent antibiotic treatment[5]. In our study, 75% were male, 33% had a previous episode of pneumonia, and 35% received prior antibiotic therapy

in the last 90 days. The multivariable analysis indicated that these three variables coupled with prior recovery of PES pathogens were risk factors for CAP caused by PES pathogens, supporting findings presented in previous studies[8, 9]. A higher percentage of patients with partial or zero living independently (33%) and those with risk of aspiration (13%) may also be related to a more difficult-to-treat aetiology of CAP, as previous studies have reported [10, 11]. The fact that patients with chronic cardiovascular disease have a lower risk of CAP caused by PES pathogens may be explained by the increased risk of pneumococcal pneumonia posed to such individuals [12].

A higher proportion of patients with CAP caused by PES pathogens received inadequate antibiotic therapy (37% vs. 5%, p=0.001) than in the non-PES CAP group. Such observance could be related to the higher 1-year mortality rate reported in the PES group. In the multivariable analysis, partial or not living independently, multilobar pneumonia, acute renal failure, and septic shock were associated with increased in-hospital mortality. These results are in agreement with previous studies of CAP in elderly populations[13, 14]. Influenza vaccination was the only factor associated with a lower risk for in-hospital mortality in the entire population. This observation is in accordance with previous studies that reported an association between influenza vaccination and reduced hospitalisation and mortality rates in the elderly [15, 16].

Our study has two limitations. First, it is a single-centre study at a teaching hospital attending to a population of more than half a million people; its results may not be extrapolated to other hospitals with different populations. Second, the prolonged recruitment period may have affected results, as patient care would have evolved

throughout this time; notwithstanding, protocol for CAP management has not changed substantially at our hospital.

This data demonstrates the importance of identifying late elderly patients at risk of CAP due to PES pathogens in order to initiate adequate antibiotic therapy. Influenza vaccination is an important, preventive measure that may improve in-hospital mortality in late elderly patients with CAP.

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Conflicts of interest: The authors declare that they have no conflicts of interest

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Table 1. Patient characteristics in PES group

Variable	No-PES (N = 572)	PES (N = 75)	P-value [a]
Age, mean (SD), years	85.7 (4.5)	85.7 (4.2)	0.715
Male sex, n (%)	307 (54)	56 (75)	**0.001**
Smoking habit			**0.001**
No smoker	331 (59)	26 (37)	**0.001**
Current smoker, n (%)	42 (7)	4 (6)	0.603
Former smoker, n (%)	193 (34)	40 (57)	**<0.001**
Current alcohol consumer, n (%)	36 (6)	6 (8)	0.456
Prior antibiotic use in the last 90 days, n (%)	128 (23)	30 (40)	**0.001**
Prior hospitalisation in the last 90 days, n (%)	38 (7)	10 (14)	**0.038**
Prior recovery of PES pathogens, n (%)	1 (0.2)	3 (4)	**0.006**
Influenza vaccine, n (%)	239 (56)	32 (62)	0.434
Pneumococcal vaccine, n (%)	109 (25)	19 (37)	0.070
Previous inhaled corticosteroids, n (%)	109 (20)	23 (32)	**0.015**
Previous systemic corticosteroids, n (%)	31 (6)	4 (7)	>0.999
Previous episode of pneumonia (last year), n (%)	74 (14)	24 (33)	**<0.001**
Comorbidities, n (%) [b]	442 (78)	64 (86)	0.082
Chronic respiratory disease	249 (44)	41 (57)	**0.044**
Non-CF Bronchiectasis	27 (5)	4 (6)	0.771
COPD	109 (19)	26 (36)	**0.001**
Chronic cardiovascular disease	130 (23)	10 (14)	0.069

Variable	No-PES (N = 572)	PES (N = 75)	P-value [a]
Diabetes mellitus	134 (24)	21 (28)	0.388
Neurological disease	122 (22)	18 (25)	0.547
Dementia	38 (7)	5 (7)	>0.999
Stroke	21 (4)	4 (6)	0.515
Parkinson's	13 (2)	3 (4)	0.413
Chronic renal disease	68 (12)	14 (19)	0.087
Chronic liver disease	14 (2)	3 (4)	0.432
Nursing home, n (%)	68 (12)	15 (21)	**0.040**
Living independently, n (%)			0.166
Total	298 (61)	34 (49)	0.059
Partial	138 (28)	26 (38)	0.111
Not living independently	51 (11)	9 (13)	0.519
Fever, n (%)	404 (72)	49 (66)	0.346
Confusion, n (%)	142 (25)	25 (34)	0.094
C-reactive protein ≥15 gr/dL, n (%)	293 (66)	30 (47)	**0.003**
Lymphocytes <724 cell/mm^3, n (%)	178 (45)	30 (50)	0.444
SOFA score, median (IQR)	3 (2; 4)	3 (2; 4)	**0.008**
PSI score, median (IQR)	120 (102; 141)	133 (118; 159)	**0.002**
Severe CAP, n (%)	137 (34)	39 (67)	**<0.001**
Bacteremia, n (%) [c]	122 (27)	20 (41)	0.051
Pleural effusion, n (%)	91 (16)	10 (14)	0.547

Variable	No-PES (N = 572)	PES (N = 75)	P-value [a]
Multilobar, n (%)	140 (24)	19 (25)	0.871
ARDS, n (%)	36 (7)	3 (4)	0.607
Acute renal failure, n (%)	214 (38)	29 (41)	0.684
Septic shock, n (%)	38 (7)	9 (12)	0.088
Appropriate empirical treatment, n (%)	537 (95)	47 (64)	**<0.001**
Do-not-resuscitate order, n (%)	51 (9)	17 (23)	**<0.001**
ICU admission, n (%)	85 (15)	12 (16)	0.795
Mechanical ventilation, n (%) [d]			0.214
Non-invasive	17 (3)	2 (3)	0.965
Invasive	23 (5)	6 (10)	0.079
Length of hospital stay, median (IQR), days	8 (6; 12)	11 (6; 16)	**0.002**
Re-admission in next month, n (%)	53 (9)	7 (9)	0.990
In-hospital mortality, n (%) [e]	48 (10)	10 (18)	0.064
30-day mortality, n (%) [e]	48 (10)	10 (18)	0.064
1-year mortality, n (%) [e]	61 (12)	14 (25)	**0.010**

Abbreviations: ARDS indicates acute respiratory distress syndrome; CAP, community acquired-pneumonia; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IQR, interquartile range; PES, *Pseudomonas aeruginosa*, extended-spectrum β-lactamase *Enterobacteriaceae*, and methicillin-resistant *Staphylococcus aureus*; PSI, pneumonia severity index; SD, standard deviation; SOFA, sequential organ failure assessment. Percentages calculated on non-missing data. [a] Comparisons between patients that did or did not present with isolation of a PES microorganism group were assessed using the chi-square test or Fisher's exact test for categorical variables. The t test or nonparametric Mann-Whitney U test were performed for continuous variables. Bold values denote statistical significance at the $p<0.05$ level. [b] Possibly >1 comorbidity. [c] Calculated only for patients with blood samples (444 in the non-PES group and 49 in the PES group). [d] Patients who initially

received non-invasive ventilation but needed subsequent intubation were included in the invasive mechanical ventilation group. [e] Calculated only for patients who did not have a DNR (491 in the non-PES group and 56 in the PES group).