

## Characteristics and Outcomes of Bacteremic Pneumococcal Pneumonia of Patients With and Without HIV Infection in Argentina

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### Abstract

*Streptococcus pneumoniae* is the main causative agent of pneumonia, with a 10 to 25 percent rate of isolation in blood cultures. Controversies exist regarding the prognostic impact of a history of human immunodeficiency virus (HIV) infection on community-acquired pneumonia.

The aim of our work was to analyze and compare the clinical presentation, radiological findings and progression of pneumococcal pneumonia in patients infected with and not infected with HIV. We retrospectively analyzed adult patients with positive blood cultures for *Streptococcus pneumoniae* and clinical and radiological findings compatible with pneumonia in the period between January 2012 and May 2017. Age, sex, comorbidities, clinical and laboratory variables, radiolog-

ical severity, progression and mortality were analyzed. Comparative analysis between HIV-positive and -negative patients was carried out. Receiver operating curves (ROC) for CURB-65 were performed to predict mortality in both groups. We included 107 patients (21 HIV-positive and 86 HIV-negative). HIV patients were on average younger (38 vs 58 years) with lower hematocrits (31.7 vs 36.5%) and fewer comorbidities (47 vs 72%). Overall mortality was 36 percent, and the area under the curve (AUC) of the CURB-65 ROC was 0.69 (95% confidence interval: 0.58–0.79) for all patients without differences between the two groups. Patients with a history of HIV infection had the same progression and mortality as the group of patients without that background.

### Introduction

*Streptococcus pneumoniae* is the main causative agent of pneumonia, with a 10 to 25 percent rate of isolation in blood cultures. Attributed mortality is 15 to 26 percent, which remains high despite improvements in health care, including the availability of intensive therapy, effective antibiotics, and specific vaccines.[1–3]

There are risk factors that predispose the development of pneumococcal pneumonia, such as smoking, socio-economic status, age, immune status, genetic susceptibility, and geographic location.[2, 4] Additional factors associated with invasive infection, such as myeloma, immunosuppression, cerebrospinal fluid fistulas and intravenous drug use, have also been described.[2, 5] However, there are still controversies regarding the prognostic impact of a history of human immunodeficiency virus (HIV) infection, which is especially relevant considering that pneumonia is a frequent complication in this group of patients despite antiretroviral

therapy. The objective of the present work was to analyze and compare the outcomes of pneumococcal bacteremic pneumonia in HIV-positive and -negative patients.

### Methods

We retrospectively analyzed patients older than 18 years with clinical and radiological findings compatible with pneumonia and isolation of *S. pneumoniae* in blood cultures in the period between January 2012 and May 2017 in a single center in Buenos Aires, Argentina.

Blood cultures were drawn at emergency admission and incubated according to standardized lab technique. Identification of microbial agents and susceptibility studies were performed according to conventional methods. All patients were tested for HIV infection.

Age, sex, comorbidities, clinical and laboratory vari-

ables, radiological severity, evolution (length of hospital stay, need for ICU admission) and mortality during hospitalization were observed. A comparative analysis was conducted between HIV-positive and -negative patients.

### Statistical analysis

The results of the normally distributed quantitative variables were expressed as means ( $\pm$  standard deviations) and those not normally distributed were expressed as medians and interquartile ranges. Qualitative variables were expressed as percentages. Normally distributed data were compared using Student's t-test and chi-squared tests were applied for differences in proportions. P-values  $<0.05$  were considered statistically significant. CURB-65 score was used to build receiver operating curves (ROC) for mortality, and multiple logistic regressions were used to test for the presence of confounders.

The data was analyzed with the statistical analysis software STATA 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP)

The work was approved by the Hospital Ethics Committee (ref. 242 - Code LUPOSO/19).

## Results

We analyzed 107 patients with community-acquired pneumonia and isolation of *S. pneumoniae* in blood cultures. Twenty-one patients were HIV-positive. The average age was 54 years ( $\pm 17.37$ ); 40% were women and 31% were admitted to the intensive care unit. The average onset of symptoms was 6.3 days ( $\pm 6.75$ ) before the consultation. The most frequent comorbidities were smoking (39%), alcoholism (20%), diabetes (17%) and cancer (17%). Radiological involvement of two or more lobes was observed in 43% of patients and the presence of a pleural effusion in 25% of cases. Regarding the laboratory tests performed at admission, the means were: PaO<sub>2</sub>/FiO<sub>2</sub> 279 ( $\pm 106$  standard deviation (SD)), urea 0.69 mg/dL ( $\pm 0.42$  SD), creatinine 1.67 mg/dL ( $\pm 1.24$  SD), sodium 133 meq/L ( $\pm 6$  SD) and glucose 149 mg/dL ( $\pm 102.35$  SD). The proportions of patients in each CURB-65 group were: 13% for group 0, 32.7% for group 1, 26.17% for group 2, 16.82% for group 3, 9.35% for group 4 and 1.87% for group 5. The mean age of HIV-positive and -negative patients was 38 vs 58 years, and HIV-positive patients had lower hematocrits (32% vs 37%) and fewer comorbidities (47 vs 72%). **Table 1** shows patient characteristics for the study population on the day of admission.

Overall mortality was 36%; mortality was higher in CURB-65 4 and 5, where it reached 75%. No differences between these two groups was observed. The mean

length of hospitalization was 11 days ( $\pm 11.41$ ). **Table 2** shows outcomes for the study population.

ROC of CURB-65 score was performed to predict global mortality. The overall area under the curve (AUC) was 0.69 (95% confidence interval (CI): 0.58–0.79): 0.71 (95% CI: 0.60–0.83) and 0.67 (95% CI: 0.47–0.87) for the HIV-negative and -positive groups, respectively, with no statistically significant difference ( $P=0.68$ ) (**Figure 1**).

In the HIV-positive group, the median CD4 count was 71 cells/mm<sup>3</sup> (interquartile range: 272). The strains that presented resistance to oxacillin had an MIC  $<4$  for penicillin, and 11% were resistant to macrolides. All isolates were sensitive to levofloxacin.

## Discussion

Lung infections in HIV patients are a common cause of morbidity and mortality, being 25 times more frequent than in the general population. Antiretroviral therapy (ART) reduces opportunistic infections; however, bacterial pneumonia remains prevalent.[6–8] The evolution and prognosis in this group of patients are controversial. Feldman et al. compared a group of HIV-positive patients with bacteremic pneumonia with an HIV-negative group, noting that HIV-positive patients had higher 14-day mortality and an increasing trend in mortality with lower CD4 levels.[9] Similarly, other studies found worse prognosis in HIV-positive patients with bacteremia.[10, 11] Factors associated with high mortality have been described, such as Karnofsky score  $<50$ , neutropenia, CD4 count  $<100$  cells/mm<sup>3</sup>, Po<sub>2</sub>  $<70$  mmHg, septic shock, and radiological progression.[12]

In other studies, the mortality rates of bacteremic pneumonia in patients with a history of HIV are similar to the control groups; however, these results may be related to high CD4 values in the cohorts studied.[1, 13, 14] In a study by Bordón et al. that included 117 patients, the evolution and prognosis were not found to be related to CD4 values or HIV-RNA levels.[15]

In our study, some significant differences were observed in the population of patients with and without HIV: HIV-positive patients were younger with lower hematocrit values and lower percentages of comorbidities. However, in both groups, the values of CURB-65 4 and 5, mortality, radiological compromise, presentation and clinical progression were similar even after adjusting for the differences mentioned above.

The state of immunodeficiency in patients with HIV included in our study (in which the median CD4 count was 71) was not associated with worse outcomes in terms of clinical progression and mortality.

Regarding the length of hospital stay and the time to

**Table 1.** Patient characteristics for the study population on the day of admission.

	HIV infection	No HIV infection	<i>P</i>
Study population, n	21	86	
<b>Demographics</b>			
Age years ( $\pm$ SD)	38 ( $\pm$ 13.53)	58 ( $\pm$ 16.14)	0.002
Male sex, n (%)	15 (71.43)	50 (58.14)	0.264
<b>Social and Medical History</b>			
Diabetes mellitus, n (%)	1 (4.76)	17 (19.77)	0.189
Current or former smoker, n (%)	8 (38.1)	35 (40.7)	0.827
Congestive heart failure n (%)	0	5 (5.81)	0.581
Obesity (BMI $\geq$ 30) n (%)	0	4 (4.65)	0.584
Chronic renal failure n (%)	1 (4.76)	8 (9.30)	0.685
Chronic obstructive pulmonary disease n (%)	0	6 (6.98)	0.595
Neoplastic disease n (%)	0	20 (23.26)	0.011
<b>Physical Exam Findings</b>			
Systolic blood pressure (mmHg)	100 ( $\pm$ 19.52)	104 ( $\pm$ 25.3)	0.433
Diastolic blood pressure (mmHg)	58 ( $\pm$ 11.52)	63( $\pm$ 15.84)	0.211
Heart rate (beats/minute)	104 ( $\pm$ 21.92)	103 ( $\pm$ 19.94)	0.828
Respiratory rate (breaths/minute)	24 ( $\pm$ 5.59)	25 ( $\pm$ 6.31)	0.642
Temperature ( $^{\circ}$ C)	37.35 ( $\pm$ 1.21)	37.14 ( $\pm$ 1.23)	0.489
Pleural effusion n (%)	2 (9.5)	25 (29)	0.09
<b>Laboratory Findings</b>			
Serum sodium (mEq/L)	133 ( $\pm$ 5.30)	133 ( $\pm$ 6.25)	0.91
Serum glucose (mg/dL)	113 ( $\pm$ 66.51)	158 ( $\pm$ 107.59)	0.07
Hematocrit (%)	31.73 ( $\pm$ 5.22)	36.56 ( $\pm$ 6.78)	0.003
Leukocytes cells/mL)	13,395 ( $\pm$ 9700)	22,078 ( $\pm$ 12725)	0.19
Urea (mg/dL)	0.55 ( $\pm$ .34)	0.72 ( $\pm$ .43)	0.09
Creatinine (mg/dL)	1.4 ( $\pm$ 1.03)	1.21 ( $\pm$ 1.29)	0.28
<b>Severity of disease on admission</b>			
CURB-65 score 4 or 5	1 (5.56)	11 (13.1)	0.36
Altered mental status	4 (20)	24 (28.4)	0.58
PaO <sub>2</sub> /FiO <sub>2</sub>	262 ( $\pm$ 111)	282 ( $\pm$ 105)	0.49
ICU Admission	6 (28.5)	27 (31.4)	0.8
Mechanical ventilation	4 (20)	20 (23.2)	1
Vasopressor use	4 (20)	24 (27.9)	0.58
CXR with $\geq$ 2 lobes	12 (57.1)	34 (40.4)	0.16

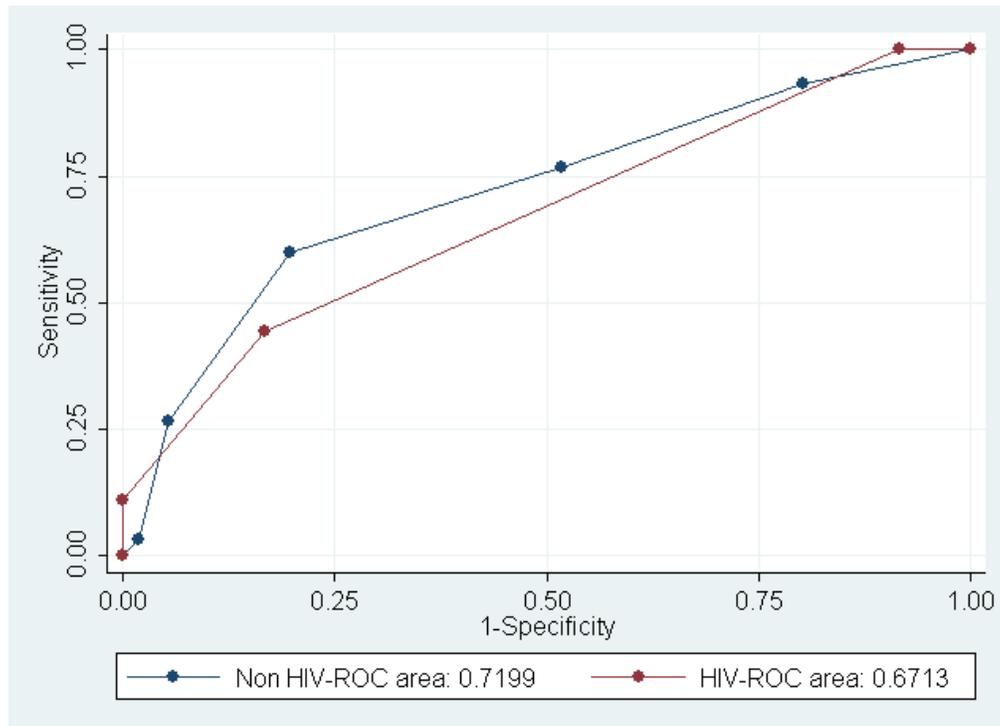
Data are presented as n (%) or mean ( $\pm$ SD).

BMI: body mass index; CXR: chest X-ray; SD: standard deviation.

**Table 2.** Outcomes for the study population.

	HIV infection	No HIV infection	<i>P</i>
Study population (n)	21	86	
Mean length of stay (days) ( $\pm$ SD)	9.14 ( $\pm$ 6.59)	12.35 ( $\pm$ 12.3)	0.25
Mortality n (%)	9 (42.8)	30 (34.8)	0.49

SD: standard deviation



**Figure 1.** Comparative ROC for CURB-65 for both groups of patients.  
ROC: receiver operating curve.

clinical stability, there are also controversies with respect to HIV-positive patients with pneumonia. Malinis et al. analyzed 118 patients with HIV and found no differences in time to clinical or hospital stability. Christensen et al. analyzed 58 HIV-positive patients diagnosed with pneumonia, compared them with 174 HIV-negative patients and found similar results.[13, 14] In the latter study, length of hospital stay did not show statistically significant differences either.

On the other hand, the mortality rate of community-acquired pneumonia with bacteremia varies among different reports; this could be due to the different study populations.[16] Several authors have found that bacteremia is a risk factor for mortality. A meta-analysis identified 11 risk factors for associated mortality, which included bacteremia.[17] García-Vidal et al. also identified bacteremia as an independent risk factor for mortality.[18] Capelastegui et al. compared 492 patients with negative blood cultures and 399 with positive cultures; bacteremia had a worse evolution (more days of hospitalization, high rates of mechanical respiratory support and shock) and greater in-hospital mortality at 15 and 30 days.[19] Similar results were observed in the study by Bordón et al.[10] Musher et al. and Kang et al. describe 29% mortality.[20, 21] Other studies concluded that the severity index CURB-65 and PSI are higher in patients with bacteremia.[19, 22]

By contrast, other authors find a poor correlation between bacteremia and the severity of the symptoms.[23] Marrie et al., in a multicenter study, found no differences in mortality, but an adjusted analysis was not performed, and severe patients were not included.[24] Another multicenter study carried out by Bordón et al. concluded that patients with bacteremia do not have a worse evolution.[25] Amaro et al. described 917 patients with pneumonia due to pneumococcus, of whom 362 presented bacteremia; greater severity and length of stay were observed in the group with bacteremia but with the same mortality.[26] In the work of Palma et al. and Cillóniz et al., no differences were found in mortality or hospitalization time.[1, 27]

In our cohort of patients, the mortality rate was higher than those reported in the literature. However, it is not possible to correlate this with the presence of bacteremia since it exceeds the purpose of the present study.

With regard to the limitations of our work, the cohort of patients studied was from a single center and, we did not have data related to the use of antiretroviral treatment or on prior antipneumococcal vaccination.

Our work shows that HIV patients with bacteremic pneumococcal pneumonia do not differ in evolution and mortality compared to patients without this background, as suggested by other authors.

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