Associations between antimicrobial susceptibility of *Streptococcus pneumoniae* and disease severity outcomes in older adults with invasive pneumococcal disease in São Paulo, Brazil

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Background

- *Streptococcus pneumoniae* may cause local acute infections or spread through the bloodstream to other sites, leading to invasive pneumococcal diseases (IPD)[1-5]
- Worldwide pneumococcal disease burden is substantial and estimated to cause 1.6 million deaths annually.[6] Vulnerable populations such as older adults, children, and high-risk groups, especially in resource-constrained areas, are particularly at risk[7,8]
- In addition to the continuous monitoring of the most prevalent serotypes, mapping of antimicrobial resistance is essential to guide future decisions on pneumococcal vaccination and public health measures.[9] In fact, *S. pneumoniae* has been progressively developing antimicrobial resistance[10]
- Data from the national IPD public health surveillance in Brazil reported an increase of multidrug-resistant (MDR) isolates from 6.3% in 2007-2009 to 25.0% in 2017-2019[11]
- This study aimed to evaluate the correlation between antimicrobial susceptibility pattern of *S. pneumoniae* and disease severity outcomes in older adults hospitalized with IPD in the city of São Paulo, Brazil

Methods

- This is an observational, retrospective, chart review study based on available information from January 2016 to December 2018 of hospitalized patients aged ≥ 60 years old with IPD (defined as an infectious episode during which pneumococci were isolated from normally sterile body fluids) at three tertiary teaching hospitals in the city of São Paulo, the largest city in Brazil
- Data collection took place between September 2020 and August 2021
- Antimicrobial resistance of *Pneumococcus sp.* was evaluated by antibiogram
- The main disease severity outcomes evaluated were hospital stay length, intensive care unit stay, antimicrobial resistance (AMR), sequelae, and complications (respiratory, cardiovascular, central nervous system (CNS), renal)
- Variables were summarized using descriptive statistics (mean, standard deviation, median and range for continuous variables, and frequency for categorical variables
- Statistical comparisons of groups of interest were performed using Chi-Square or Fisher Exact tests for categorical variables and the non-parametric tests Mann-Whitney (for comparisons between two groups) or Kruskal-Wallis (for comparisons between three groups) for continuous variables, following non-normal distributions. The association between the length of hospital stay and age was assessed by Spearman correlation. All statistical tests were two-sided considering a significance level of 5%

Results

- A total of 94 patients were included in the study, with the majority (89.4%) having community-onset IPD. The mean patient age was 70.3 ± 8.6 years, and most patients (71.3%) were aged between 60–74 years; 53.2% were male. IPD cases were classified as non-meningitis IPD in 89.4% of patients, while meningitis IPD occurred in 10.6% of patients
- Antimicrobial susceptibility testing was performed on 90 out of 94 patients. During hospitalization, 94.4% of patients received antibiotic treatment, with 89.4% requiring more than one class of antibiotics. During the study period, AMR was observed in 43.3% of isolates. Resistance to a single antibiotic or ≥2 antibiotic classes was observed in 21.1% and 22.2% of cases, respectively
- Statistical analysis revealed that limited demographic or clinical outcome data were associated with AMR. Patients with CNS complications, such as new-onset seizures, had higher rates of AMR (27.8% with CNS complications were resistant to at least one antibiotic class, compared to 0.0% without CNS complications, FS=0.0101; **Table 1**). In contrast, no statistically significant differences were found between groups for the remaining disease severity outcomes including complications or sequelae (**Tables 2-5**)

Table 1. Complications in IPD patients with or without antimicrobial resistance

	No antibiotic resistance (n=51)	Resistant to ≥1 antibiotic class (n=39)	*P*-value
Respiratory, n (%)	40 (78.4%)	26 (66.7%)	CS: 0.2111
If yes (more than one possible option):			
Requirement for supplemental oxygen, n (%)	36 (90.0%)	23 (88.5%)	FS: >0.9999
Need for mechanical ventilation, n (%)	19 (47.5%)	15 (57.7%)	CS: 0.4182
If yes, number of days			MW: 0.7803
Mean ± standard deviation	5.5 ± 5.0	7.2 ± 7.7	
Median [Q1, Q3]	3 [1, 9]	5.5 [1, 11]	
Range	1-19	1-28	
Adult respiratory distress syndrome, n (%)	18 (45.0%)	18 (69.2%)	CS: 0.0534
Aspiration pneumonia, n (%)	0 (0.0%)	0 (0.0%)	NA
Parapneumonic effusion, n (%)	7 (17.5%)	3 (11.5%)	FS: 0.7280
Other, n (%)	10 (25.0%)	6 (23.1%)	CS: 0.8586
Cardiovascular, n (%)	26 (51.0%)	18 (46.2%)	CS: 0.6499
If yes (more than one possible option):			
Myocardial infarction, n (%)	1 (3.8%)	0 (0.0%)	FS: >0.9999
Congestive heart failure, n (%)	5 (19.2%)	5 (27.8%)	FS: 0.7161
Cardiac arrest, n (%)	8 (30.8%)	10 (55.6%)	CS: 0.1001
Endocarditis, n (%)	0 (0.0%)	1 (5.6%)	FS: 0.4091
Septic shock, n (%)	17 (65.4%)	12 (66.7%)	CS: 0.9297
Other, n (%)	16 (61.5%)	6 (33.3%)	CS: 0.0658
Central nervous system, n (%)	24 (47.1%)	18 (46.2%)	CS: 0.9320
If yes (more than one possible option):			
New-onset stroke, n (%)	2 (8.3%)	2 (11.1%)	FS: >0.9999
New-onset seizures, n (%)	0 (0.0%)	5 (27.8%)	FS: 0.0101
Alteration of mental status, n (%)	21 (87.5%)	16 (88.9%)	FS: >0.9999
Other, n (%)	15 (62.5%)	10 (55.6%)	CS: 0.6500
Renal, n (%)	20 (39.2%)	14 (35.9%)	CS: 0.7476
If yes (more than one possible option):			
New onset of renal failure requiring dialysis, n (%)	6 (30.0%)	6 (42.9%)	FS: 0.6807
Other, n (%)	16 (80.0%)	8 (57.1%)	FS: 0.2522
Other, n (%)	15 (29.4%)	13 (33.3%)	CS: 0.6905

Table 2. Hospitalization characteristics of IPD patients with or without antimicrobial resistance

	No antibiotic resistance (n=51)	Resistant to ≥1 antibiotic class (n=39)	*P*-value
Length of hospitalization (days)			
Mean ± standard deviation	14.6 ± 14.5	18.4 ± 18.6	MW: 0.343
Median [Q1, Q3]	10 [4, 21]	11 [5, 27]	
Range	1-70	1-93	
Missing values	1	0	
Patient required Intensive Care Unit (ICU) stay, n (%)	26 (54.2%)	20 (55.6%)	CS: 0.899
Unknown	3	3	
If yes, length of ICU stay (days)			
Mean ± standard deviation	7.3 ± 5.8	8.7 ± 7.7	MW: 0.723
Median	7 [2, 10]	7 [2, 11.5]	
Range	1-19	1-28	
Missing values	5	0	

Table 3. Use of antibiotics by IPD patients with or without antimicrobial resistance

	No antibiotic resistance (n=51)	Resistant to ≥1 antibiotic class (n=39)	*P*-value
Antibiotic use, n (%)	45 (93.8%)	37 (97.4%)	FS: 0.6266
If yes:			
One antibiotic class	4 (8.9%)	5 (13.5%)	FS: 0.7247
More than one antibiotic class	41 (91.1%)	32 (86.5%)	
2 classes	25	13	
3 classes	7	6	
4 classes	5	9	
5 classes	1	2	
6 classes	1	1	
7 classes	0	1	
Unknown	2	0	
Length of antibiotic use (days)			KW: 0.4925
Mean ± standard deviation	10.7 ± 12.5	10.7 ± 9.7	
Median [Q1, Q3]	7 [4, 10]	8 [5, 15]	
Range	1-51	1-42	

Figure 1. Location of infection IPD patients with or without antimicrobial resistance

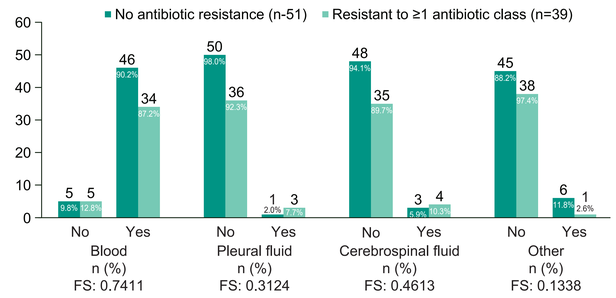

Table 4. Mortality and sequela of IPD patients with or without antimicrobial resistance

	No antibiotic resistance (n=51)	Resistant to ≥1 antibiotic class (n=39)	*P*-value
Patient died in hospital, n (%)			
Yes	23 (45.1%)	16 (41.0%)	CS: 0.6992
No	28 (54.9%)	23 (59.0%)	
If the patient did not die:			
Patient present sequela, n (%)	8 (44.4%)	3 (30.0%)	FS: 0.6888
Missing values	23	16	
If yes (more than one possible option):			
Hearing loss of meningitis, n (%)	0 (0.0%)	1 (50.0%)	NA
Chronic respiratory failure or impairment due to pneumonia, n (%)	4 (50.0%)	1 (33.3%)	NA
Cardiovascular, n (%)	0 (0.0%)	0 (0.0%)	NA
Permanent renal impaired function, n (%)	0 (0.0%)	0 (0.0%)	NA
Neurologic sequela due to meningitis, n (%)	0 (0.0%)	1 (33.3%)	NA
Other, n (%)	5 (62.5%)	1 (33.3%)	NA

Limitations

- Due to the study design, data in chart review may be incomplete or missing, number of patients may be insufficient for some exploratory analyses, IPD might be underdiagnosed due to missing bacteriologic pneumococcal confirmation, and serotype characterization was also unavailable

Conclusions

Our study showed high rates of AMR in older adults with IPD. Notably, there appears to be an association between AMR and the occurrence of new-onset seizures. Further investigation is warranted to elucidate the impact of AMR on clinical outcomes and to provide additional evidence supporting the implementation of preventive strategies aimed at mitigating infection-related complications.

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