

Serotypes and antibiotic susceptibility of *Streptococcus pneumoniae* isolated from hospitalized patients with community-acquired pneumonia in Italy

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Abstract

Background: Pneumonia remain an important public health problem. The primary objective was to determine the proportion of community-acquired pneumonia that is attributable to *Streptococcus pneumoniae* infection; secondary objectives were the description of community-acquired pneumonia attributable to *Streptococcus pneumoniae* according to socio-demographic and clinical variables, the clinical evolution of community-acquired pneumonia and the description of the serotype distribution of vaccine-preventable disease and antibiotic resistance rate of pneumococcal infections.

Methods: An observational, prospective study was conducted on consecutive patients coming from the community, who were hospitalized with pneumonia. Data on admission, at discharge and 30 days after discharge were collected. Logistic regression models were used to evaluate the risk factors independently associated with pneumococcal pneumonia.

Results: Among the 193 patients enrolled in the study, the etiology of community-acquired pneumonia was identified in 60 patients (33%) and 35 (18%) of evaluable patients had community-acquired pneumonia due to *Streptococcus pneumoniae*. Of all clinical characteristics, if no previous antibiotic treatment was performed, there was a 13-fold higher risk of presenting community-acquired pneumonia due to *Streptococcus pneumoniae* (odds ratio, 12.9; 95% confidence interval, 1.42–117.9). Moreover, the most frequent isolated serotypes were 35F, 3 and 24 (29%, 23% and 16%, respectively).

Conclusion: The most frequent serotypes in pneumococcal community-acquired pneumonia are 35F, 3, 24, 6 and 7A, and thus almost 50% of *Streptococcus pneumoniae* strains could be covered by pneumococcal conjugate vaccine 13 in adult patients with risk factors for pneumococcal infections.

Keywords

Pneumonia, vaccine, pneumococcal disease

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Introduction

Pneumococcal disease represents a major cause of morbidity and mortality worldwide, and it is usually recognized as either invasive (invasive pneumococcal disease (IPD)) or non-invasive.¹ IPD is a serious condition characterized by either the presence of bacteremia or an involvement of major organs, in which *Streptococcus pneumoniae* is isolated from normally sterile biofluids, and occurs in up to 25% of cases of pneumococcal disease with a fatality rate of at least 10%.² Non-IPD is mainly represented by community-acquired pneumonia (CAP), which is also associated with a significant mortality, especially in the elderly and in patients with

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chronic respiratory diseases and immunosuppression.^{1,3} As new therapies aimed at improving outcomes in CAP patients have not been developed over the past two decades, vaccination has become more and more important in preventing pneumococcal disease.^{1,2,4} Nevertheless, the overall burden of respiratory diseases due to *S. pneumoniae*, the beneficial of herd immunity from pediatric vaccinations and the potential effect of the new recommended vaccination programs for adults are difficult to evaluate. This is mainly due to a lack of data regarding vaccination coverage in adult patients, difficulties in identifying the etiology of respiratory infections and, therefore, the scarcity of data regarding distribution of pneumococcal serotypes.⁵⁻⁷ Most of the available studies on pneumococcal disease are on IPD, while studies on non-IPD are mainly randomized controlled trials (RCTs) or meta-analysis.^{2,8,9,10} Although some observational, real-life studies on pneumococcal pneumonia were conducted in both the United States and Europe, data on non-IPD in Italy are missing.⁵⁻⁷ Specifically, both type and rate of pneumococcal vaccination in adult patients with CAP as well as the type pneumococcal serotypes involved in this disease have not been evaluated yet in Italy.

Methods

In order to collect real-life data on vaccination coverage and serotype identification in CAP, we conducted a prospective, observational, cohort study including CAP patients admitted at the Respiratory Ward of the IRCCS Policlinico Hospital, Milan, Italy, from October 2011 to October 2012.

The primary outcome considered for the sample size calculation is the proportion of patients positive to *S. pneumoniae* diagnosed by blood culture at baseline visit. Published data vary noticeably among different studies. A prospective study on 184 Sweden patients with CAP admitted to the Department of Infectious Disease reported 14.7% of patients positive to blood culture.⁹ Assuming 5% of non-evaluable patients, when the sample size is 350 (corresponding to 333 evaluable patients), a two-sided 95% confidence interval using the large sample normal approximation will extend 3.8% from the observed proportion of patients for an expected proportion of 14.7%.¹¹

Ethics approval of study protocol, protocol amendments, informed consent forms and other relevant documents was obtained prior to study initiation from the Independent Ethic Committee (IEC). Informed consent was obtained by each patient prior to enrollment in the study.

Blood samples, urinary antigens, sputum and/or nasopharyngeal swab, tracheal aspirate and pleural fluid (when available) were collected on admission. All samples were analyzed for pathogen identification at the Policlinico Hospital (local laboratory) and for polymerase chain reaction (PCR) testing, antibiotic resistance patterns and serotyping of *S. pneumoniae* samples at Florence (central laboratory).

All statistical analyses were run using SPSS 20 (IBM). Categorical data are presented as absolute number (n) and percentage (%). Normally distributed data are shown as mean with standard deviation (SD), whereas non-normally distributed data are presented as median with interquartile range (IQR).

Results

A total of 193 patients (age: 78 (66–84) years, 113 male, 58%) were enrolled. The majority of them had moderate-to-severe pneumonia: 63% were included in the Pneumonia Severity Index risk-class IV-V, while 20% met severe sepsis criteria.^{12,13} Among the entire study population, 26% received influenza vaccination during the previous year while 6% received the 23-valent polysaccharide vaccine (PPV23). A total of 158 patients should have been received pneumococcal vaccine according to national guidelines, but among them only 9 patients were previously vaccinated (1). The etiology of CAP was identified in 60 patients (33%) and among them 35 (18%) had *S. pneumoniae*: 2% of samples showed resistance to a beta-lactam and 6% to quinolone. In all, 26 patients had at least one *S. pneumoniae* sample with a typable serotype. The majority of patients with pneumococcal CAP were treated with a combination therapy with ceftriaxone and azithromycin (40%), followed by association of piperacillin/tazobactam and levofloxacin (29%), levofloxacin monotherapy (17%), association of ceftriaxone and levofloxacin, or piperacillin/tazobactam and azithromycin (both 3%), and monotherapy with piperacillin/tazobactam or clarithromycin (both 3%). Concerning hospital resources utilization, three patients (9%) with pneumococcal CAP required ventilatory support either on admission or during hospitalization, the median (IQR) length of stay was 8 (7–14) days and two (6%) patients were re-hospitalized during 30 days after discharge. Finally, 14 (7%) patients died during hospitalization and 4 (2%) patients during the 30 days after discharge.

This study shows that the most frequent serotypes identified in hospitalized patients with CAP in our center were 35F (29%), 3 (23%), 24 (16%), 6 and 7A (10%). Furthermore, we showed that among hospitalized patients with CAP, only the 6% of those meeting the criteria for pneumococcal vaccination were actually vaccinated. Finally, we found that the pneumococcal strains identified in our population were not resistant to macrolides and had low resistance rate to both beta-lactam (2%) and quinolones (6%).

Discussion

The pneumococcal serotypes identified in our study are substantially consistent with previous literature, except for the interesting finding of a high prevalence of serotype 35F (29%).⁵⁻⁷ Few recent experiences showed an increase of serotype 35F among children carriers, especially after the

extensive use of pneumococcal conjugate vaccine (PCV7) and adult patients with both IPD and non-IPD, even if it was more likely to be associated with colonization than disease.^{14,15} According to our results, we might speculate that PCV13 could potentially be protective in about 50% of available serotype cases in CAP patients, a finding partly consistent with previous studies showing a potential coverage from PCV13 between 34% and 80% of cases.⁵⁻⁷ Moreover, our interesting finding of a lower rate of antibiotic resistances of *S. pneumoniae*, and particularly macrolide resistance, is slightly different from previous studies.^{16,17} This result could potentially affect the choice of antibiotic therapy for *S. pneumoniae*, at least in our geographical area.

A major limitation of our study consists in its monocenter design and in the enrollment of less patients respectful to the calculated sample size, with a reduction of the generalizability of our results. However, this is the first prospective and real-life experience in Italy designed according to a high level of microbiological investigations aimed at identifying the proportion of CAP that is attributable to *S. pneumoniae* and at describing serotypes distribution and antibiotic resistance patterns of pneumococcal isolates.

Conclusion

In conclusion, our study found that the most frequent serotypes in pneumococcal CAP are 35F, 3, 24, 6 and 7A and that almost 50% of *S. pneumoniae* strains could be covered by PCV 13 in adult patients with risk factors for pneumococcal infections.

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Declaration of conflicting interests

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Ethical approval

The study complies with Italian legislation on observational studies (Circolare Ministeriale n.6 del 02/09/2002 published on G.U. n. 214 del 12/9/2002) and clinical guidelines for the classification and conduct of observational studies on drugs AIFA (GU del 31/03/2008). The protocol is in agreement with the principles defined by the 18th World Medical Assembly (Helsinki, 1964) and subsequent amendments established by the 29th (Tokyo, 1975), the 35th (Venice, 1983), the 41st (Hong Kong, 1989) and the 52nd (Edinburgh, 2000) World Medical Assembly, and in accordance with the note of

clarification on paragraph 29 which has been added to the WMA General Assembly, held in Washington in 2002 and in accordance with the revision of paragraph 30 of the Declaration of Helsinki, held in Tokyo in 2004 and to the WMA general Assembly, held in Seoul in 2008. The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices such as *Good Pharmacoepidemiology Practices* (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), the International Society for Pharmacoconomics and Outcomes Research (ISPOR) guidances, Pharmaceutical Research and Manufacturers Association (PhRMA) guidelines and similar. Ethical approval of study protocol, protocol amendments, informed consent forms and other relevant documents was obtained prior to study initiation from the Independent Ethic Committee (IEC), protocol number Picture B1851132 Sponsor Medidata.

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Informed consent

Written informed consent was obtained from all subjects before the study.

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