

Role of *Streptococcus pneumoniae* infection in chronic obstructive pulmonary disease patients in Italy

Marco Mantero, Stefano Aliberti, Chiara Azzari, Maria Moriondo, Francesco Nieddu, Francesco Blasi and Marta Di Pasquale

Abstract

Background: The aim of this study was to determine the incidence of exacerbations due to *Streptococcus pneumoniae* in chronic obstructive pulmonary disease (COPD) patients during stable state.

Methods: We conducted a prospective, observational, cohort study including stable COPD patients, who were evaluated at least every 4 months over a 24-month period at the Respiratory Unit of the IRCCS Policlinico Hospital in Milan, Italy, from 2012 to 2015. Sputum samples were collected at enrollment during stable state to evaluate the frequency of *S. pneumoniae* colonization and in case of an acute exacerbation to evaluate the incidence of pneumococcal infection.

Results: A total of 79 stable patients with moderate to very severe COPD were enrolled. A total of 217 samples were collected, and 27% ($n = 59$) of those were positive for *S. pneumoniae*. A total of four exacerbations due to *S. pneumoniae* occurred during follow up (0.31 per 100 person/month). Among positive samples of *S. pneumoniae*, 109 serotypes were identified. The most frequent serotypes in moderate-to-severe COPD patients during both stable state and exacerbation were 19F (12%), 18 (10%), 19A and 9V (9%) and 35 F (7%). Only 32% of COPD patients were effectively vaccinated for *S. pneumoniae* with PPV23 vaccine.

Conclusion: The most frequent *S. pneumoniae* serotypes in COPD patients are 19F, 18, 19A, 9V and 35 F, and that almost 50% of *S. pneumoniae* strains could be covered by PCV13 in adult COPD patients.

Keywords: COPD, pneumococcal disease, vaccine

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Introduction

The role of *Streptococcus pneumoniae* in chronic obstructive pulmonary disease (COPD) patients during both stable state and exacerbation is controversial.¹ Lower respiratory tract infections (LRTIs) due to *S. pneumoniae* carry a significant morbidity and mortality worldwide, especially among elderly people, immunocompromised patients and those affected by chronic respiratory diseases.^{2–5} As new therapies have not been developed over the past 20 years, vaccination seems to be one of the major tools to reduce the burden of pneumococcal

disease, especially among patients with known risk factors for LRTIs, such as those with COPD.^{2,6,7}

The overall rate of pneumococcal colonization in COPD patients and its role during exacerbation is difficult to evaluate. The potential benefit of recent vaccination programs designed for these patients is still unknown and data regarding vaccination coverage and distribution of pneumococcal serotypes in COPD patients during stable state and exacerbation are lacking.^{8–11} Very few studies on pneumococcal infection in

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COPD patients are currently available, and real-life data on respiratory tract infections due to *S. pneumoniae* in Italy are lacking.¹ Specifically, there is a lack of data regarding the type and rate of vaccination in COPD patients and moreover pneumococcal serotypes involved are not well characterized. Therefore, we aimed at describing the real-life incidence of exacerbations due to *S. pneumoniae* in COPD patients during stable state.

Methods

Study design

We conducted a prospective, observational, cohort study including stable COPD patients who were evaluated at least every 4 months over a 24-month period at the Respiratory Unit of the IRCCS Policlinico Hospital in Milan, Italy, from 2012 to 2015.

Study population

Inclusion criteria. All outpatients with a diagnosis of moderate-to-severe COPD at the enrollment visit and presence of at least one exacerbation during the past year (but not in the last 30 days) and chronic sputum production. Ethics approval of study protocol, protocol amendments, informed consent forms and other relevant documents were obtained prior to study initiation from the Independent Ethic Committee. Informed consent was obtained by each patient prior to enrollment in the study.

Exclusion criteria

Patients with a diagnosis of asthma or bronchiectasis at the enrollment visit or with immunosuppressive or other life-threatening disorders.

Study definitions

Moderate-to-severe COPD was defined as a forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) ratio < lower limit of normal (LLN) and FEV1 < 60%.

COPD exacerbation was defined as a sustained worsening of the patient condition from the stable state and beyond normal day to day variations, acute in onset and needing a change in regular medication. A stable disease was considered as

absence of exacerbation episodes during the last 30 days.

S. pneumoniae colonization was present when *S. pneumoniae* was found in two different sputum cultures recollected within 4 months from each other, in absence of an exacerbation event. Exacerbation caused by an *S. pneumoniae* infection was defined as the concomitant presence (during the same visit) of an ongoing exacerbation according to clinical evaluation and a sputum sample positive for *S. pneumoniae*.

Data collection

At each visit, demographic information and medical history, including the presence of a pre-existing microbial colonization, were collected and physical examination performed. Moreover, at each visit patients were questioned about the status of their chronic respiratory symptoms in order to identify previous or ongoing episodes of exacerbation.

Microbiological work up

Sputum samples were collected at enrollment during stable state to evaluate the frequency of *S. pneumoniae* colonization and in case of an acute exacerbation to evaluate the incidence of pneumococcal infection. 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 in Florence, Italy (central laboratory). DNA was extracted by a commercial kit for PCR amplification. To confirm the extraction, each DNA sample was tested for its ability to be amplified with B-globin specific primers. *S. pneumoniae* was detected using real-time PCR, and the same technique was used to find the presence of specific antibiotic resistance genes (specifically for beta-lactam, macrolides and quinolones). PCR was used also to describe the different serotypes of *S. pneumoniae*, finding the different serotype genes.

Statistical analysis

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, whereas non-normally distributed data

are presented as median with interquartile range (IQR). The incidence rate was computed as the number of exacerbations concomitant to *S. pneumoniae* infection divided by the person-time of observation.

Results

A total of 79 stable patients with moderate to very severe COPD was enrolled. The majority of them were male (81%) and former smokers (59%), with a median (IQR) age of 74 (70–78.5). Median (IQR) duration of COPD was 6.6 (3.6–10.4) years.

The number of exacerbation episodes in the previous year was 2.0 (1.0–3.0). A total of 68% of patients had an influenza vaccination during the year before, while only 32% of patients had a 23-valent polysaccharide vaccine (PPV23) vaccination during the previous 10 years, despite national guidelines suggesting that every COPD patient should receive a pneumococcal vaccination.²

A total of 59 (91%) patients had at least one sputum sample collected during the study period. A total of 217 samples were collected, and 27% ($n = 59$) of those were positive for *S. pneumoniae*. Among patients with a positive sample for *S. pneumoniae*, 17 (27%) patients were found to be colonized at least at one visit during the follow-up period: in particular, 16 (25%) and 3 (5%) patients were colonized at 4-month and 8-month follow-up visits, respectively.

Overall four exacerbations due to *S. pneumoniae* occurred during follow up (0.31 per 100 person/month). COPD exacerbations were 37, and were mostly treated with levofloxacin (49%) and amoxicillin/clavulanate (19%).

Among positive samples for *S. pneumoniae*, 109 serotypes were identified. The most frequent serotypes in moderate-to-severe COPD patients during both stable state and exacerbation were 19F (12%), 18 (10%), 19A and 9V (9%) and 35 F (7%). Only 32% of COPD patients were effectively vaccinated for *S. pneumoniae* with PPV23 vaccine.

Finally, we found that pneumococcal strains identified in our population were resistant to neither macrolides, nor beta-lactams nor quinolones.

Discussion

The most frequent serotypes in moderate-to-severe COPD patients during both stable state and exacerbation were 19F, 18, 19A, 9V and 35 F. The serotypes identified in our study are consistent with previous experiences, except the interesting new finding of high prevalence of serotype 35F.^{1,6–10} Few recent studies showed an increase of serotype 35F among children carriers, especially after the extensive use of pneumococcal conjugate vaccine (PCV7) and adult patients with both invasive and noninvasive pneumococcal disease, even if it was more likely to be associated with colonization than disease.^{11,12}

According to our results, we might speculate that PCV13 could potentially be protective in about 48% of isolated serotypes in COPD patients, findings partly consistent with previous studies that show a potential coverage from PCV13 between 34% and 80% of cases.^{1,8–11}

In patients with COPD, *S. pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* are the main pathogens causing acute exacerbation of COPD (AECOPD) episodes^{1,13,14} These bacteria may chronically colonize the airways and cause exacerbations after a simple viral upper respiratory infection or an environmental stress.¹⁵ Nevertheless, studies also point out that a significant number of AECOPD infections may come from bacterial strains that are new to the patient.¹³

Pneumococcal vaccination could be useful both in decreasing *S. pneumoniae* colonization and therefore subsequent exacerbations, and in decreasing new pneumococcal infections in non-colonized patients.

Moreover, another interesting finding of our studies is absence of antibiotic resistance, particularly macrolide resistance, which is, on the contrary, described in previous studies.^{16–18} 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 of its monocentric design which impacts the generalizability of our results. Another limitation consists of the clinical challenge to discern between an acute COPD exacerbation and a pneumococcal pneumonia, in the setting of outpatients with a positive sputum culture for *S. pneumoniae*. Adding

a chest X-ray (CXR) to the evaluation may also not resolve the situation in obese patients or in elderly patients with several comorbidities, as their CXR findings could be equivocal.

However, this is the first prospective and real-life experience in Italy designed according to a high level microbiological investigation with the aim at identifying the proportion of COPD colonization and acute exacerbations attributable to *S. pneumoniae* and describing serotype distribution and antibiotic resistance patterns of pneumococcal isolates.

Conclusion

In conclusion, our study found that the most frequent *S. pneumoniae* serotypes in COPD patients are 19F, 18, 19A, 9V and 35 F, and that almost 50% of *S. pneumoniae* strains could be covered by PCV13 in adult COPD patients.

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Conflict of interest statement

F. Blasi declared financial relationships with Bayer Healthcare, Griffols, AstraZeneca, Basilea, Zambon, Novartis, Chiesi, Menarini, Dompè, Guidotti, GSK, Pfizer, Teva.

S. Aliberti declared financial relationships with Bayern Healthcare, Aradigm Corporation, Griffols, AstraZeneca, Basilea, Zambon, Novartis, Raptor, Chiesi, Actavis UK Ltd.

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