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# *Pseudomonas aeruginosa* in Chronic Obstructive Pulmonary Disease Patients with Frequent Hospitalized Exacerbations: A Prospective Multicentre Study

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**Keywords**
Chronic obstructive pulmonary disease · Readmission · Exacerbation · *Pseudomonas aeruginosa* · Risk factors

**Abstract**
***Background:*** *Pseudomonas aeruginosa* (PA) is a common microorganism related to severe exacerbations in Chronic Obstructive Pulmonary Disease (COPD). However, their role in COPD patients with frequent hospitalized exacerbations (FHE) is not well described. ***Objectives:*** We aimed to determine prevalence, risk factors, susceptibility patterns and impact on outcomes of PA in COPD patients with FHE. ***Methods:*** Prospective observational multicentre study that included COPD patients with FHE. The cohort was stratified in 2 groups according to the presence or absence of PA isolation in sputum. Patients were followed up for 12 months. ***Results:*** We enrolled 207 COPD patients with FHE. In 119 patients (57%), a valid sputum culture was collected. Of them, PA was isolated in 21 patients (18%). The risk factors associated with PA were prior use of systemic corticosteroids (OR 3.3, 95% CI 1.2–9.7, $p = 0.01$) and prior isolation of PA (OR 4.36, 95% CI 1.4–13.4, $p < 0.01$). Patients with PA had an increased risk of having ≥3 readmissions (OR 4.1, 95% CI 1.3–12.8, $p = 0.01$) and higher PA isolation rate (OR 7.7, 95% CI 2.4–24.6, $p < 0.001$) during the follow-up period. In 14 patients (67%), PA was resistant to at least one antibiotic tested. PA persisted in the sputum in 70% of patients. ***Conclusions:*** The presence of PA was related to 3 or more readmissions during the 1-year follow-up and PA persisted in the sputum despite an appropriate antibiotic treatment. This finding suggested an important role of PA in the course of the disease of COPD patients with FHE.



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## Introduction

Exacerbations of Chronic Obstructive Pulmonary Disease (COPD) that require hospitalization are associated with poor clinical outcomes and are responsible for most of the economic burden of the disease [1–3]. Patients admitted with an exacerbation have an increased risk of future hospital readmissions [4, 5], which is also related with a progressive increase in the risk of death [6]. Therefore, COPD patients with frequent hospitalized exacerbations (FHE) are a population with important clinical and social implications [7, 8]. Characterizing these patients at the time they experience a second severe exacerbation, which makes them frequent exacerbators [9], may be clinically relevant.

Respiratory infections are the most important cause of severe exacerbations in COPD [10]. Among causative microorganisms, *Pseudomonas aeruginosa* (PA) is the most frequently isolated in severe COPD patients [11, 12]. PA has the ability to generate resistance against first line antibiotics used to treat exacerbations [13, 14] and may persist in the airways after an appropriate antibiotic treatment in severe COPD patients [15]. It has been postulated that PA may play an important role in the natural history of COPD [16] and several studies have related its presence with worse clinical outcomes [17, 18]. However, in COPD patients with FHE, limited data regarding PA prevalence, resistance patterns and impact on clinical outcomes are available.

We hypothesized that PA plays an important role in patients with COPD and FHE. Therefore, the aim of our study is to determine prevalence, risk factors, antibiotic susceptibility patterns and impact on outcomes of PA in a prospective cohort of COPD patients identified at the time they become frequently hospitalized exacerbators.

## Methods

We conducted a prospective multicentre observational study in 3 hospitals in Spain (Hospital de la Santa Creu i Sant Pau, Barcelona, Complejo Hospitalario Universitario de A Coruña, A Coruña, and Hospital Comarcal de Mollet, Mollet del Vallés) from March 2012 to March 2015. The study was approved by the institutional review board (IIBSP-200920). Written consent was waived because of the non-interventional design.

*Subjects*

Inclusion criteria was COPD patients with FHE, defined as COPD patients admitted for the second exacerbation period within 12 months of the initial one.

Diagnosis of COPD was confirmed by a forced spirometry showing post-bronchodilator forced expiratory volume in 1 s/forced vital capacity ratio ≤70%. Exacerbation was defined as an acute event characterized by worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medications requiring hospitalization [19].

Exclusion criteria included other airway diseases as primary diagnosis (such as bronchiectasis not related to COPD, asthma and/or interstitial lung diseases), pneumonia or heart failure at admission. Patients with a new prescription of chronic treatment with macrolides in the last year and patients with a suspected underlying malignancy or pre-existing medical condition with a life expectancy of less than 6 months were also excluded.

*Data Collection*

Information collected included demographic data, co-morbid conditions, current treatments, smoking history, functional status, number of exacerbations during the last year, previous isolation of PA and prior antibiotic and corticosteroids treatment. Clinical signs including Anthonisen criteria [20], laboratory tests and radiology results were assessed at the time of hospital admission. Patients were followed-up for 12 months after hospital discharge, from event reports by electronic records of each hospital.

*Microbiology*

Spontaneous sputum culture was collected during the first 48 h of admission. Samples were processed and antimicrobial susceptibility testing was performed as previously described [15]. Good quality samples were defined as <10 squamous epithelial cells and >25 leukocytes per field and only potential pathogenic microorganisms (PPMs) were evaluated.

PA was classified as resistant (PAR) when it was not susceptible to at least one of the following antibiotic classes: antipseudomonal fluoroquinolones, antipseudomonal cephalosporins, antipseudomonal penicillins plus beta-lactamase inhibitors, antipseudomonal carbapenems, aminoglycosides, monobactams and polymixins. Multidrug resistance (MDR) was defined as PA resistant to one or more agents in 3 or more of the aforementioned antimicrobial classes [21].

Spontaneous sputum cultures were collected during the follow-up at physician discretion. The presence of PA was evaluated at 3, 6, 9 and 12 months. Information of PA isolations in sputum during the previous year was also registered.

*Study Groups*

For the purpose of the study, patients were divided in 2 groups according to the presence of PA in the sputum culture at admission. Patients with isolation of PA were assigned to the PA group and patients with no PPMs isolation in the sputum culture were assigned to the non-PPMs group. Patients with isolation of other PPMs different from PA were excluded from the comparative analysis due to the small sample and its heterogeneity.

*Study Outcomes*

Outcomes evaluated were short (30- and 90-day) and long-term (180- and 365-day) readmissions and mortality, time to first readmission, number of hospital readmissions and PA isolation during the follow-up period of 1 year.

Readmission was considered a new hospital admission due to an exacerbation after hospital discharge. Mortality was analysed as

death from all causes from the first day of admission to completion of 1-year follow-up.

PA isolation during the follow-up included new isolations and PA persistence. PA persistence was defined as a new positive PA sputum culture after at least 10 days of appropriate antibiotic treatment, according to the in vitro susceptibility, as we previously described [15].

*Statistical Analysis*

Univariate statistics was used to test the association of demographic and clinical characteristics with the presence of PA. Categorical variables are presented by frequencies and percentages and statistical differences were analysed using $\chi^2$ test or Fisher exact test when required. Continuous variables are presented as mean and SD or median and interquartile range (IQR) when data was not distributed normally. Statistical differences among continuous variables were analysed using Student *t* test or their corresponding non-parametrical test when was required. We defined statistical significance as a 2-tailed $p < 0.05$.

We performed logistic regression analyses using clinical outcomes evaluated as dependent variables and the presence of PA as independent variable. A secondary analysis was performed including only patients with PA (sensitive versus resistant). All analyses were performed with SPSS 19.0 software program (SPSS Inc, Chicago, IL, USA).

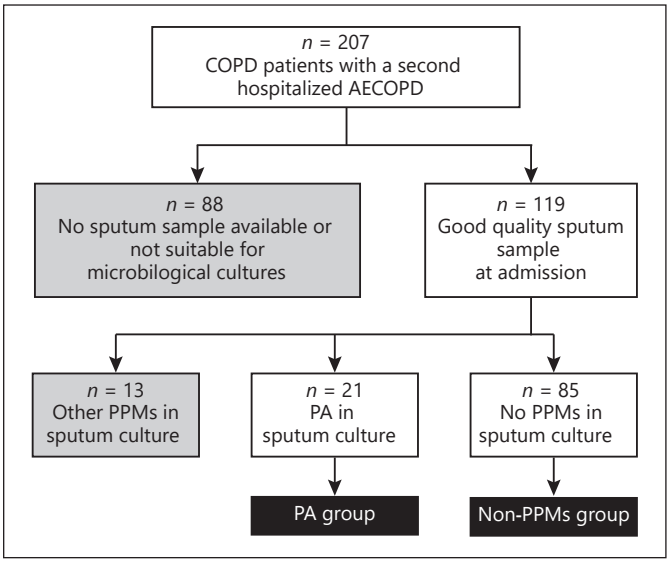


**Fig. 1.** Study flowchart diagram. COPD, chronic obstructive pulmonary disease; AECOPD, acute exacerbation chronic obstructive pulmonary disease; PA, *Pseudomonas aeruginosa*; PPMs, potential pathogenic microorganisms.

## Results

During the study period, 207 COPD patients with FHE were included. The mean age was 72.2 years (SD 8.5), 171 of them (83%) were men and 78 (38%) were current smokers. The median forced expiratory volume in 1 s was 35% (IQR 21) of predicted, Charlson co-morbidity index was median 4 (IQR 3) and main co-morbidities were heart failure (37%) and diabetes (26%). One hundred and eighteen patients (57%) had chronic respiratory failure receiving long-term oxygen therapy, and had a median MRC breathlessness scale of 4 (IQR 1).

In 119 patients (57%), a good-quality spontaneous sputum culture was collected in the first 48 h of admission. Anthonisen criteria type I (3 criteria) or II (2 criteria) was present in 92 of these patients (77%) suggesting an infectious exacerbation. In 25 patients (21%), a prior isolation of PA was found. Patients were stratified in 2 groups: PA group when PA was isolated in sputum culture ($n = 21$, 18%) and non-PPMs group when the sputum culture was negative for any PPM ($n = 85$, 71%). In 13 patients (11%), other PPMs where isolated in sputum culture, including *Moraxella catharralis* ($n = 3$, 2%), *Streptococcus pneumoniae* ($n = 2$, 2%), *Haemophilus influenzae* ($n = 2$, 2%) *and Klebsiella pneumoniae* ($n = 2$, 2%). Figure 1 shows the study flowchart.

*Patient Characteristics*

Table 1 shows the characteristics of study population, grouped by whether they had PA in the sputum (PA group) or a negative sputum culture (non-PPMs group). No differences were found among demographics, comorbid conditions, functional status, medications used, laboratory tests and Anthonisen criteria on admission. However, patients with PA were more likely to receive systemic corticosteroids in the previous 3 months to the admission (OR 3.38, 95% CI 1.2–9.1, $p = 0.01$) and to have a prior isolation of PA (OR 4.3, 95% CI 1.4–13.4, $p < 0.01$).

*Study Outcomes*

Table 2 shows study outcomes evaluated. Patients with PA were more likely to have 3 or more readmissions during the follow-up period compared to the non-PPM group (33 vs. 11%, OR 4.1, 95% CI 1.3–12.8, $p = 0.01$; Fig. 2a). Moreover, in those patients in whom control sputum was performed during the follow-up ($n = 97$), a higher number of PA isolations was observed in the PA group (71 vs. 24%, OR 7.7, 95% CI 2.4–24.6, $p < 0.001$), with temporal differences that increased every 3 months (Fig. 2b).

There were no differences in the other outcomes evaluated, including short- and long-term readmission, number of readmissions, time to first readmission and short-

**Table 1.** Patient demographics, clinical characteristics, co-morbid conditions, prior treatments, clinical signs and laboratory tests among patients with and without PA

| Variables | Non-PPMs group ($n$ = 85) | PA group ($n$ = 21) | $p$ value |
|---|---|---|---|
| *Demographics* | | | |
| Age, years, mean ± SD | 71 (8) | 71 (8) | 0.8 |
| Male gender | 73 (85) | 14 (66) | 0.1 |
| BMI, mean ± SD, kg/m$^2$ | 26 (5) | 25 (5) | 0.3 |
| *Co-morbid conditions* | | | |
| Current smoker | 32 (38) | 4 (19) | 0.1 |
| Charlson co-morbidity index, IQR | 4 (3) | 3.5 (2.7) | 0.5 |
| Diabetes mellitus | 17 (20) | 6 (29) | 0.4 |
| Heart failure | 28 (33) | 10 (48) | 0.2 |
| Prior malignancy | 9 (11) | 4 (19) | 0.3 |
| Stroke | 2 (2) | 0 (0) | 0.9 |
| Chronic liver disease | 5 (6) | 1 (5) | 0.9 |
| Chronic kidney disease | 7 (8) | 5 (24) | 0.1 |
| GERD | 5 (6) | 1 (5) | 0.9 |
| *Functional status* | | | |
| FEV1, IQR, % | 37 (26) | 32 (13) | 0.4 |
| GOLD score D | 80 (94) | 18 (86) | 0.2 |
| Non-hospitalized exacerbations, IQR, prior year | 1 (1) | 1 (1) | 0.8 |
| *Medications* | | | |
| ICS | 82 (96) | 19 (90) | 0.3 |
| LABA | 80 (94) | 18 (86) | 0.2 |
| LAMA | 77 (91) | 18 (86) | 0.4 |
| Roflumilast | 4 (5) | 2 (9) | 0.3 |
| Chronic macrolide | 4 (5) | 0 (0) | 0.6 |
| Long term oxygen therapy | 48 (56) | 13 (62) | 0.6 |
| *Prior treatment* | | | |
| Antibiotics (prior 3 months) | 52 (61) | 14 (67) | 0.6 |
| SCS (prior 3 months) | 24 (28) | 12 (57) | **0.01** |
| Time to prior AECOPD admission, IQR, days | 89 (156) | 59 (118) | 0.6 |
| Prior ICU admission | 18 (21) | 6 (29) | 0.7 |
| *Clinical signs* | | | |
| Sputum purulence | 45 (53) | 15 (71) | 0.1 |
| Anthonisen criteria [20], $n$ (%) | | | |
| Type I | 39 (46) | 13 (62) | 0.4 |
| Type II | 24 (28) | 5 (24) | 0.7 |
| Type III | 22 (26) | 3 (14) | 0.2 |
| *Laboratory tests* | | | |
| Leukocytes, IQR, U/mL | 10,240 (5,790) | 11,000 (6,605) | 0.6 |
| Eosinophils, IQR, U/mL | 0.8 (1.6) | 0.8 (1.1) | 0.7 |
| pO2, IQR, mm Hg | 59 (15) | 55 (18) | 0.3 |
| pCO2, IQR, mm Hg | 44 (19) | 49 (15) | 0.2 |
| paO2/FiO2, IQR | 257 (75) | 258 (62) | 0.6 |
| C-Reactive protein, IQR, mg/L | 22 (50) | 42 (61) | 0.1 |
| *Microbiology* | | | |
| Prior PA isolation | 11 (13) | 12 (57) | **<0.01** |

Data is presented as $n$ (%), and mean (SD) or median (IQR) when required. $p$ values in bold indicates statistically significant differences. IQR, interquartile range; PPMs, potential pathogenic microorganisms; PA, *Pseudomonas aeruginosa*; BMI, body mass index; GERD, gastroesophageal reflux disease; FEV1, forced expiratory volume in 1 s; COPD, chronic obstructive pulmonary disease; GOLD, global initiative for chronic obstructive lung disease; ICS, inhaled corticosteroids; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; SCS, systemic corticosteroids; ICU, intensive care unit; pO2, oxygen partial pressure; pCO2, carbon dioxide partial pressure; FiO2, fraction of inspired oxygen.

**Table 2.** Clinical outcomes evaluated during the follow-up (12 months), between patients with and without PA

| Outcomes | Non-PPMs group ($n$ = 85) | PA group ($n$ = 21) | $p$ value |
|---|---|---|---|
| 30-Day readmission | 20 (24) | 2 (9) | 0.2 |
| 90-Day readmission | 36 (44) | 6 (32) | 0.3 |
| 180-Day readmission | 45 (55) | 13 (68) | 0.3 |
| 365-Day readmission | 61 (75) | 15 (79) | 0.9 |
| Number readmissions/1,000 days*, IQR | 2.7 (5.5) | 2.7 (8.2) | 0.7 |
| ≥2 readmissions during the follow-up | 23 (28) | 8 (38.1) | 0.3 |
| ≥3 readmissions during the follow-up | 9 (11) | 7 (33) | **0.01** |
| Time to readmission, IQR | 64 (117) | 118 (104) | 0.4 |
| PA isolation during the follow-up‡ | 19/80 (24) | 12/17 (71) | **<0.001** |
| Time to PA isolation during follow-up, mean ± SD | 169 (104) | 135 (118) | 0.4 |
| 30-Day mortality | 4 (5) | 0 (0) | 0.6 |
| 90-Day mortality | 7 (8) | 3 (14.3) | 0.4 |
| 180-Day mortality | 10 (12) | 3 (14.3) | 0.7 |
| 365-Day mortality | 19 (22) | 5 (23.8) | 0.9 |

Data is presented as $n$ (%) and mean (SD) or median (IQR) when required.

* Number of readmissions/days of follow-up 1,000 days. ‡ Over patients with sputum culture collected during the follow-up. $p$ values in bold indicates statistically significant differences.

IQR, interquartile range; PPMs, potential pathogenic microorganisms; PA, *Pseudomonas aeruginosa*.

and long-term mortality. A Cox survival test was performed evaluating mortality (Hazard Ratio [HR] 2.29 [95% CI 0.74–7.12], $p$ = 0.15) and readmissions (HR 0.95 [95% CI 0.53–1.68], $p$ = 0.85), with no differences among groups.

Six patients (28%) of the PA group had prior isolation and PA-positive sputum during the follow-up. When compared to other patients with PA at admission, no differences in clinical outcomes evaluated were found (data not show).

*Pseudomonas aeruginosa Resistant Patterns*

At the time of hospital admission, 14 patients with PA (67%) had resistance to at least one antimicrobial class (PAR), and only 7 patients (33%) had pansensitive PA (PAS). Among PAR patients, 5 (35%) were MDR. There were no statistical differences among patient's characteristics and clinical outcomes among patients with PAS, PAR and MDR PA (data not shown).

## Discussion

The main finding of our study is that COPD patients with FHE have a high prevalence of PA, especially PA-resistant strains. The presence of PA at the moment of the patient become a FHE is associated with an increased risk of 3 or more readmissions during the follow-up period. In addition, PA persists in the sputum in most of the patients and PA isolations increase during the follow-up, which suggests an important role of PA in the course of the disease of these severe COPD with FHE.

Severe COPD exacerbation that requires hospitalization results in a significant impact in the natural course of COPD [22]. Patients admitted with an exacerbation experienced a marked decline in their lung function, worse quality of life and shorter survival [3, 6, 23]. In addition, hospitalized COPD patients have an increased risk of new hospital readmission [4, 5]. Previous studies have identified "frequent exacerbator phenotype," which is independent of disease severity, defined as those COPD patients who had 2 or more exacerbations [9]. Exacerbation prevention and interventions to reduce re-hospitalizations have been considered a key component of COPD-management strategies [19, 24]. However, limited data is available regarding COPD patients who require subsequent hospitalization due to exacerbations. Thus, the subgroups of patients represent a target population to implement these strategies. Our prospective cohort showed that COPD patients with FHE are an elderly and mostly male population, with multiples co-morbidities and with chronic respiratory failure in most of the cases. This group of patients tend

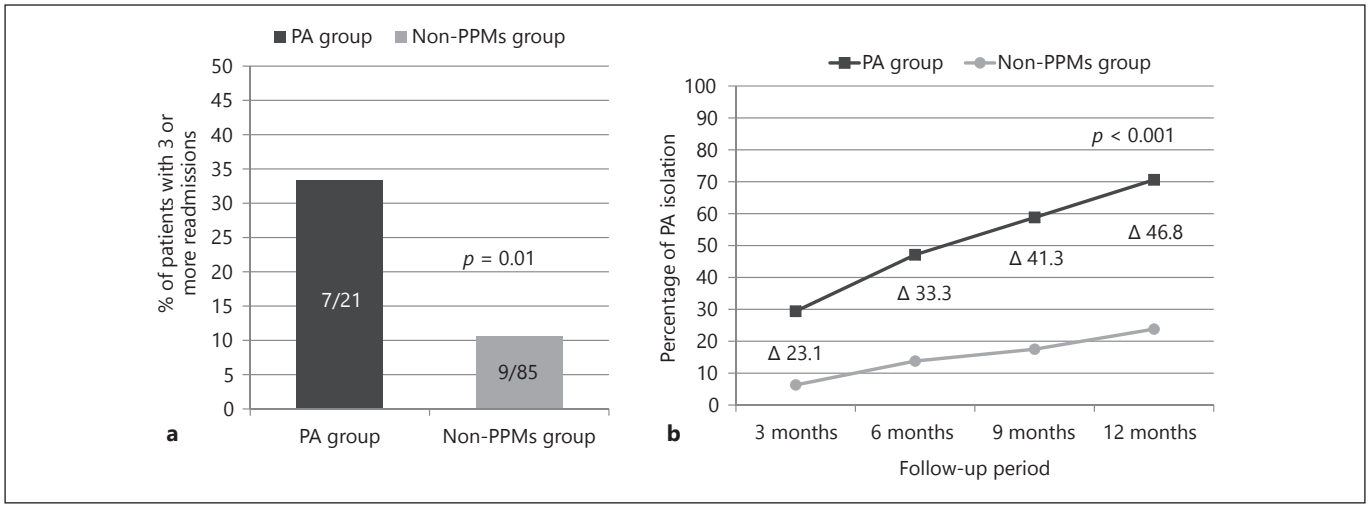


**Fig. 2. a** Percentage of patients with 3 or more readmissions during the follow-up among COPD patients with PA and without PPMs in sputum samples. $p = 0.01$. **b** Percentage of PA isolation during the follow-up among both groups. Temporal differential among groups was calculated every 3 months. $p < 0.001$. PA, *Pseudomonas aeruginosa*; PPMs, potential pathogenic microorganisms.

to be excluded from clinical trials, which focus on interventions that reduce severe exacerbations [25–27]. Our study is a novel one, as it addresses a group of patients that require a better characterization of their disease progression in order to reduce readmissions after a COPD exacerbation.

PA was the most common PPM isolated in our cohort of severe COPD patients with FHE. The presence of PA in the sputum at admission was observed in 10% of the whole cohort and in 18% of patients where a valid sputum culture was performed, which is concordant with previous studies that included hospitalized COPD patients [12, 28, 29] and confirms the importance of PA in this population. In our study, risk factors for PA were prior PA isolation and previous use of systemic corticosteroids. Prior isolation of PA was also detected as the strongest risk factor in another prospective study that included 188 hospitalized COPD patients [12]. Use of systemic corticosteroids was also reported in several studies [12, 30]. These findings may suggest the important issue of an appropriate antipseudomonal antibiotic empirical treatment in COPD patients with these risk factors.

PA is associated with worse clinical outcomes in COPD patients [18, 31, 32]. In our study, we found that COPD patients with PA were at higher risk to have 3 or more readmissions during the follow-up period compared with the non-PPMs group. Hospital readmission is common in severe COPD patients and it is associated with an increased long-term risk of death [6]. Although several studies have been performed in order to detect factors associated to hospital readmissions in COPD [33–35], in our knowledge, none of them has identified the presence of PA as a potentially modifiable one. In addition, we demonstrated that PA persists in the sputum despite an appropriate antibiotic treatment in most of the patients although with a different pattern of antibiotic resistance. This finding suggests that PA chronically infects these patients as previous studies have reported [15, 17, 36] and new antibiotic strategies, including inhaled therapy, may be considered in this population. Further studies are needed to better understand the relationship of PA with other clinical outcomes related to the evolution, relapses and therapeutically failures in COPD patients.

An important clinical concern related to PA is its acquisition of resistance to one or more antimicrobial agents [14, 37]. We previously demonstrated that hospitalized COPD patients had a high incidence of PAR, which was associated with PA persistence in the sputum after antibiotic treatment. On the other hand, COPD patients admitted with PAS had higher short-term mortality, suggesting the presence of virulence characteristics independent of the resistance patterns [15]. In this study, prevalence of PAR was very high (67%), as other authors previously demonstrated in severe COPD patients [37, 38]. However, no differences in clinical outcomes evaluated were observed in this group of patients, probably due to the small sample size ($n = 7$) of patients with sensitive PA.

Our study has several limitations. First, although it was a prospective multicentre study that included more than 200 COPD patients with FHE, only 57% patients had a good quality sputum culture on admission and limited the generality of the results. Second, our cohort comprehended predominantly male patients, although the low number of women is concordant with other Spanish studies in hospitalized COPD patients and is probably related to the lower prevalence of COPD in women [6, 12, 31]. Third, the isolation of PA in spontaneous sputum can either represent upper airway colonization or lower respiratory tract infection, although all patients included in the study had an acute exacerbation based on signs and symptoms. And finally, as it was an observational study, sputum samples were collected at physician discretion, in spite of the fact that 91% of the patients had at least one sputum control collected during the follow-up.

## Conclusions

Our data demonstrated that PA plays an important role in the course of COPD in patients with FHE, by increasing percentage of 3 or more readmissions and persisting in patient's airways during the follow-up. However, 1-year mortality was not different among patients with and without PA. Further studies are needed to better understand the underlying mechanisms that are responsible for these findings.


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