

Bacterial flora in the sputum and comorbidity in patients with acute exacerbations of COPD

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Objective: To determine in patients admitted with an acute exacerbation of chronic obstructive pulmonary disease (AE-COPD) the association between the isolation of potential pathogens in a conventional sputum culture and comorbidities.

Patients and methods: The ESMI study is a multicenter observational study. Patients with AE-COPD admitted to the Internal Medicine departments of 70 hospitals were included. The clinical characteristics, treatments, and comorbidities were gathered. The results of conventional sputum cultures were recorded.

Results: A total of 536 patients were included, of which 161 produced valid sputum and a potentially pathogenic microorganism was isolated from 88 subjects (16.4%). The isolation of *Pseudomonas aeruginosa* (30.7%) was associated with a greater severity of the lung disease (previous admissions [$P=0.026$], dyspnea scale [$P=0.047$], post-bronchodilator forced expiratory volume in 1 second (FEV₁) [$P=0.005$], and the BODEx index [$P=0.009$]); also with higher prevalence of cor pulmonale ($P=0.017$), heart failure ($P=0.048$), and cerebrovascular disease ($P=0.026$). *Streptococcus pneumoniae* (26.1%) was associated with more comorbidity according to number of diseases ($P=0.018$); notably, peripheral artery disease ($P=0.033$), hypertension ($P=0.029$), dyslipidemia ($P=0.039$), osteoporosis ($P=0.0001$), and depression ($P=0.005$).

Conclusion: Patients with AE-COPD and *P. aeruginosa* present higher severity of COPD, while those with *S. pneumoniae* present greater comorbidity. The potentially pathogenic microorganism obtained in the sputum culture depends on the associated comorbidities.

Keywords: chronic obstructive pulmonary disease, comorbidities, hospitalization, sputum culture, etiology of exacerbations

Introduction

Acute exacerbations of chronic obstructive pulmonary disease (AE-COPD) have a great impact on health status,¹ disease progression,² and prognosis.³

Up to 50%–70% of AE-COPD can be attributed to respiratory infections by viruses or bacteria, even more in the most severe patients.⁴ Finding a purulent sputum suggests, but does not prove, a bacterial etiology, since 25%–50% of COPD patients are colonized by potentially pathogenic microorganisms (PPM).⁵ Bacterial colonization has been associated with the frequency and severity of COPD exacerbations.⁶

Most guidelines recommend the use of antibiotics whenever two or more of the Anthonisen's criteria,⁷ ie, increased dyspnea, increased sputum volume, and increased sputum purulence, are met. Nevertheless, sputum purulence seems to be the main factor associated with infection.^{8,9}

The choice of antimicrobial agent depends on the suspected microorganism, based on the clinical circumstances,¹⁰ the severity of the COPD,¹¹ and the presence of comorbidities (diabetes mellitus, liver cirrhosis, chronic kidney failure, or heart disease), infections, or previous antibiotherapy.

Even though the presence of comorbidities is associated with a higher risk of therapeutic failure and modifies the choice of antibiotic according to recommendations of scientific societies,^{12,13} such indications are mainly based on expert opinion, not on prospective studies. Hence, studies are needed to prove whether the presence of comorbidities bears any relation to the microorganism causing AE-COPD and might help to choose an antibiotic treatment empirically. This way both therapeutic failure and occurrence of resistance could be reduced.

Our primary aim was to assess the comorbidities of patients admitted to Internal Medicine services and its association to bacteriological isolation through conventional sputum culture, seeking to obtain clinical features that might help a microbiological diagnosis.

Materials and methods

The ESMI (Spanish acronym for COPD in Internal Medicine Services) is an epidemiological multicenter research study, cross-sectional in the first stage and longitudinal later on. The inclusion period lasted a year (October 2009 to October 2010) and its methodology has been previously described elsewhere.¹⁴ In brief, the ten first consecutive patients attended to in each of 70 participating hospitals for AE-COPD were studied, whether they required hospitalization or not. The main aim was to describe the comorbidities and their relation to mortality and hospital readmissions within the first 3 months after discharge.

For this research, only patients admitted with a confirmed AE-COPD were included, since guidelines recommend carrying out a sputum culture in this population, that usually presents with a severe or very severe exacerbation along with therapeutic failure.^{15,16} In conclusion, this study was a multicenter, cross-sectional study conducted to identify isolated bacteria in the sputum of exacerbated COPD patients and to relate them to the comorbidities. The COPD diagnosis required spirometric confirmation (post-bronchodilator FEV₁/forced vital capacity (FVC) <0.7). Patients admitted for causes other than AE-COPD and those who could not undergo the spirometry or did not meet the spirometric criteria were excluded.

All patients included were assessed during admission, and their clinical and functional data were gathered through a specifically designed questionnaire. The Charlson index¹⁷ was used to assess comorbidities, without age adjustments and including COPD, as well as a number of other diseases not included in this index that we considered especially relevant, such as history of myocardial infarction, arterial

hypertension, venous thromboembolic disease, arrhythmia, anemia, dyslipidemia, or osteoporosis.¹⁴

Other data gathered included body mass index, the modified Medical Research Council (mMRC) dyspnea scale,¹⁸ the usual treatment prior to admission, basal gasometry at admission, and C-reactive protein (CRP). The functional status was also assessed, using Katz index¹⁹ at baseline. The BODEx index²⁰ (replaces exercise capacity with exacerbations) score was calculated.

Finally, conventional sputum samples were taken during the admission according to the usual clinical practice. The sputum was considered valid following the criteria of Murray and Washington.²¹

In order to compare clinical characteristics in relation to the sputum results, patients were divided according to the microorganism isolated in their culture, comparing them with the rest of the patients with a valid culture but different microorganism results.

Eventually, this resulted in the division of patients into three groups, and based on whether FEV₁ is above or under 50%,^{10,22} we grouped the patients depending on the isolation of *Pseudomonas aeruginosa* or Enterobacteriaceae (group 1); *Streptococcus pneumoniae*, *Haemophilus influenzae* or *Moraxella catarrhalis* (group 2); or non-potential pathogen microorganisms (nPPM) (group 3).

Statistical analysis

Qualitative variables are expressed as absolute frequency and percentages (%), and quantitative variables as mean and standard deviation in case of normal distribution, and as median otherwise. For the bivariate analysis, we used the chi-square test or Fisher's exact test whenever it was required. To study the differences between averages, we used Student's *t*-test or Mann-Whitney *U*-test whenever appropriate. The analysis was carried out with the SPSS 15.0 statistical package, and every analysis was based on the bilateral hypothesis with a statistical significance level under $P < 0.05$.

The study was approved by the Clinical Trials Committee of the Hospital Mútua de Terrassa that acted as a coordinating center. All patients accepted taking part freely and signed an informed consent document.

Results

Out of a total of 679 identified patients, 606 were included in the ESMI study. Of these, 70 (11.5%) were discharged directly from Emergency Department, not requiring hospitalization in the ward, and were hence excluded. Compared with patients who did require hospitalization, those discharged

from Emergency Department were younger and had better pulmonary function and fewer comorbidities ($P<0.001$). Furthermore, it was possible to obtain a conventional sputum sample from a smaller percentage of this group (26.1% vs 47.8%, $P<0.05$).

A sputum sample was obtained from 256 (47.8%) out of 536 patients. The most frequent reasons for not obtaining it from the remaining 280 (52.2%) patients were that they could not expectorate (101 patients, 18.8%) and that they were not asked to during their hospitalization (172 patients, 32.1%). In the case of seven other patients, the cause was not registered. Figure 1 shows the flowchart of participants.

Characteristics of patients

The clinical and demographic characteristics of patients are presented in Table 1. The mean age was 73.2 (9.5) years (range 41–94). In all, 486 (90.8%) were men, with an average post-bronchodilator % predicted FEV₁ of 48.3 (15.7), and their average Charlson index score was 3.14 (2.0). Compared with the participants who did not produce sputum, the COPD patients who produced a sputum sample had a significantly higher smoking exposure, suffered more hospitalizations for AE-COPD in the previous year, and required long-term oxygen therapy ($P<0.05$).

Table 2 presents the characteristics of exacerbations. Prior to admission, systemic corticosteroids or antibiotics had been administered to 21.9% and 31.7% of subjects, respectively.

Compared with the participants who did not produce sputum, the COPD patients who produced a sputum sample more frequently experienced an increase of expectoration, change of color in the sputum, and fever. Furthermore, their hospital stays were longer ($P<0.05$). The sputum was valid for culture in 161 patients. Compared with those who did not provide a sputum, they had shown symptoms prior to admission for more days (6.4 vs 5.2; $P=0.038$), they had higher CRP values (mg/L) in Emergency Department (63.2 vs 35; $P=0.03$) and their hospital stay was longer (10.9 vs 9.1 days; $P=0.04$).

Bacteriologic isolation

Out of 161 patients who provided a sputum sample that was valid for culture, saprophytic flora (nPPM) was isolated in 73 (44.8%). The culture was positive for PPM in 88 of all 536 AE-COPD cases who required hospitalization (16.4%). The most frequently isolated microorganism was *P. aeruginosa* in 27 (30.7%), followed by *S. pneumoniae* in 23 (26.1%), Enterobacteriaceae in 18 (20.4%), *H. influenzae* in 14 cases (15.9%), and finally *M. catharrhalis* in 6 (6.8%) (Figure 2).

Bacterial flora in the sputum and comorbidity

Table 3 presents the various comorbidities according to isolation in sputum cultures. In Figure 3, we show the different characteristics of patients according to the microbiological diagnostic of the sputum culture.

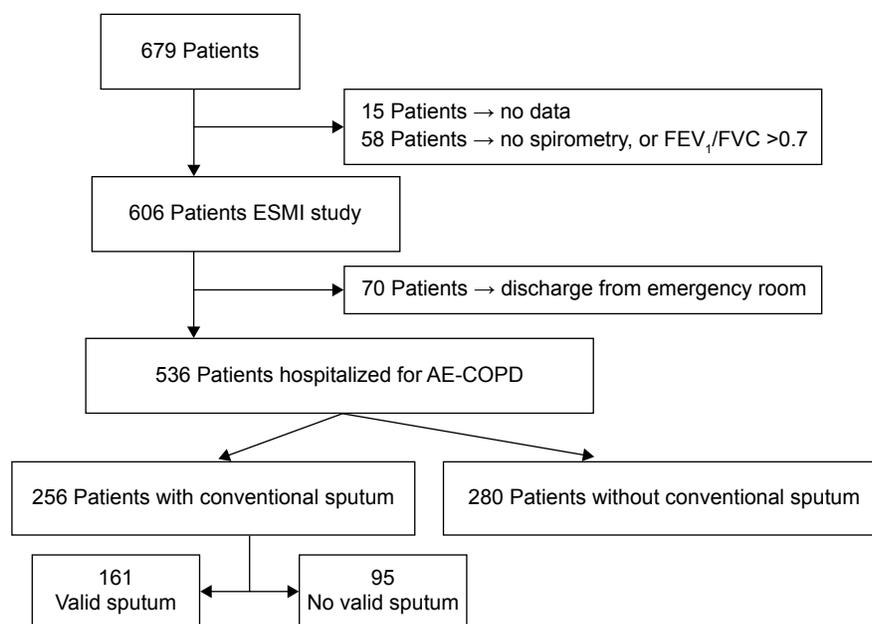


Figure 1 Flowchart of the patients.

Abbreviations: AE-COPD, acute exacerbation of chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.

Table 1 Characteristics of all study patients

| | Total (n=536) | With sputum (n=256) | Without sputum (n=280) | P-value |
|---|-----------------|---------------------|------------------------|------------------|
| Age, mean \pm SD, years | 73.19 \pm 9.6 | 73.68 \pm 9.2 | 72.7 \pm 9.9 | 0.26 |
| Male sex | 486 (90.8) | 234 (91.8) | 252 (90) | 0.48 |
| BMI \pm SD | 27.4 \pm 4.8 | 27.3 \pm 4.5 | 27.6 \pm 5.1 | 0.40 |
| Smoking status | | | | |
| Ex-smokers | 506 (94.4) | 246 (96.1) | 260 (92.9) | 0.10 |
| Never | 30 (5.6) | 10 (3.9) | 20 (7.1) | |
| Smoking history, mean \pm SD, packs/year | 56.6 \pm 27.5 | 59.3 \pm 26.5 | 54.1 \pm 28.3 | 0.03 |
| First admission for AE-COPD | 112 (20.9) | 39 (15.2) | 73 (26.2) | 0.002 |
| Hospitalized for AE previous year | 394 (73.5) | 199 (77.7) | 195 (69.6) | 0.03 |
| Hospitalization for AE previous year, mean \pm SD, number | 1.6 \pm 1.6 | 1.8 \pm 1.66 | 1.4 \pm 1.6 | 0.006 |
| Hospitalization for AE previous year, mean \pm SD, days | 14.6 \pm 17.0 | 17.3 \pm 18.3 | 12.1 \pm 15.3 | <0.001 |
| Charlson index | 3.1 \pm 2.0 | 3.2 \pm 2.02 | 3.05 \pm 1.99 | 0.29 |
| Katz index | 5.2 \pm 1.3 | 5.19 \pm 1.38 | 5.27 \pm 1.3 | 0.49 |
| Dyspnea scale (mMRC) | 2.3 \pm 1.1 | 2.4 \pm 1.05 | 2.32 \pm 1.13 | 0.37 |
| Spirometry post-PBD ^a | | | | |
| FEV ₁ \pm SD, mL | 1,186 \pm 503 | 1,164 \pm 500 | 1,207 \pm 508 | 0.36 |
| FVC \pm SD, mL | 2,243 \pm 840 | 2,241 \pm 807 | 2,244 \pm 872 | 0.97 |
| FEV ₁ /FVC \pm SD | 55.2 \pm 32.9 | 52.5 \pm 11.7 | 57.9 \pm 44.5 | 0.09 |
| FEV ₁ % \pm SD | 48.3 \pm 15.7 | 48.6 \pm 15.4 | 48.1 \pm 15.9 | 0.72 |
| FVC% \pm SD | 68.5 \pm 18.5 | 68.8 \pm 18.5 | 68.5 \pm 18.6 | 0.83 |
| COPD grade (GOLD) | | | | |
| Moderate (50–80) | 176 (42.4) | 81 (39.7) | 95 (45) | 0.14 |
| Severe (30–49) | 190 (45.8) | 103 (50.5) | 87 (41.2) | |
| Very severe (<30) | 49 (11.8) | 20 (9.8) | 29 (13.7) | |
| Treatment prior admission | | | | |
| Long-term oxygen therapy | 220 (41) | 119 (46.5) | 101 (36.2) | 0.02 |
| CPAP | 47 (8.8) | 20 (7.8) | 27 (9.7) | 0.45 |

Notes: Data presented as absolute frequencies (percentage), or mean (standard deviation). ^aData of spirometric parameters of 415 patients (spirometry in the last 6 months). Bold font denotes statistical significance.

Abbreviations: BMI, body mass index; AE, acute exacerbation; mMRC, modified Medical Research Council; PBD, post-bronchodilator; GOLD, Global Obstructive Lung Diseases; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.

Table 2 Characteristics of the patients and the acute exacerbation

| | Total (n=536) | With sputum (n=256) | Without sputum (n=280) | P-value |
|---|-----------------|---------------------|------------------------|------------------|
| Symptoms of AE, n (%) | | | | |
| Increased dyspnea | 530 (98.9) | 251 (98) | 279 (99.6) | 0.11 |
| Increased expectoration | 382 (73.3) | 211 (84.4) | 171 (63.1) | <0.001 |
| Change in the sputum | 394 (75.6) | 218 (87.2) | 176 (64.9) | <0.001 |
| Fever | 191 (36.7) | 117 (46.8) | 74 (27.3) | <0.001 |
| Anthonisen grade, n (%) | | | | |
| Class I | 395 (73.8) | 214 (83.6) | 181 (64.9) | <0.001 |
| Class II | 15 (2.8) | 10 (3.9) | 5 (1.8) | |
| Class III | 125 (23.4) | 32 (12.5) | 93 (33.4) | |
| Laboratory data, mean \pm SD | | | | |
| CRP (mg/L) | 49.2 \pm 82.6 | 53.4 \pm 87.4 | 44.9 \pm 77.7 | 0.39 |
| Arterial blood analysis, mean \pm SD | | | | |
| pO ₂ (mmHg) | 60.1 \pm 16.7 | 59.8 \pm 16.8 | 60.5 \pm 16.8 | 0.65 |
| pCO ₂ (mmHg) | 47.6 \pm 13.5 | 47.72 \pm 14.2 | 47.43 \pm 12.8 | 0.82 |
| HCO ₃ (mEq/L) | 28.4 \pm 5.2 | 28.5 \pm 5.2 | 28.3 \pm 5.25 | 0.73 |
| pH | 7.39 \pm 0.07 | 7.4 \pm 0.08 | 7.39 \pm 0.07 | 0.25 |
| Oral corticosteroids prior admission, n (%) | 117 (21.9) | 62 (24.2) | 55 (19.7) | 0.21 |
| Antibiotics prior admission, n (%) | 170 (31.7) | 81 (31.6) | 89 (31.8) | 0.97 |
| Days of clinical symptoms, mean \pm SD | 6.06 \pm 6.3 | 6.03 \pm 5.23 | 6.08 \pm 7.2 | 0.92 |
| Length of stay, mean \pm SD | 9.3 \pm 7.5 | 10.3 \pm 7.02 | 8.4 \pm 7.9 | 0.004 |
| Mortality during hospitalization, n (%) | 8 (1.6) | 6 (2.4) | 2 (0.7) | 0.16 |

Notes: Data presented as absolute frequencies (percentage), or mean (standard deviation). Bold font denotes statistical significance.

Abbreviations: AE, acute exacerbation; CRP, C-reactive protein; pO₂, partial arterial oxygen pressure; pCO₂, partial arterial carbon dioxide pressure; HCO₃, bicarbonate.

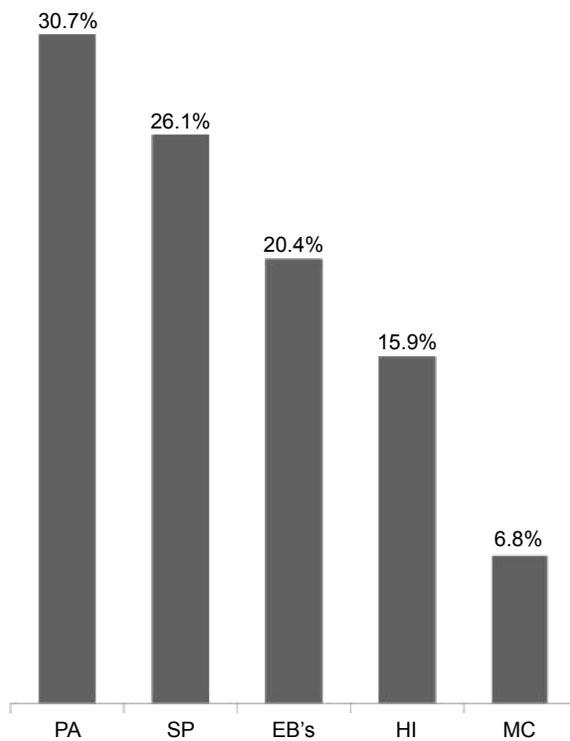


Figure 2 Potential pathogen microorganism isolated in sputum during exacerbation of COPD.

Abbreviations: PA, *Pseudomonas aeruginosa*; SP, *Streptococcus pneumoniae*; EB, Enterobacteriaceae; HI, *Haemophilus influenzae*; MC, *Moraxella catharrhalis*.

Patients with *P. aeruginosa* isolation in their sputum (27) more frequently had cor pulmonale ($P=0.01$), heart failure ($P=0.04$), and cerebrovascular disease ($P=0.02$). Also, these patients have a more severe (mean %FEV₁ 41.1 vs 49.1; $P=0.005$), higher BODEx index scores (6 vs 4.7; $P=0.008$), greater probability of having required admissions for AE-COPD during the previous year (92.6% vs 71.6%; $P=0.02$), greater dyspnea according to the mMRC scale (2.7 vs 2.3; $P=0.047$), a higher number of exacerbations (according to stratification used in BODE; $P=0.01$), greater purulence of sputum at admission ($P=0.02$), and they more frequently used inhaled corticosteroids (100% vs 88%, $P=0.04$). The number of hospitalizations during the previous year (2.3 vs 1.7; $P=0.07$) and of days of hospital stay (14.5 vs 10.2; $P=0.05$) were higher, but not significantly.

Patients with *S. pneumoniae* isolation had more comorbidities (5.9 vs 2.7; $P=0.002$), and greater probability of having a Charlson index above three, though without statistical significance (52.2% vs 32.6%; $P=0.07$). The comorbidities more frequently associated with *S. pneumoniae* isolation were hypertension ($P=0.04$), dyslipidemia ($P=0.03$), peripheral vascular disease ($P=0.03$), osteoporosis ($P=0.000$), and depression ($P=0.005$). According to the characteristics of the present exacerbation, these patients had fewer previous

Table 3 Comorbidities and the result of sputum culture

| Comorbidities | Total (n=536) | Valid sputum (n=161) | <i>Pseudomonas aeruginosa</i> (n=27) | <i>Streptococcus pneumoniae</i> (n=23) | EB (n=18) | <i>Haemophilus influenzae</i> (n=14) | <i>Moraxella catharrhalis</i> (n=6) | nPPM (n=73) |
|-----------------------------|---------------|----------------------|--------------------------------------|--|-----------|--------------------------------------|-------------------------------------|-------------|
| Arterial hypertension | 351 (65.5) | 104 (63.8) | 18 (66.7) | 19 (82.6)* | 7 (38.9)* | 10 (71.4) | 3 (50) | 45 (61.6) |
| Diabetes mellitus | 156 (29.1) | 42 (25.8) | 9 (33.3) | 9 (39.1) | 2 (11.1) | 4 (28.6) | 0 (0) | 18 (24.7) |
| Dyslipidemia | 183 (34.1) | 66 (40.5)* | 11 (40.7) | 14 (60.9)* | 2 (11.1)* | 7 (50) | 1 (16.7) | 30 (41.1) |
| Ischemic heart disease | 117 (21.9) | 39 (23.9) | 8 (29.6) | 4 (17.4) | 3 (16.6) | 4 (28.6) | 2 (33.3) | 16 (21.9) |
| Acute myocardial infarction | 65 (21.1) | 22 (13.5) | 4 (14.8) | 4 (17.4) | 1 (5.5) | 2 (14.3) | 1 (16.7) | 10 (13.7) |
| Heart failure | 191 (35.6) | 56 (34.4) | 14 (51.9)* | 9 (39.1) | 9 (50) | 3 (21.4) | 1 (16.7) | 20 (27.4) |
| Atrial fibrillation | 125 (23.3) | 45 (27.6) | 11 (40.7) | 5 (21.7) | 3 (16.6) | 8 (57.1)* | 1 (16.7) | 16 (21.9) |
| Peripheral arterial disease | 93 (17.4) | 24 (14.7)* | 4 (14.8) | 7 (30.4)* | 0 (0)* | 2 (14.3) | 1 (16.7) | 10 (13.7) |
| Cerebrovascular disease | 66 (12.3) | 28 (17.3) | 9 (33.3)* | 6 (26.1) | 2 (11.1) | 1 (7.1) | 1 (16.7) | 9 (12.5) |
| Chronic renal failure | 90 (16.8) | 24 (14.7) | 4 (14.8) | 6 (26.1) | 1 (5.5) | 1 (7.1) | 2 (33.3) | 10 (13.7) |
| Cor pulmonale | 136 (25.5) | 45 (27.6) | 13 (48.1)* | 10 (43.5) | 3 (16.6) | 3 (21.4) | 2 (33.3) | 14 (19.2)* |
| OSA | 64 (11.9) | 22 (13.5) | 6 (22.2) | 3 (13) | 4 (28.6) | 1 (7.1) | 0 (0) | 8 (11) |
| Neoplasm | 64 (11.9) | 21 (12.9) | 3 (11.1) | 4 (17.4) | 1 (5.5) | 0 (0) | 1 (16.7) | 12 (16.4) |
| Depression | 81 (15.1) | 33 (20.2)* | 7 (25.9) | 10 (43.5)* | 3 (16.6) | 2 (14.3) | 1 (16.7) | 9 (12.3)* |
| Osteoporosis | 86 (16) | 32 (19.6) | 7 (25.9) | 12 (52.2)* | 1 (5.5) | 1 (7.1) | 1 (16.7) | 10 (13.7) |
| Chronic liver disease | 32 (6.0) | 15 (9.2) | 1 (3.7) | 3 (13) | 5 (27.7)* | 0 (0) | 1 (16.7) | 5 (6.8) |
| Peptic ulcer | 51 (9.5) | 16 (9.8) | 0 (0)* | 3 (13) | 3 (16.6) | 4 (28.6)* | 1 (16.7) | 5 (6.8) |
| Ferropenic anemia | 51 (9.5) | 19 (11.7) | 4 (14.8) | 2 (8.7) | 1 (5.6) | 4 (28.6) | 1 (16.7) | 7 (9.6) |
| Charlson index (±SD) | 3.1±2 | 3.1±1.9 | 3.5±2.1 | 3.56±1.5 | 3±1.9 | 2.5±1.5 | 3.6±2.8 | 3.1±2 |

Notes: Data presented as absolute (relative) frequencies, or mean (standard derivation). * $P<0.05$.

Abbreviations: OSA, obstructive sleep apnea-hypopnea syndrome; EB, Enterobacteriaceae; nPPM, non-potential pathogen microorganisms.

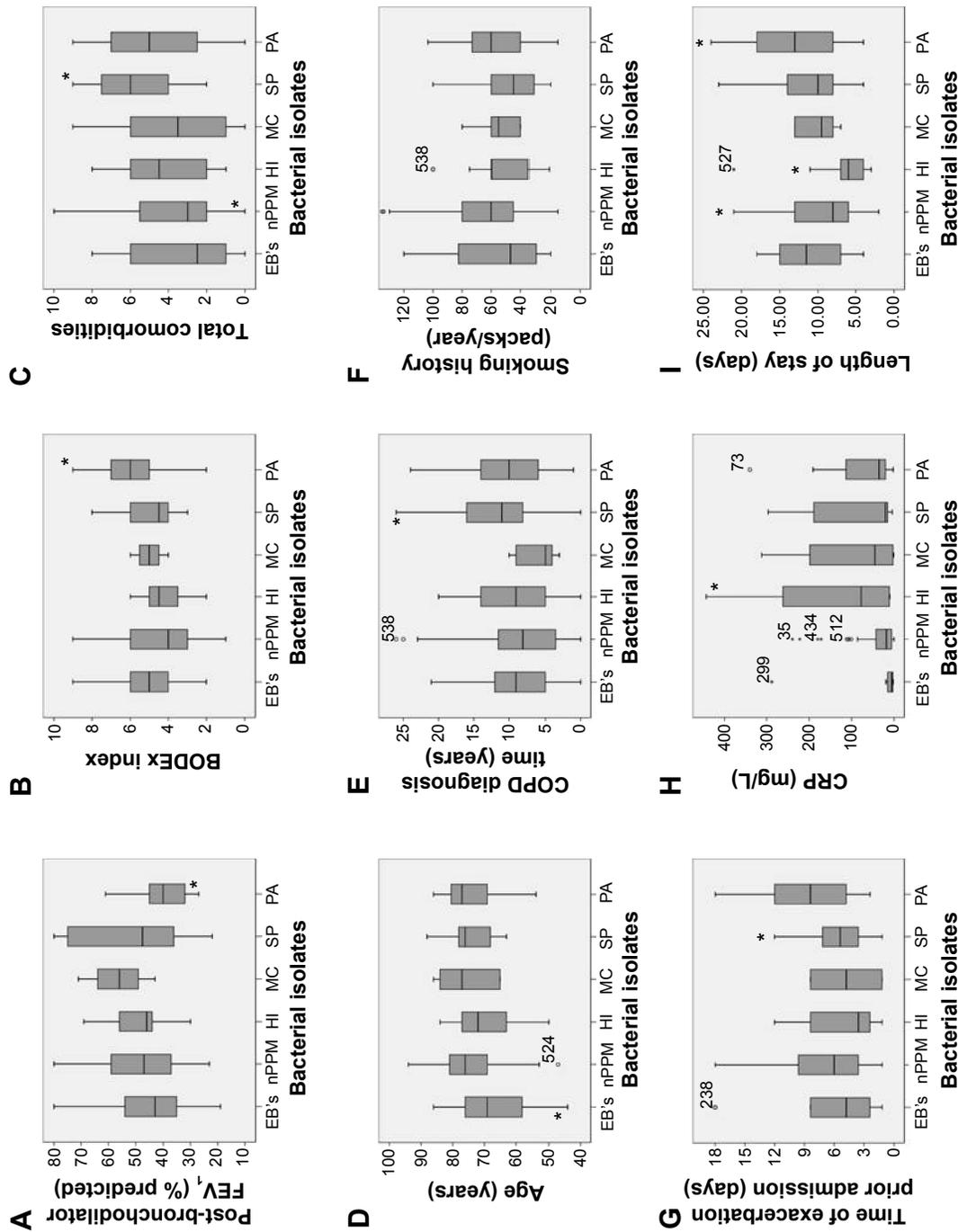


Figure 3 Characteristics according to sputum culture results.

Notes: *Represents $P < 0.05$. Mean values, as well as standard deviations and ranges for all groups of patients. Horizontal bars represent mean values, boxes represent mean (\pm SD) values, and vertical bars represent ranges. **(A)** Post-bronchodilator FEV₁ (% predicted). **(B)** BODEx index. **(C)** Total comorbidities (number of comorbidities). **(D)** Age (years). **(E)** COPD diagnosis time (years). **(F)** Smoking history (packs/year). **(G)** Time of exacerbation prior admission (days). **(H)** C-reactive protein (mg/L). **(I)** Length of stay (days).

Abbreviations: EB, Enterobacteriaceae; nPPM, non-potentially pathogenic microorganisms; HI, *Haemophilus influenzae*; MC, *Moraxella catharrhalis*; SP, *Streptococcus pneumoniae*; PA, *Pseudomonas aeruginosa*; CRP, C-reactive protein; FEV₁, forced expiratory volume in 1 second.

days with symptoms (4.7 vs 6.7; $P=0.01$), and according to the Anthonisen criteria greater increase of sputum ($P=0.02$) and of purulence ($P=0.04$). As for the previous treatment, they presented more use of β -lactams prior to admission ($P=0.02$) and statins ($P=0.002$). According to the treatment during the exacerbation, there was greater use of diuretics ($P=0.02$). There is a tendency to a greater smoking history measured in packs/year (48.5 vs 59.5; $P=0.06$) and a longer span of time between exacerbation and COPD diagnosis, in years (12.2 vs 9.1; $P=0.04$).

Patients with Enterobacteriaceae isolation were younger (66.6 vs 74 years; $P=0.04$), had lesser functional impairment according to Katz index (5.6 vs 5.2; $P=0.04$), and more frequently presented with mild liver disease ($P=0.01$). Also notable, they showed less fever ($P=0.02$) and comorbidities (arterial hypertension [$P=0.022$], dyslipidemia [$P=0.007$], and peripheral vascular disease [$P=0.046$]). Comparing the treatment of this group of patients, we found the less use of statins ($P=0.001$) and a greater need of continuous positive airway pressure ($P=0.01$). Finally, no differences appear as for AE-COPD severity factors.

Comparing patients with *H. influenzae* isolation in the sputum with the non-*H. influenzae* group, their differential characteristics are a greater presence of peptic ulcer ($P=0.04$) and atrial fibrillation ($P=0.01$). Comparing treatments, they have lesser need of home oxygen therapy ($P=0.03$). They also required fewer days of hospital stay over the previous 12 months ($P=0.04$) and in the current AE-COPD admission ($P=0.02$).

No differences are clear when comparing patients with *M. catharralis* isolation in the sputum with the remainder.

Finally, if we compare patients with nPPM isolation in the sputum (73 patients) with the rest of the group, their differential characteristics are fewer admissions over the previous year ($P=0.01$), lesser presence of sputum increase ($P=0.008$) and sputum purulence ($P=0.02$), lesser presence of cor pulmonale ($P=0.02$), less depression ($P=0.03$), less need of continuous positive airway pressure ($P=0.003$), shorter hospital stays ($P=0.02$), lower CRP values ($P=0.04$), and fewer associated comorbidities ($P=0.046$). As for severity of the COPD, they had a lower FVC in milliliter ($P=0.03$).

We analyzed the characteristics of patients according to the results of the sputum culture, by grouping these results according to the isolation of *P. aeruginosa* or Enterobacteriaceae (group 1); *S. pneumoniae*, *H. influenzae*, or *M. catharralis* (group 2); or nPPM (group 3). The results are presented in Table 4. COPD patients in group 1 had significantly more admission in the previous year, increased sputum, and more heart failure; while those in group 2 had more osteoporosis ($P<0.05$).

Discussion

Our study shows that COPD patients hospitalized for an AE-COPD with *P. aeruginosa* isolation present greater severity of their disease, with worse levels of respiratory parameters as measured with the predicted %FEV₁ after bronchodilatation, greater dyspnea by the mMRC scale, higher scores in the BODEx index, and more hospitalizations over the previous year. The isolation of *S. pneumoniae*, in turn, is associated

Table 4 Characteristics of patients according to sputum culture groups

| Comorbidities | Total (n=536) | Group 1 (n=45) | Group 2 (n=43) | Group 3 (n=73) | P-value |
|--------------------------------|---------------|----------------|----------------|----------------|---------|
| Admission in the previous year | 121 (75.2) | 39 (86.7) | 34 (79.1) | 48 (65.8) | 0.030 |
| First admission for AE-COPD | 28 (17.4) | 3 (10.7) | 8 (28.6) | 17 (60.7) | 0.067 |
| LTOT | 79 (49.1) | 24 (53.3) | 19 (44.2) | 36 (49.3) | 0.691 |
| Antibiotics previous admission | 53 (32.9) | 18 (40) | 12 (27.9) | 23 (31.5) | 0.455 |
| Corticoids previous admission | 38 (23.6) | 13 (28.9) | 9 (20.9) | 16 (21.9) | 0.612 |
| Increased sputum | 135 (84.9) | 41 (93.2) | 38 (90.5) | 56 (76.7) | 0.027 |
| Change in expectoration | 139 (87.4) | 42 (95.5) | 38 (90.5) | 59 (80.8) | 0.054 |
| Heart failure | 56 (34.8) | 23 (51.1) | 13 (30.2) | 20 (27.4) | 0.024 |
| Cerebrovascular disease | 28 (17.5) | 11 (24.4) | 8 (18.6) | 9 (12.5) | 0.248 |
| Chronic renal failure | 24 (14.9) | 5 (11.1) | 9 (20.9) | 10 (13.7) | 0.402 |
| Cor pulmonale | 45 (28) | 16 (35.6) | 15 (33.3) | 14 (31.1) | 0.078 |
| OSA | 22 (13.7) | 10 (22.2) | 4 (9.3) | 8 (11) | 0.139 |
| Neoplasm | 21 (13) | 4 (8.9) | 5 (11.6) | 12 (16.4) | 0.472 |
| Depression | 32 (19.9) | 10 (22.2) | 13 (30.2) | 9 (12.3) | 0.059 |
| Osteoporosis | 32 (19.9) | 8 (17.8) | 14 (32.6) | 10 (13.7) | 0.045 |
| Peripheral arterial disease | 24 (14.9) | 4 (8.9) | 10 (23.3) | 10 (13.7) | 0.155 |

Notes: Data presented as absolute (relative) frequencies or mean (standard deviation). Group 1: *Pseudomonas aeruginosa* or Enterobacteriaceae. Group 2: *Streptococcus pneumoniae* or *Haemophilus influenzae* or *Moraxella catharralis*. Group 3: non-potential pathogen microorganisms.

Abbreviations: AE-COPD, acute exacerbation of chronic obstructive pulmonary disease; LTOT, long-term oxygen therapy; OSA, obstructive sleep apnea-hypopnea syndrome.

with more associated comorbidities, assessed by the number of comorbidities or with the Charlson index. Finally, patients with isolation of enterobacteria are younger, have less functional impairment, and more use of non-invasive mechanical ventilation similar to continuous positive airway pressure. Thus, we have noted that the diseases associated to COPD differ depending on the microorganism isolated in the sputum.

These data are relevant for clinical practice, as they help decide the empirical antibiotic treatment for each kind of patients in those AE-COPD that require hospitalization. Presently, according to clinical practice guidelines,^{15,16} it is advised to determine the antibiotic treatment for AE-COPD depending on the patient's comorbidities, since they affect the risk of therapeutic failure. According to our results, this comorbidity varies depending on the etiology of the bacterial exacerbation.

Only a recent study has described the identification of bacterial etiology in relation to the clinical characteristics of patients. Miravittles et al¹⁰ identified factors independently associated with bacterial growth, such as current smoking and *H. influenzae*; longer periods between exacerbations and *S. pneumoniae*; or decrease in FEV₁ and *P. aeruginosa*.

Traditionally, bacterial identification has been defined depending on the severity of the COPD, since *S. pneumoniae*, *H. influenzae*, and *M. catharralis* are isolated in patients with predicted FEV₁ >50%, and Enterobacteriaceae and *P. aeruginosa* in those with FEV₁ <50%, as verified by Miravittles et al¹⁰ and Eller et al.²²

Other authors have also identified a greater growth of *P. aeruginosa* in patients with lower levels of FEV₁,^{23,24} and other factors of greater severity of COPD.^{25,26} García-Vidal et al²⁷ defined the BODEx index, the number of hospital admissions in the previous year, treatment with corticoids, and prior isolation of *P. aeruginosa* as risk factors.

COPD is a heterogeneous disease that requires categorizing patients in subgroups in order to optimize their management in clinical practice, identifying traits of the disease with clinical significance. Likewise, there are exacerbation subtypes depending on the number of previous days with symptoms,²⁸ or by etiology. There have been attempts to typify different exacerbation subtypes through biomarkers. Bafadhel et al²⁹ described three types of exacerbation: bacterial, viral, and eosinophilic. Among the bacterial causes, comorbidity might orient us toward a certain etiological agent.

On bacterial etiology the conventional study of sputum plays an important role. It is the simplest and most accessible method for diagnosing the etiology of bacterial infections in AE-COPD. Nevertheless, its value is debatable in some cases

due to bacterial colonization in certain patients,³⁰ and to the increasing importance of other, non-bacterial etiologies such as respiratory viruses, that are isolated in more than 50% of cases, frequently associated with bacteria.³¹ Most guidelines recommend conducting a sputum culture in case of severe exacerbation, the presence of risk factors for multiresistant bacteria, or if there is therapeutic failure.^{16,17,32,33}

Most studies have focused on the risk factors for growth in the sputum culture for *P. aeruginosa*, while obtaining similar results to ours about other microorganisms (although with better results in obtaining valid sputum samples from patients admitted with AE-COPD, as they induced sputum). For instance, a study similar to ours²⁷ included 188 patients, obtaining quality sputum samples from 119 subjects (63%). Of the quality cultures, 55% were for PPM and the remaining 45% for nPPM, identical to our results.

One of the factors predicting growth of PPM in cultures is the purulence of the sputum, but it must be observed by clinicians, since it is less reliable when reported by the patients themselves.³⁴ This has led researchers to look for other predictors of purulence in the sputum, such as FEV₁ <35% and body mass index <22.³⁵ Also, Larsen et al²³ identified the number of neutrophils in peripheral blood as a predictor of growth in the sputum. Roche et al²⁴ associated it to the presence of bronchiectasis, chronic home oxygen therapy, and lower levels of FEV₁%. Recently, Bafadhel et al³⁶ had shown that patients with persistently positive sputum samples have particularly severe neutrophilic airway inflammation and poor clinical outcomes, and the *H. influenzae* was the most commonly isolated pathogen.

Thus, for instance, the presence of Anthonisen's criteria (type I) in patients with decreased lung function has been described as indicative of antibiotic treatment.³⁷ Nevertheless, recent studies point out that purulence in the sputum remains the most important factor.⁹

Finally, we observed that the most frequently isolated microorganism was *P. aeruginosa* (30.7%), followed by *S. pneumoniae* (26.1%), Enterobacteriaceae (20.4%), *H. influenzae* (15.9%), and *M. catharralis* (6.8%). We did not encounter any patient with *Staphylococcus aureus*. Other authors in Spain have also identified a similar rate.^{25,27}

Our study has several limitations. First, the reduced number of women, similar to other studies conducted in Spain, probably due to its late entry to smoking in Spain. Second, most of the patients included in the study had been hospitalized in Internal Medicine Services, and probably presented more associated pathologies than those admitted to Pneumology departments. In Spain, 40%–50% of

COPD exacerbations are attended to in Internal Medicine Services, which usually care for older patients with more comorbidities;³⁸ however, the data about mortality and readmissions shown in our study are similar to those obtained by another paper, studying 1,200 patients admitted to a variety of services and hospitals.³⁹ Also, the difficulty of identifying the etiology of exacerbation through the sputum has been pointed out before. In addition, a significant percentage of the patients were already being treated with antibiotics prior to their hospitalization, which hampers studying their case through conventional sputum samples. A final limitation is that computed tomography was not undertaken as part of the study protocol, so we are not in a position to determine whether the presence of bronchiectasis was an important cofactor in these subjects.

In summary, the etiology of bacterial infections in AE-COPD can be implied through characteristics of patients such as their associated comorbidities. *P. aeruginosa*, for instance, is associated with a greater severity of COPD itself; *S. pneumoniae*, with a disease not as severe but with a longer time of evolution, more comorbidities, and more vascular risk factors; and Enterobacteriaceae are associated with younger patients in need of continuous positive airway pressure.

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Author contributions

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

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