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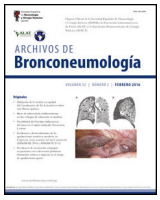

Original Article

Bacterial Patterns and Empiric Antibiotic Use in COPD Patients With Community-Acquired Pneumonia

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ABSTRACT

Introduction: Chronic obstructive pulmonary disease (COPD) is strongly associated with the development of community-acquired pneumonia (CAP). Limited data are available on risk factors for difficult to manage bacteria such as *Pseudomonas aeruginosa* in COPD patients with CAP. Our objective was to assess the microbiological patterns associated with risk factors that determine empiric antibiotic therapy in hospitalized COPD patients with CAP.

Methods: We performed a secondary data analysis of an international, multicenter, observational, point-prevalence study involving hospitalized COPD patients with CAP from March to June 2015. After identifying the risk factors associated with different microorganisms, we developed a scoring system to guide decision-making about empiric anti-pseudomonal antibiotic therapy in this population.

Results: We enrolled 689 hospitalized COPD patients with CAP with documented microbiological testing. The most frequent microorganisms isolated were *Streptococcus pneumoniae* (8%) and Gram-negative bacteria (8%), *P. aeruginosa* (7%) and *Haemophilus influenzae* (3%). We developed a scoring system incorporating the variables independently associated with *P. aeruginosa* that include a previous *P. aeruginosa* isolation or infection (OR 14.2 [95%CI 5.7–35.2]), hospitalization in the past 12 months (OR 3.7 [1.5–9.2]), and bronchiectasis (OR 3.2 [1.4–7.2]). Empiric anti-pseudomonal antibiotics were overutilized in COPD patients with CAP. The new scoring system has the potential to reduce empiric anti-pseudomonal antibiotic use from 54.1% to 6.2%.

Abbreviations: CAP, community acquired pneumonia; COPD, chronic obstructive pulmonary disease; CT, computed tomography; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; GLIMP, Global Initiative for Methicillin-resistant *Staphylococcus aureus* Pneumonia; GNB, gram-negative bacteria; MRSA, methicillin resistant *Staphylococcus aureus*; OR, odds ratio; PAS-COPD, *Pseudomonas aeruginosa* score in COPD; SPP, species.

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Conclusions: COPD patients with CAP present different microbiological profiles associated with unique risk factors. Anti-pseudomonal treatment is a critical decision when selecting empiric antibiotic therapy. We developed a COPD scoring system to guide decision-making about empiric anti-pseudomonal antibiotic therapy.

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Background

Chronic obstructive pulmonary disease (COPD) currently affects more than 250 million people worldwide, and by the year 2060, it is estimated that COPD will account for more than 6 million deaths annually, making it the fifth leading cause of death.[1] Community acquired pneumonia (CAP) and COPD exacerbations are two important complications associated with increased morbidity, mortality, costs, hospitalizations, and readmissions.[2–7] Furthermore, CAP in COPD patients compared with COPD exacerbations is associated with longer length of hospital stay, higher mortality and greater economic impact.[8] COPD is a heterogeneous disease in which multiple risk factors may lead to the development of CAP.[9,10] When CAP occurs in COPD patients, clinicians are challenged in deciding the appropriate selection of antibiotics.

Recently published CAP clinical practice guidelines recommend microbiological confirmation and treatment for *Pseudomonas aeruginosa* in patients with prior respiratory infection or colonization with *P. aeruginosa*, recent hospitalization, exposure to parenteral antibiotics, and locally validated risk factors.[11] Previous studies have reported that hospitalized CAP patients with COPD have more infections caused by *P. aeruginosa*, especially those with bronchiectasis and severe disease (Forced expiratory volume in one second [FEV_1 < 50%]).[12–14] However, most of these studies recruited small sample sizes, were conducted in single centers, evaluated a unique pathogen, or considered COPD as a homogeneous entity.[12–16] Limited data are available on the association of risk factors in COPD patients with CAP and difficult-to-manage bacteria, such as *P. aeruginosa*, other Gram-negative bacteria (GNB), and Methicillin Resistant *Staphylococcus aureus* (MRSA). The aim of this study was to assess the microbiological patterns associated with risk factors that determine empiric antibiotic therapy in hospitalized COPD patients with CAP.

Methods

Study design

This study was designed using data retrieved from an international multicenter, observational, point-prevalence study (Global Initiative for Methicillin-resistant *Staphylococcus aureus* Pneumonia [GLIMP]).[17] Adult immunocompetent COPD patients hospitalized with CAP from 37 countries in all continents were selected.[17]

The patients were enrolled on four randomly selected days. We included patients with bacterial tests done (blood and respiratory cultures, pneumococcus and legionella urinary antigen and/or influenza testing) during the first 24 h of admission. Respiratory samples collection included sputum, pleural fluid, endotracheal aspirate, and/or bronchoalveolar lavage according to local standard protocols. Investigators did not actively participate or alter the clinical decisions, procedures, management of microbiological samples, or treatment decisions, which were performed according to local protocols and local standards of care.

Inclusion and exclusion criteria

In the original cohort of GLIMP, all adult patients (>18 years old) admitted to the hospital with CAP were screened for the study inclusion. Patients with a diagnosis of hospital-acquired or ventilator-associated pneumonia or tracheotomized were excluded.

COPD group stratification

Data collection were stratified according to the following COPD groups of potential risk factors found in the literature: demographics (age, gender)[18]; prior pulmonary disease (asthma, bronchiectasis, and FEV_1)[12,13]; non-pulmonary comorbidities (diabetes, heart failure, liver disease, obesity, stroke)[19]; chronic medication use (inhaled or systemic corticosteroids and oxygen therapy)[12,13,20] and healthcare system or pathogen exposure during the previous year (previous hospitalizations in the past 12 months, intravenous antibiotic use in the past 12 months, nursing home residence, and *P. aeruginosa*, MRSA or extended spectrum beta-lactamase bacteria exposure).[13,15]

Definitions

CAP was defined by the presence of pulmonary infiltrates diagnosed by chest imaging (chest radiography, lung ultrasound or computed tomography [CT]) during the first 48 h of hospital admission and at least one of the following: (a) cough with or without sputum production; (b) fever (rectal or oral temperature >37.8 °C) or hypothermia (<36 °C) and/or (c) systemic inflammation (leukocytosis > 10,000 cm^{-3}, leucopenia < 4000 cm^{-3}, bandemia > 10%, increased C-reactive protein or procalcitonin levels).

COPD was defined by Global initiative for Obstructive Lung Disease (GOLD) criteria,[21] as patient > 40 years old who has dyspnea, chronic cough or sputum production, and/or a history of exposure to risk factors for the disease, with a post-bronchodilator FEV_1/FVC ratio under 0.7.

Bronchiectasis was defined as the presence of abnormal dilatation of bronchi on CT scan of the thorax as reported in the case report form.

Microbiology pathogens were stratified in the following groups: (a) None (no pathogen isolated), (b) *P. aeruginosa*, (c) GNB, (d) *Haemophilus influenzae*, (e) *S. aureus*, (f) *Streptococcus pneumoniae*, (g) *Streptococcus* spp., (h) Mixed flora and (i) Atypical bacteria. The GNB group included *Acinetobacter baumannii*, *Coxiella burnetii*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus* spp., *Moraxella catarrhalis*, *Enterobacter* spp., *Pasteurella multocida*, *Pseudomonas pseudomallei*, *Salmonella* spp., and *Serratia* spp. Atypical bacteria included *Chlamydia pneumophila, Chlamydia psittaci*, *Legionella* spp., and *Mycoplasma pneumoniae*. Viruses, fungi and mycobacteria, since they are not treated with conventional antibiotics were included in the "non-bacterial group".

Treatment groups. Anti-pseudomonal antibiotic therapy was stratified in five groups: (1) anti-pseudomonal beta-lactam monotherapy (piperacillin-tazobactam, imipenem, meropenem, cefepime, ceftazidime, aztreonam); (2) fluoroquinolone

monotherapy (ciprofloxacin or levofloxacin); (3) combination of anti-pseudomonal (beta-lactam plus either aminoglycoside, fluoroquinolone or colistin or fluoroquinolone plus aminoglycoside, respectively); (4) non-conventional antipseudomonal antibiotics (monotherapy with colistin or aminoglycoside [gentamicin, tobramycin, or amikacin], or combination of colistin plus fluoroquinolone, or colistin plus aminoglycoside; and (5) patients without anti-pseudomonal treatment.

Anti-pseudomonal antibiotic use was classified as correct use (patients with CAP caused by *P. aeruginosa* and treated with anti-pseudomonal agents); correct non-use (patients without *P. aeruginosa* and not empirically treated for *P. aeruginosa* CAP); undertreatment (patients with CAP caused by *P. aeruginosa* and not treated for *P. aeruginosa* CAP); and overtreatment (patients without CAP caused by *P. aeruginosa* that received treatment with anti-pseudomonal antibiotics).

Data collection

Research Electronic Data Capture (REDCap) was used to collect and manage all data.[22] Data collection included demographics, respiratory and non-respiratory comorbidities, chronic therapies, other non-medical conditions, severity of pneumonia, empiric antibiotic usage, and microbiological tests results.

Ethical considerations

This study was approved by the Institutional Review Board of the University of Texas Health San Antonio, (coordinating center located in San Antonio, Texas, USA with number HSC20150184E). Full data were confidential according to the current legislation. Patient identifiers were removed before analysis to maintain strict patient confidentiality. For these reasons, the institutional review board decided informed consent was not necessary. All associated centers followed local, regional, or national ethics regulations. The study was designed and conducted in accordance with the Declaration of Helsinki.

Statistical analysis

The sample size was defined by the total number of immunocompetent COPD patients with CAP on the dates selected by the investigators in GLIMP study.[17] Two-sided Chi-square or Fisher Exact tests were used for the analysis of categorical variables, when appropriate. The normal distribution of continuous variables was tested using the Kolmogorov–Smirnov test. The Student's *t*-test was used to compare continuous variables expressed as means and standard deviation (SD) in case of a parametric distribution. Risk factors associated with CAP pathogen (*P. aeruginosa*, GNB, MRSA, and *S. pneumoniae*) were assessed with a logistic regression analysis. Multivariate analysis was performed in all the COPD patients with microbial tests performed for CAP pathogens, and a scoring system (PAS-COPD) based on rounded β value was developed for *P. aeruginosa* with independent risk factors. The discriminative ability of the PAS-COPD to predict the presence of PA was assessed by the area under the receiver operating characteristic (ROC) curve. The ROC curves were used to identify the optimal cutoff values for the outcome associations. All statistical analyses were performed using SPSS 24.0 (SPSS Inc., Chicago, IL, USA), and a p-value < 0.05 was considered statistically significant.

Results

Among 3217 hospitalized patients with CAP and microbiological testing performed, 689 (21%) patients were immunocompetent with COPD. COPD patients had a mean age of 72 (±11) years, 67% were male, 11% had very severe airflow limitation ($FEV_1 \leq 30\%$), 10% had bronchiectasis, and 5% had prior *P. aeruginosa* infection (Fig. 1). The most frequently identified demographic characteristic in addition to being male was the prior use of oral antibiotics in the past 12 months ($n = 354$ [51%]), low respiratory tract infections in the past 12 months ($n = 350$ [51%]), hospitalization in the past 12 months ($n = 318$ [46%]) and use of inhaled corticosteroids ($n = 318$ [46%]), respectively (Fig. 1).

Microbiological patterns

The microbiological identification occurred in 213 (31%) of all the COPD patients with CAP (Fig. 2). The most prevalent pathogens were GNB ($n = 57$; 8%), *S. pneumoniae* ($n = 57$; 8%), *P. aeruginosa* ($n = 45$; 7%), *H. influenzae* ($n = 20$; 3%), and *S. aureus* ($n = 14$; 2%, MRSA $n = 9$; 1.9%), respectively (Fig. 2). Distinct microbiological patterns for *P. aeruginosa*, *S. pneumoniae*, *S. aureus* and mixed anaerobic flora were associated with risk factors in COPD patients (Fig. 3). *P. aeruginosa* was independently associated with a previous *P. aeruginosa* isolation or infection (OR 14.2 [95%CI 5.7–35.2]), hospitalization in the past 12 months (OR 3.7 [1.5–9.2]), and bronchiectasis (OR 3.2 [1.4–7.2]) (Figs. 3 and 4a). In the bivariate analysis other pathogens such as S. pneumoniae was associated with bronchiectasis in COPD patients with CAP (19% vs. 7%; p-value < 0.01), and *S. aureus* was associated with prior MRSA isolation (11% vs. 2%; p-value < 0.049) and nursing home residence (7% vs 2%; p-value < 0.03), but none of these conditions were independently associated with *S. aureus* CAP in the multivariate analysis (Fig. 3). Mixed anaerobic flora was associated with being bedridden (2% vs 0%, p-value = 0.01) (Fig. 3). Inhaled and oral corticosteroids treatment was not related to any microorganism. We developed a decision tree analysis focused on assessing the risk of *P. aeruginosa* CAP in three independently associated COPD risk factors (hospitalization in the past 12 months, bronchiectasis, and prior *P. aeruginosa* infection/colonization) (Fig. 4b). For instance, patients with bronchiectasis and without any previous hospitalizations in the past 12 months, and no evidence of prior *P. aeruginosa*, had no *P. aeruginosa* CAP (0%), whereas 70% of patients with previous hospitalizations, bronchiectasis, and prior *P. aeruginosa* infection/colonization had *P. aeruginosa* CAP. A *P. aeruginosa* CAP score in COPD (PAS-COPD) was created to define the prevalence of *P. aeruginosa* with 3 points for prior *P. aeruginosa* infection/colonization, 1 point for hospitalization in the past 12 months, and 1 for bronchiectasis, for a total score of 5 (Fig. 5a). The ability of PAS-COPD to identify patients with *P. aeruginosa* was an area under the curve–ROC of 0.784 (0.705–0.864, $p < 0.001$) (Fig. 5b). The PAS-COPD was stratified as 0, 1, 2, or ≥3 points with a *P. aeruginosa* CAP prevalence of 2%, 5%, 20% and 50%, respectively (Fig. 5c).

Anti-pseudomonal antibiotic utilization

Empiric anti-pseudomonal antibiotics were used in 413 (60%) of all COPD patients hospitalized with CAP, with 197 (62%) for patients with prior hospitalization in the past 12 months, 25 (78%) for those with a prior *P. aeruginosa* infection/colonization, and 56 (84%) for those with bronchiectasis (Fig. 6a). The most frequently prescribed antibiotics were anti-pseudomonal beta-lactam monotherapy ($n = 179$; 26%), anti-pseudomonal fluoroquinolones ($n = 124$; 18%), and combination therapy ($n = 96$; 14%) of a beta-lactam with either a fluoroquinolone, aminoglycoside, or colistin, respectively. A distinct treatment pattern was not found of anti-pseudomonal antibiotic use according to the above-mentioned risk factors (Fig. 6a). Patients with a PAS-COPD of 0, 1, 2, and ≥3 received anti pseudomonal treatment in 55%, 60%, 82%, and 78% of the cases, respectively (Fig. 6b). The prevalence

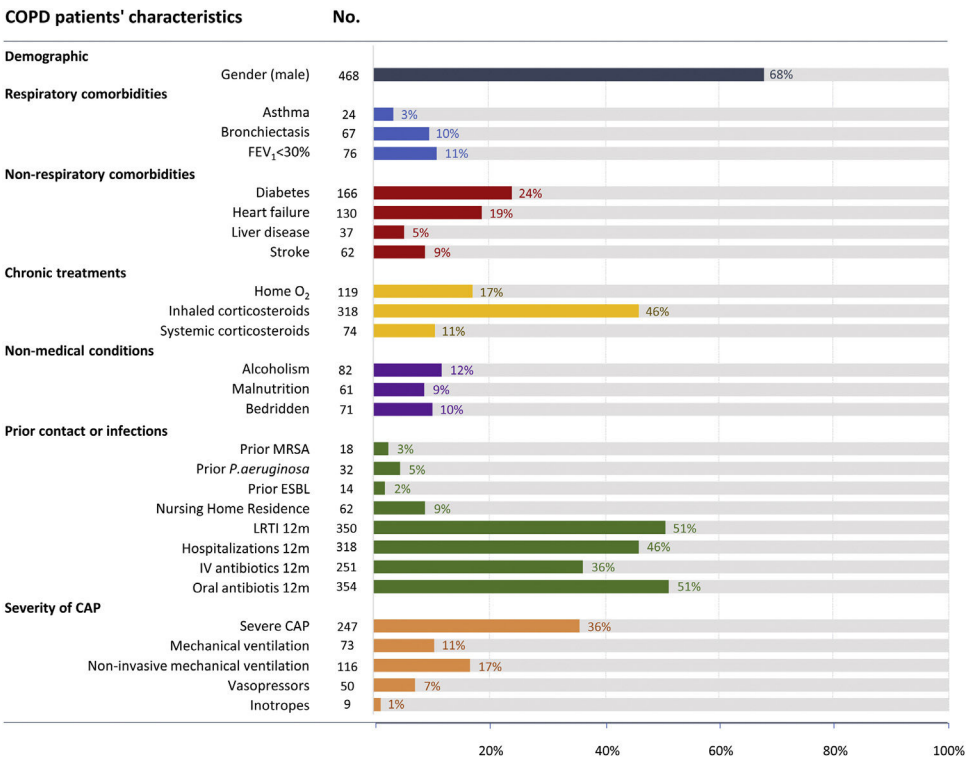

Fig. 1. Characteristics of hospitalized COPD patients with CAP. Footnote Fig. 1. FEV_1: forced expiratory capacity in one second, MRSA: methicillin resistant *Staphylococcus aureus*, ESBL: extended spectrum β-Lactamases, LRTI: low respiratory tract infection, IV: intravenous.

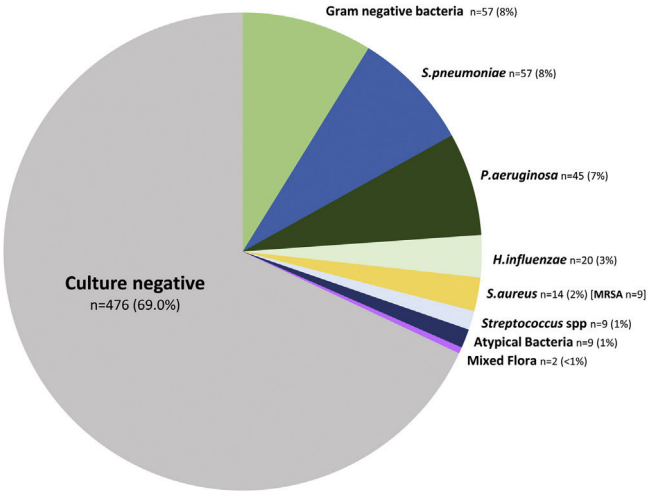

Fig. 2. Bacterial culture results in hospitalized COPD patients with CAP.

of appropriate use, appropriate non-use, undertreatment, and overtreatment of anti-pseudomonal antibiotics were 5.4%, 39.3%, 1.2%, and 54.1%. Avoiding antipseudomonal agents in patients with PAS-COPD score ≤ 1 (*P. aeruginosa* CAP prevalence ≤ 5%) the potential appropriate use, appropriate non-use, undertreatment, and overtreatment of anti-pseudomonal antibiotics would be 3.3%, 87.2%, 3.2%, and 6.2%, respectively (Fig. 6c).

Discussion

Distinct microbiological patterns for *P. aeruginosa* and *S. pneumoniae* were associated with specific risk factors in COPD patients. *P. aeruginosa* CAP was associated with previous infection/colonization with *P. aeruginosa*, hospitalization during the previous 12 months, and bronchiectasis. Anti-pseudomonal antibiotics are routinely overused in COPD patients with CAP. A PAS-COPD score might help to rationalize the use of anti-pseudomonal agents in COPD patients with CAP.

In the present study, *P. aeruginosa* was the predominant microorganism associated with a higher number of risk factors in hospitalized COPD patients with CAP. *P. aeruginosa* CAP was independently associated with prior *P. aeruginosa* infection/colonization, prior hospitalization in the past 12 months, and bronchiectasis. These results are aligned but somewhat divergent from prior evidence suggesting that COPD risk factors are heterogeneous.[12–14,18,20,23] Similar risk factors have been described in hospitalized patients with CAP or in patients with COPD exacerbations.[24–28] Prior infection/colonization with *P. aeruginosa* suggests that this pathogen may remain in the airways of COPD patients until a point of disbalance causing pneumonia. In addition, previous hospitalizations in the past 12 months suggests that a previous contact with the healthcare system may increase the risk of acquiring a pathogen related to previous contamination or exposure. Chronic bacterial infection is prevalent in patients with bronchiectasis and COPD and are usually difficult to eradicated despite multiple antibiotic treatments.[29–32] Our data support the association of a prior *P. aeruginosa* infection/colonization, prior hospitalization in the past 12 months, and bronchiectasis with *P. aeruginosa* CAP in COPD patients. Poor pulmonary function testing, although previously associated with *P. aeruginosa*, seems to be linked to other overlapping conditions, such as prior infection/colonization with *P. aeruginosa* or the presence of bronchiectasis. Therefore, our stratification was limited by identifying patients with a diagnosis of very severe COPD according to the FEV_1 ratio below 30%. Similar findings have been suggested in patients with acute exacerbations of COPD or CAP.[26,33–35]

One group of pathogens, namely GNB, was not independently associated with unique COPD risk factors. *S. pneumoniae*, which was the most prevalent microorganism, was found to be

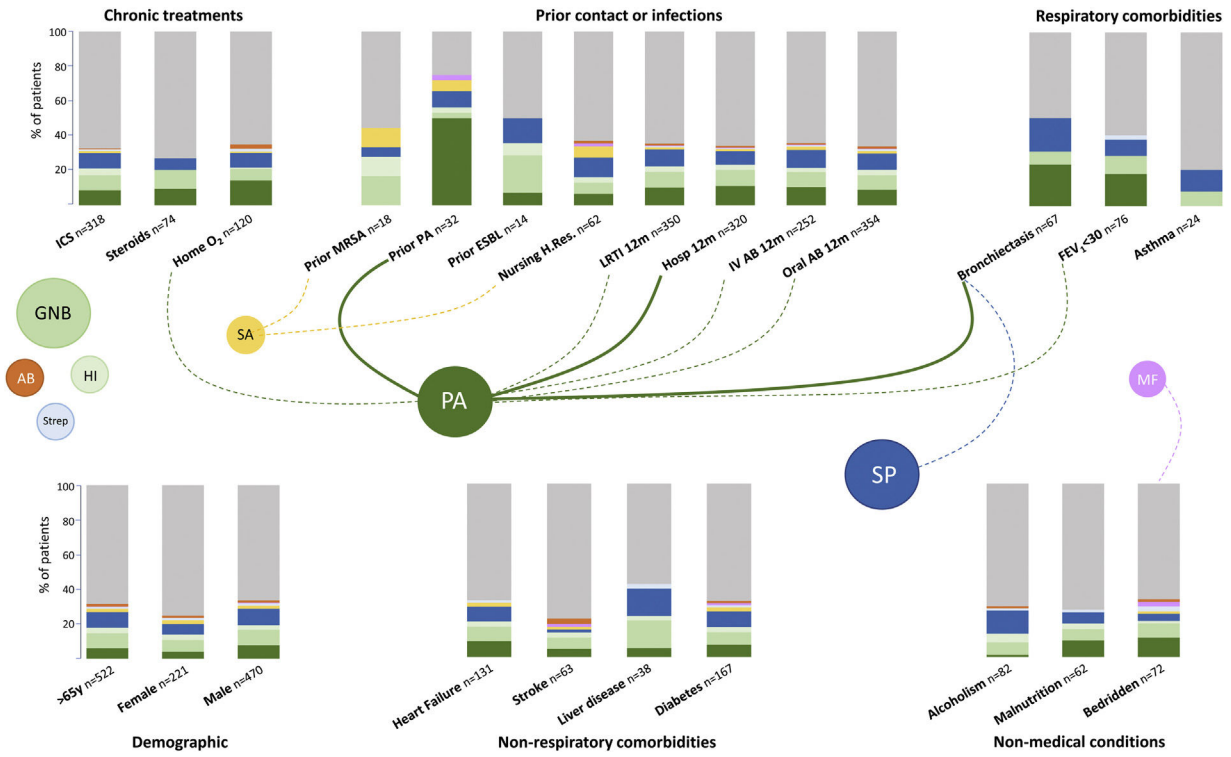

Fig. 3. Microbiological patterns associated with distinct COPD risk factors in hospitalized patients with CAP. Bar colors represent the different percentages of bacterial isolations for each risk factor. Dashed lines represent a statistically significant difference (prevalence of the bacteria comparing patients with and without the specific risk factor) in the bivariate and the solid lines in the multivariate analysis, respectively. Footnote Fig. 3. GNB: Gram negative bacteria, SP: *S. pneumoniae*, PA: *P. aeruginosa*, SA: *S. aureus*, HI: *H. influenzae*, Strep: *Streptococcus* spp, AB: Atypical bacteria, MF: Mixed flora. ICS: inhaled corticosteroids, MRSA: methicillin resistant *Staphylococcus aureus*, ESBL: extended spectrum β-Lactamases, LRTI: low respiratory tract infection, IV: intravenous, Ab: antibiotic, Hosp: hospitalization, Nursing H.Res: nursing home residence, FEV_1: forced expiratory capacity in one second.

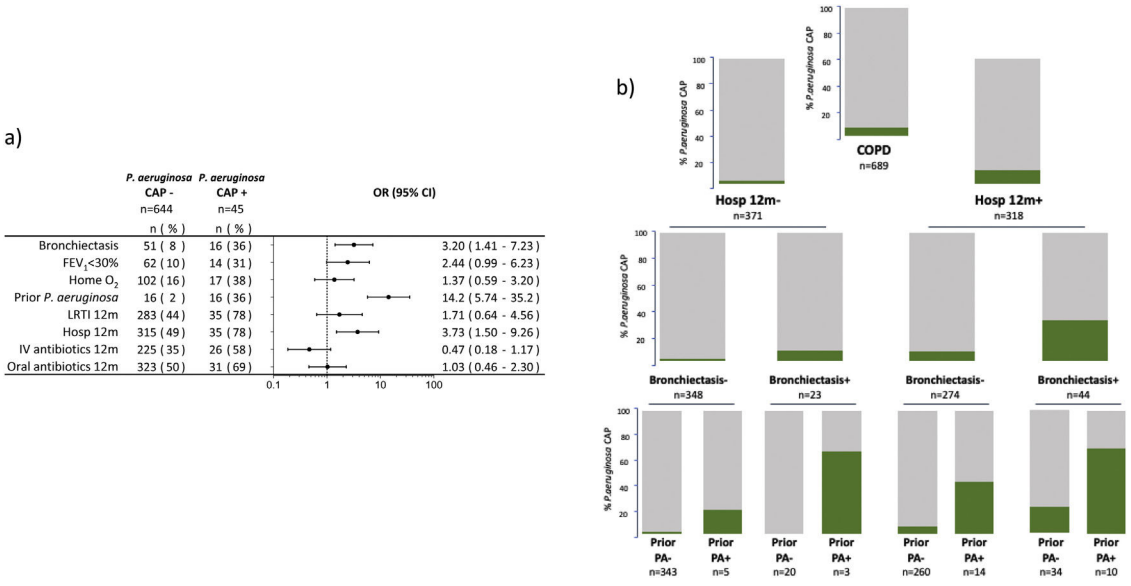

Fig. 4. (a) Multivariate analysis of the risk factors associated with *P. aeruginosa* CAP among hospitalized patients with COPD. (b) Bar graphs decision tree analysis representing the prevalence of *P. aeruginosa* CAP by the three independently associated risk factors (prior hospitalization in the past 12 months, bronchiectasis, and prior *P. aeruginosa* infection or colonization). Footnote Fig. 4. Hosp: hospitalization, PA: *P. aeruginosa*, CAP: Community acquired pneumonia.

associated in the univariate analysis, but not in the multivariate analysis in COPD patients with bronchiectasis that developed CAP. As mentioned above, bronchiectasis in patients with COPD was previously associated with increased bronchial inflammation, frequent airway colonization by several microorganisms, and severe airflow obstruction.[36] Finally, low prevalent pathogens, such as *H. influenzae* (3%) and *S. aureus* (2%), were not associated with COPD risk factors. Our results support the recommendations of the 2019 American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) clinical practice guidelines for the management of CAP, where MRSA and *P. aeruginosa* should be detected and treated in patients with pathogen specific risk factors.[11] In patients with COPD requiring hospitalization for CAP, the most important pathogen for which the conventional treatment should be altered

a)

	β	OR	PAS-COPD
Prior *P.aeruginosa*	2.654	14.21	3 points
Hospitalizations 12m	1.317	3.73	1 point
Bronchiectasis	1.162	3.20	1 point

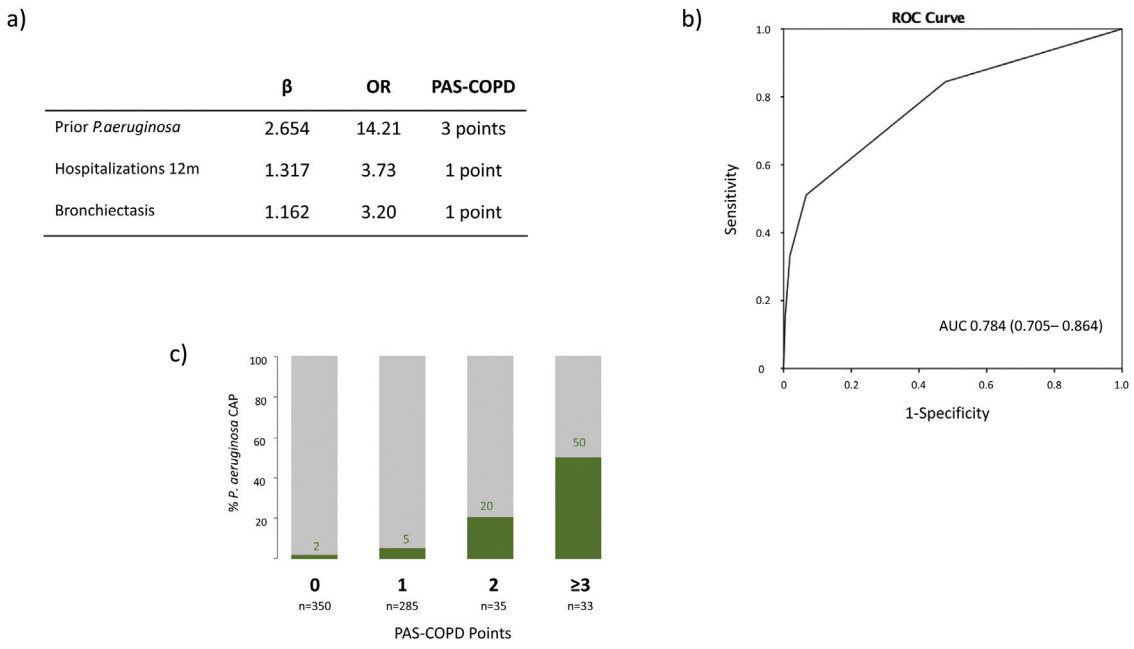

Fig. 5. (a) Table representing the points assigned to the three independently associated risk factors included in the *Pseudomonas aeruginosa* score (PAS) for COPD patients. (b) Receiver operating curve of the PAS-COPD performance to predict *P. aeruginosa* CAP. (c) Actual distribution of the prevalence of *P. aeruginosa* CAP according to the number of points of the PAS-COPD.

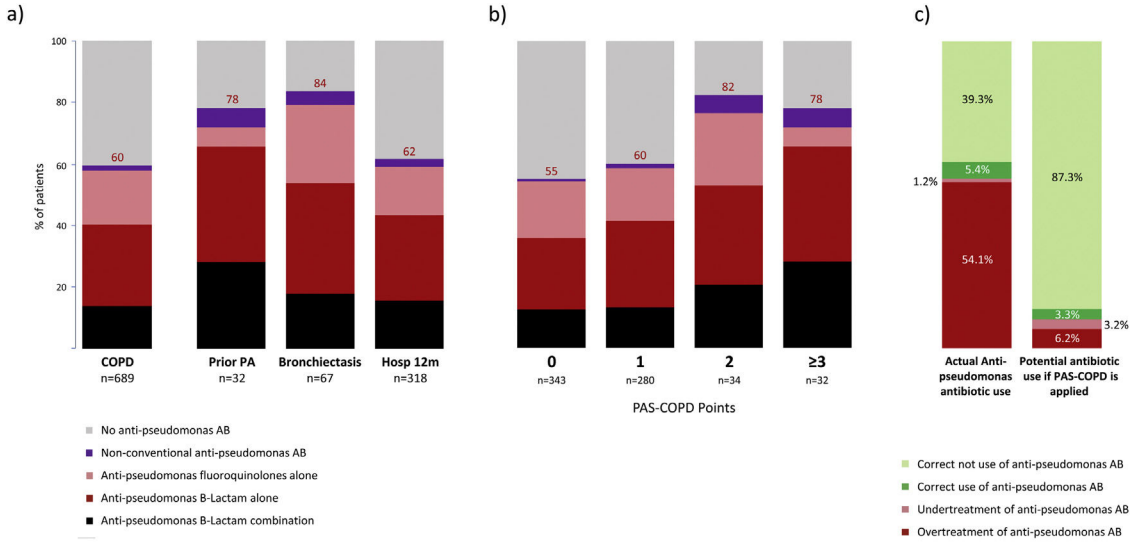

Fig. 6. (a) Actual empiric anti-pseudomonal antibiotic use for COPD patients stratified according to the three independent risk factors associated to *P. aeruginosa* CAP. (b) Actual empiric anti-pseudomonal antibiotic use for COPD patients stratified according to PAS-COPD score. (c) Distribution of appropriate use, appropriate non-use, undertreatment and overtreatment of empiric anti-pseudomonal antibiotics in the actual cohort of COPD patients with CAP and the potential empiric anti-pseudomonal antibiotic utilization if the PAS-COPD were applied in clinical practice. Footnote Fig. 6. Hosp: hospitalization, PA: *P. aeruginosa*; PAS-COPD: *P. aeruginosa* score for COPD.

was *P. aeruginosa*. Future studies should explore how these risk factors interact and how they can increase the risk of *P. aeruginosa* infection.

A *P. aeruginosa* decision tree and a newly developed *P. aeruginosa* score suggest that patients with COPD and CAP have a different prevalence of *P. aeruginosa* infection according to presence or absence of the combination risk factors. Previously designed scores attempting to identify multidrug resistant bacteria, such as *P. aeruginosa,* considered COPD a risk factor with varying results.[15,37,38] However, these scores were not specific for *P. aeruginosa* and did not focus on patients with COPD, but rather used COPD as an individual risk factor. We developed a simple score with three variables independently associated with *P. aeruginosa* among patients with COPD and hospitalized with CAP. Our PAS-COPD can be dichotomized to separate a low (<6%) vs. high (20% or higher) prevalence *P. aeruginosa* CAP group that may potentially guide rational selection of appropriate anti-pseudomonal antibiotics. A low PAS-COPD score (0 or 1 point) suggests that patients may receive CAP antibiotics without any anti-pseudomonal coverage; in contrast a high PAS-COPD score suggests the need of anti-pseudomonal coverage. This finding is significant because it suggests that only 10% of COPD patients hospitalized with CAP may need anti-pseudomonal coverage.

The largest motivation to perform this study was the clinical concern of excessive anti-pseudomonal antibiotic usage among COPD patients that developed CAP. Our clinical gestalt was

consistent with what we found in the actual anti-pseudomonal antibiotic utilization. Our results suggest that two-thirds of COPD patients that develop CAP received at least one anti-pseudomonal antibiotic. Although empirical antibiotic therapy covering *P. aeruginosa* is indicated in certain patients,[39] the high anti-pseudomonal antibiotic utilization (>60%) is not justified given the low prevalence of *P. aeruginosa* CAP (7%). Other authors have suggested that anti-pseudomonal antibiotics are overused in patients with CAP, particularly in those with COPD.[37] It is interesting that the most commonly used anti-pseudomonal antibiotics were beta-lactam antibiotic monotherapy (27%), fluoroquinolones monotherapy (17%), followed by combinations of a beta-lactam antibiotic plus a fluoroquinolone, colistin, or aminoglycoside (14%). There is great concern about antimicrobial resistance, and this leads toward higher antimicrobial usage and in particular combination of anti-pseudomonal antibiotics. Recent CAP guidelines recommend using anti-pseudomonal agents in patients with prior isolation of this organism, especially from the respiratory tract; recent hospitalization; and exposure to parenteral antibiotics.[11] In our study, the utilization of PAS-COPD might be able to reduce anti-pseudomonal antibiotic overuse from 54.1% to 6.2%. It is suggested that at least 20% of COPD patients hospitalized with CAP might require empirical anti-pseudomonal antibiotic coverage. Also, the prevalence of *P.aeruginosa* in COPD patients with a score of 0 and 1 points were 2% and 5%, respectively, whereas the prevalence in those with 2 or $\geq$3 points was 20% and 50%, respectively. For this reason, it would be reasonable not starting antipseudomonal treatment when PAS-COPD $\leq$ 1 due to the low risk of Pseudomonas etiology. However, a validation score and hospital implementation programs are needed to improve anti-pseudomonal antibiotic overuse in COPD patients with CAP.

The present study has several limitations. Due to multicenter study design, different local standards of care were used. GLIMP is an observational point-prevalence study and was designed to address microbial prevalence and empiric antibiotic use per local standards of care and did not have information about clinical outcomes. For this reason, this study cannot define causal relationships. Otherwise, in over 60% of cases, the etiological agent for the CAP could not be found. Therefore, our results are a representation of what occurs in real life and are similar to prior evidence,[40] and this is why our analysis focused on the patients with microbiological testing performed attempting to minimize possible bias. Also, the diagnosis of COPD preceded the hospitalization due to CAP and it was defined according to the GOLD criteria,[21] but it was not mandatory to document the FEV1/FVC ratio in the case report form. Similarly, we do not have the thorax CT images to confirm the diagnosis, the severity of bronchiectasis or the doses of inhaled corticosteroids.

In conclusion, microbiological patterns differ according to unique risk factors in COPD patients requiring hospitalization due to CAP. *P. aeruginosa* represents the most concerning pathogen among COPD patients who developed CAP. Our *P. aeruginosa* score attempts to assist providers in the appropriate use of empiric anti-pseudomonal therapy and prevent the unnecessary overuse of these antibiotics in COPD patients hospitalized with CAP. Future validation and implementation studies will help us determine the impact of these findings in the routine clinical practice.

Authors' contributions

SP, FA, JMC, NJS and MIR wrote and edited the manuscript. SA and MIR designed the study and performed statistical analysis. SA, PJM, AR, OS, FS, AU, BM, CNM, MK, and MIR enrolled patients. SA, JG, PJM, AR, OS, FS, GS, AU, BM, CNM, AA and MK contributed intellectually to the final version of the manuscript, and all authors read and approved it.

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Conflict of interest

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