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Microbiology and outcomes of community acquired pneumonia in non cystic-fibrosis bronchiectasis patients

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Summary *Background:* It is general belief that Non-cystic fibrosis bronchiectasis (NCFB) is characterized by frequent community-acquired pneumonia. Nonetheless, the knowledge on clinical characteristics of CAP in NCFBE is poor and no specific recommendations are available. We aim to investigate clinical and microbiological characteristics of NCFBE patients with CAP.
Methods: Prospective observational study of 3495 CAP patients (2000–2011).
Results: We found 90 (2.0%) NCFBE-CAP that in comparison with non-bronchiectatic CAP (n, 3405) showed older age (mean ± [SD], NCFBE-CAP 73 ± 14 *vs*. CAP 65 ± 19yrs), more vaccinations (pneumococcal: 35% *vs*. 14%; influenza: 60% *vs*. 42%), comorbidities (n ≥ 2: 43% vs. 25%), previous antibiotics (38% vs. 22%), and inhaled steroids (53% vs. 16%) ($p < 0.05$ each). *Streptococcus pneumoniae* was the most frequent isolate in both groups (NCFBE-CAP 44.4% vs. CAP 42.7%; $p = 0.821$) followed by respiratory virus, mixed infections and atypical bacteria. Considering overall frequencies of the main pathogens (including monomicrobial and mixed infections) *Pseudomonas aeruginosa* (15.5% vs. 2.9%; $p < 0.001$) and *Enterobacteriaceae* (8.8%

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vs. 2.4%; p = 0.025) were more prevalent in NCFBE-CAP patients than in CAP.

Despite these clinical and microbiological differences, NCFBE-CAP showed similar outcomes to CAP patients (mortality, length of hospital stay, etc.).

Conclusions: NCFBE-CAP patients are usually older and have more comorbidities but similar outcomes than general CAP population. Usual CAP pathogens, such as S. *pneumoniae*, are also involved in NCFBE-CAP but *P. aeruginosa* and other *Enterobacteriaceae* were globally more frequent than in CAP. Therefore, a wide microbiological investigation should be recommended in all NCFBE-CAP cases as well as routine pneumococcal vaccination for prevention of pneumonia.

Introduction

Non-cystic fibrosis bronchiectasis (NCFBE) is defined by the presence of abnormal and irreversible bronchial widening secondary to a non-CF cause and is usually characterized by[1] chronic inflammatory disease,[2] frequent respiratory infections, including pneumonia[1–3] progressive loss of lung function,[4] worsening in quality of life and[5] a considerable economic burden over time.[3,4]

Few data are available about incidence of NCFBE, but in the USA an overall prevalence of 52 per 100 000 has been reported.[5]

Severe or recurrent pneumonia is considered a potential cause of bronchiectasis but also the initial clinical manifestation of NCFBE despite poor scientific evidence.[6–8] Nevertheless, the scientific literature on the prevalence of pneumonia among NCFBE patients is limited.[6,7,9] Moreover, the diagnosis of NCFBE is frequently achieved with a considerable delay due to the need of an HRCT scan and many patients may suffer different episodes of pulmonary infection and a progression in lung damage before the diagnosis is confirmed. Therefore, the presence of bronchiectasis is usually considered a risk condition for community-acquired pneumonia (CAP) although this association has been clearly demonstrated only for bronchiectasis secondary to primary antibody deficiencies.[10]

In addition, as almost 40–60% of NCFBE patients suffer chronic airway infection by potential multidrug resistant (MDR) pathogens,[6,11,12] NCFBE patients are considered at risk of *Pseudomonas aeruginosa* and current CAP guidelines consider NCFBE a risk factor for treatment failure due to inadequate antibiotic coverage.[13,14] Unfortunately, the information on the etiology and outcomes of pneumonia in NCFBE is extremely scarce nowadays and no specific clinical recommendations are currently available.

We aimed to investigate clinical characterization, microbial etiology and outcomes of CAP in NCFBE patients in comparison with non-bronchiectatic patients with the objective to clarify clinical recommendations to treat CAP in NCFBE patients.

Materials and methods

Study population

We prospectively studied 4413 consecutive cases of adults patients admitted to the emergency department with suspicion of CAP from 2000 to 2011 in an 850-bed tertiary care university hospital in Barcelona, Spain. Among these, we investigated patients with an established or new diagnosis of NCFBE confirmed by HRCT. The exclusion criteria were: a) severe immunosuppression, such as in solid-organ or bone-marrow transplantation or AIDS, or receiving chemotherapy or other immunosuppressive drugs (>20 mg prednisone-equivalent per day for ≥2 weeks); b) hospitalization in the preceding 21 days; c) active tuberculosis; d) Health care-associated pneumonia (HCAP) excepting nursing home (although HCAP criteria were defined in 2005, they had been individually set as exclusion criteria for our CAP database since 1996), e) cystic fibrosis and f) cases with confirmed alternative diagnosis at the end of follow-up. Cystic fibrosis was systematically ruled out in all bronchiectatic patients in the study (sweat test and genetic screening according to European guidelines).[15]

Definitions

CAP and other definitions are described in the online supplemental material. Concordant opinions were required by two independent reviewers (the attending physician and a medical researcher external to data analysis) of chest x-rays and CT scans, when available, to confirm diagnosis of pneumonia and exclude "simple exacerbations of NCFBE or any other chronic respiratory disease (COPD, etc.)".

NCFBE was defined clinically and radiologically and not related to CF, and was confirmed by high-resolution computerized tomography (HRCT). CT scan had been performed before CAP episode or during hospital admission or CAP follow-up by the attending physician for two main reasons: late response to treatment or diagnostic screening due to clinical and/or radiological suspicion (chest X-rays) of bronchiectasis and/or other subsistent respiratory disease. Chronic bronchial infection was defined as at least 2 respiratory isolates of the same pathogen in the last year (3 months apart) before pneumonia.[16]

Data collection and follow-up

Data collection during hospital admission (including demographics, comorbidities, previous vaccinations and antimicrobial therapy, signs and symptoms of clinical presentation, complete and systematic microbiological

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investigations, antimicrobial therapy and steroids) and follow-up is widely described in the online supplemental material.[17] All surviving patients were re-examined or at least telephonically contacted 4–6 weeks after discharge from the emergency care unit in the outpatients' clinic in order to assess clinical resolution (30-day mortality rate). PSI and CURB-65 classes were assigned according to the original authors' designations.

Antibiotic therapy was recorded in all cases and its adequacy to current Spanish guidelines for CAP[18] treatment was evaluated such as its appropriateness[19,20] according to microbiological findings in those patients with a known microbial etiology of pneumonia.

The prospective collection of clinical data was approved by the Institutional Review Board. Patients' identification remained anonymous and informed consent was considered unnecessary due to the observational nature of the study. All reported data are the result of the clinical routine activity and all tests and procedures were ordered by the attending physicians, not involved in this study.

Statistical analysis

We performed a secondary analysis of a prospectively analysis collected CAP database in order to investigate NCFBE subgroup. We show n (%) for categorical variables and median (IQR) for continuous variables with non-normal distribution or mean ± SD for those with normal distribution. Categorical variables were compared with the chi-square test or Fisher's exact test. Continuous variables were compared using the Student's t-test or the nonparametric Mann–Whitney U test. Univariate and multivariate logistic regression analyses were performed to identify variables available at presentation in the emergency room of our Hospital that predicted hospitalization, ICU admission (dependent variable, see online supplemental material) 30-day mortality and prolonged length of stay (LOS>7 days; cut-off value the median value of LOS).

Univariate and multivariate logistic regression analyses were performed to identify variables predictive of patients' hospitalization, ICU admission, 30-day mortality and prolonged LOS (dependent variables). The variables analyzed univariately were: age (<65 vs. ≥65 years), gender, smoking, influenza vaccination, pneumococcal vaccination, inhaled corticosteroids, previous antibiotic, bronchiectasis, COPD, chronic cardiovascular disease, diabetes mellitus, neurological disease, chronic renal disease, chronic liver disease, cough, sputum, dyspnoea, chest pain, fever, altered mental status, PSI class (I-III vs. IV-V), CURB-65 (1-2 vs. 3-5), serum creatinine (<1.5 vs. ≥1.5 mg/dL), C-RP (<18 vs. ≥18 mg/dL[median]), WBC count (<4 vs. ≥4 × 10^9 cell/L), platelets count (<100 vs. ≥100 × 10^9 cell/L), respiration rate (<30 vs. ≥30 breaths per min.), systolic blood pressure (<90 vs. ≥90 mmHg), temperature (<36 vs. ≥36 °C), $SatO_2$ (<92 vs. ≥92%), PaO_2/FiO_2 (<250 vs. ≥250), pleural effusion, multilobar infiltration, ARDS, acute renal failure, etiology, and bacteraemia.

Variables that showed a significant result univariately ($p < 0.1$) were included in the corresponding multivariate logistic regression backward stepwise model. Variables highly correlated were excluded from multivariate analyses. The Hosmer–Lemeshow goodness-of-fit test was performed to assess the overall fit of the model[21]. All tests were two-tailed and significance was set at 5%. All analyses were performed with IBM SPSS Statistics 18.0 (Armonk, New York, USA).

Results

General characteristics of the study population

After excluding patients with immunodepression and nosocomial pneumonia (previous hospitalization in the last 3 months) we analyzed 3731 CAP and NCFBE were described in 124 patients but they were confirmed by HRCT only in 111 cases (3.0%) (Fig. 1). Overall, 188 patients had more than one episode of CAP during the study period (162 patients with 2 episodes of pneumonia, 26 with 3 episodes) but only first episode was considered for the final analysis. It is worth noting that NCFBE patients had significantly more recurrent pneumonia (mean rate of CAP 1.23; n of recurrent CAP, 21 [18.9%]) than non-bronchiectatic patients (mean rate 1.059; n of recurrent CAP, 202 [5.6%]) ($p < 0.001$). We finally analyzed 3495 patients including 3405 CAP and 90 NCFBE-CAP patients.

A total of 52 (58%) NCBE-CAP patients had an NCFBE diagnosis prior to pneumonia, whereas 38 (42%) patients were diagnosed during the current CAP episode by HRCT scan showing diffuse multilobar bronchiectasis also affecting lobes not involved in pneumonia, that were considered, therefore, pre-existing to pneumonia. Data of clinical history, clinical presentation and outcomes from patients diagnosed of NCFBE before and during CAP were compared, showing no significant differences between the 2 groups (on-line supplement Table 1b).

To further confirm the homogeneity of NCFBE patients (diagnosed before or during CAP) we exclusively compared NCFBE patients diagnosed before pneumonia (n, 52) with CAP group (on-line supplement Table 1b) and found no differences from the overall analysis including all NCFBE patients (Tables 1 and 2).

Globally, the underlying etiologies of bronchiectasis were: idiopathic 27 (30%), previous tuberculosis 28 (31%), other post-infectious causes 8 (9%), primary immunological abnormalities 5 (6%), COPD 17 (19%), asthma 3 (3%), ciliary dyskinesia 1 (1%), Mounier–Kuhn syndrome 1 (1%).

Comparison of CAP and CAP-NCFBE patients

The differences in baseline characteristics between patients with CAP and those with CAP and NCFBE are summarized in Table 1. The NCFBE group showed older age and more females, higher rates of vaccinations, more comorbidities and previous treatment with inhaled (ICs), oral corticosteroids and antibiotics in the last month. Moreover, NCFBE patients presented more expectoration, dyspnoea, and leukocytosis and needed more hospitalization but showed similar PSI and CURB-65 scores (Tables 1 and 2).

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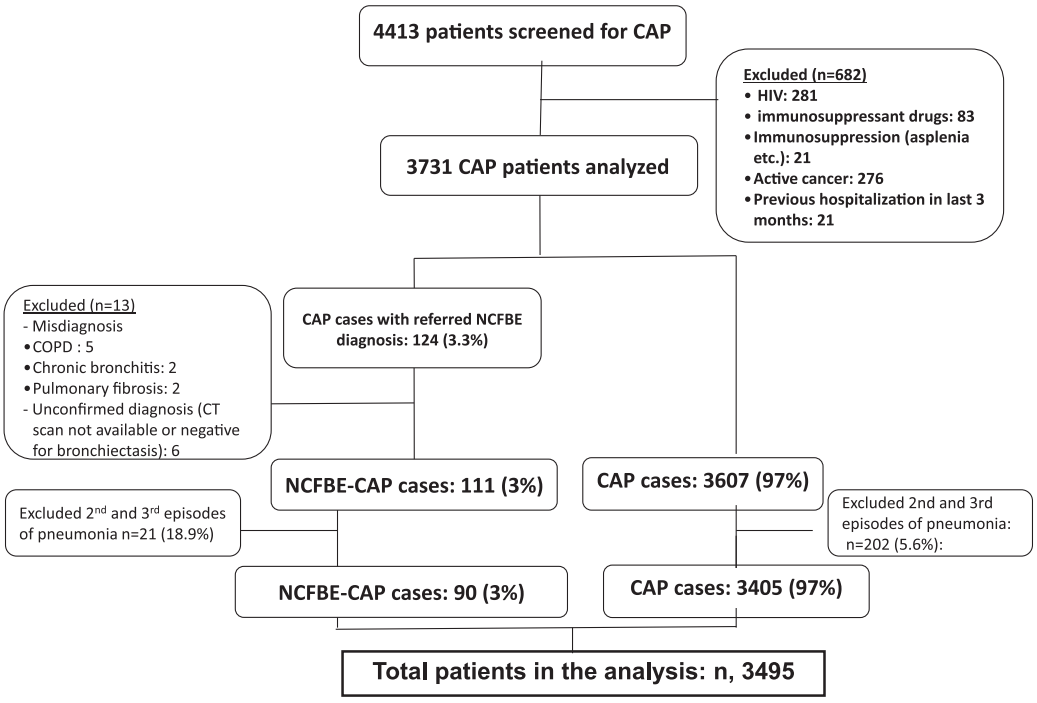

Figure 1 Flow diagram of the selected population. Abbreviations: NCFBE, non-cystic fibrosis bronchiectasis; CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; CT, computed tomography.

Microbial etiology

Microbiological diagnosis was achieved in 41.1% of CAP patients (n, 1399) and in 50.0% (n, 45) of NCFBE-CAP subgroup ($p = 0.091$).

Streptococcus pneumoniae was largely the most prevalent causative pathogen of CAP in both groups, followed by respiratory virus, mixed infections and atypical bacteria (Table 3). Among cases of polymicrobial infection *P. aeruginosa* (*plus* other) was more frequent in NCFBE-CAP (13.3%) than in CAP (1.0%; $p < 0.01$), while other combinations (with *S. pneumoniae* [8.9% vs. 8.3], *Haemophilus influenzae* [4.4% vs. 2.9%], etc.) were similarly distributed between the two groups.

Table 4 shows the overall prevalence rates of main pathogens as isolated alone (monomicrobial pneumonia) and/or in combination with any other pathogen (mixed infection), *P. aeruginosa* and *Enterobacteriaceae* being more frequent among NCFBE-CAP than in CAP.

Only 10 NCFBE patients (11.1%) had a known chronic bronchial infection prior to the pneumonia episode (6 cases of *P. aeruginosa*, 2 of MSSA; 1 of *Escherichia coli*, 1 *H. influenzae*): in 3 of them the "chronic" microorganism coincided with etiology of pneumonia and in 4 cases the "chronic" microorganism was isolated in CAP as well, but in association with a new pathogen; globally 7 of 10 cases of chronic bronchial infection showed the same pathogen during CAP.

Antibiotic treatment

Data on antibiotic treatment were available in 3462 (99%) patients. The most frequent regimens were beta-lactam *plus* macrolide ($n = 1188$, 34.3%), fluoroquinolone monotherapy ($n = 916$, 26.5%), fluoroquinolones *plus* beta-lactam ($n = 758$, 21.9%). These regimens were similarly administered in patients with and without NCFBE (all, $p > 0.05$).

Antibiotic therapy was adequate (according to current Spanish guidelines for CAP treatment[18]) in most cases but less frequently in NCFBE-CAP than in CAP (NCFBE-CAP, 77.8% vs. CAP, 89.0% of cases; $p = 0.020$), mostly because of the administration of a combination of a beta-lactam *plus* a glycopeptide or an aminoglycoside (covering possible MDR infections). However, the antibiotic therapy was also appropriate in relation with microbial etiology in most cases of CAP (93.8%, $n = 1069$) and NCFBE-CAP (87.8%, $n = 36$; $p = 0.126$).

Among cases of *P. aeruginosa* infection, there was a rate of appropriate therapy (according to microbial etiology) of 43% (3 out of 7 cases) in NCFBE-CAP and 33% (13 out of 40 cases) in the CAP group ($p = 0.680$); this mild and non significant difference was due to the increased trend to cover potential MDR pathogens among NCFBE patients, compared to CAP.

Outcomes and prognostic factors

A non significant trend to increased hospitalization (particularly ICU) was observed in the NCFBE-CAP group, but no differences were observed in mortality and/or any other severity marker such as MV, LOS, pulmonary and systemic complications of pneumonia between the two groups (Table 2), despite significant differences in age and number of comorbidities.

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Table 1 Characteristics of patients with and without Non-CF Bronchiectasis (n = 3495).

Variable	NCFBE-CAP (n = 90)	CAP (n = 3405)	p-Value[a]
Demographic			
Age (years), mean ± SD	73 ± 14	65 ± 19	**0.001**
Age ≥65 years, n (%)	73 (81)	1996 (58.6)	**<0.001**
Sex (male), n (%)	31 (34.4)	22,087 (61.3)	**<0.001**
Smoking, n (%)			**<0.001**
No smoker	56 (62.2)	1512 (44.8)	
Current smoker	6 (6.7%)	860 (25.5)	
Ex-smoker	28 (31.1)	1005 (29.8)	
Alcohol, n (%)			0.133
No alcohol consumer	80 (89.9)	2732 (81.6)	
Current alcohol consumer	9 (8.2)	495 (14.8)	
Ex-alcohol consumer	35 (2.7)	122 (3.6)	
Previous antibiotic, n (%)	32 (37.6)	711 (21.8)	<0.001
Nursing home residence, n (%)	3 (3.3%)	82 (2.4)	0.584
Influenza vaccine, n (%)	42 (60.0)	1167 (41.5)	**<0.001**
Pneumococcal vaccine, n (%)	24 (34.8)	397 (14.2)	**<0.001**
Inhaled corticosteroid, n (%)	47 (52.8)	525 (15.6)	**<0.001**
Systemic corticosteroid, n (%)	4 (5.1)	47 (1.5)	**0.012**
Number of comorbidities ≥2, n (%)	39 (43.3)	847 (24.9)	**<0.001**
Chronic cardiovascular disease	17 (18.9)	586 (17.3)	0.693
Diabetes mellitus	10 (11.5)	544 (16.5)	0.210
Neurological disease	13 (14.4)	596 (17.7)	0.428
Chronic renal disease	6 (6.7)	209 (6.2)	0.847
Haemodialysis	0 (0)	7 (0.2%)	1.000
Chronic liver disease	6 (6.7)	147 (4.3)	0.288
COPD	17 (19.0)	507 (14.9)	0.373
Clinical findings, n (%)			
Cough	76 (84.4)	2748 (79.7)	0.259
Sputum	66 (75.0)	1877 (56.9)	**<0.001**
Dyspnoea	70 (78.8)	2188 (65.3)	**0.009**
Chest pain	38 (42.2)	1396 (41.8)	0.937
Fever	76 (87.4)	2684 (82.73)	0.252
Altered mental status	13 (14.4)	608 (18.0)	0.389
Vital signs			
Respiration rate (breaths per min.), median (IQR)	24.5 (20.0–32.0)	24.0 (20.0–30.0)	0.276
Respiration rate ≥30 breaths per min., n (%)	25 (29.8)	878 (28.2)	0.754
Temperature (°C), median (IQR)	37.6 (36.6–38.2)	37.6 (36.6–38.3)	0.307
Temperature <36 °C, n (%)	4 (4.9)	185 (5.9)	0.673
Systolic blood pressure (mmHg), median (IQR)	139.5 (116.5–154.0)	130.0 (114.0–149.0)	0.051
Systolic blood pressure <90 mmHg, n (%)	1 (1.1)	129 (3.9)	0.108
Laboratory findings			
Creatinine (mg/dL), median (IQR)	1.0 (0.8–1.2)	1.0 (0.9–1.4)	0.059
C-reactive protein level (mg/dL), median (IQR)	16.0 (5.0–23.7)	17.7 (8.9–27.1)	0.074
C-reactive protein level ≥18 mg/dL, n (%)	33 (45.2)	1349 (49.4)	0.482
WBC count ($\times 10^9$ cell/L), median (IQR)	14.7 (9.9–19.7)	12.6 (8.9–17.3)	**0.017**
Leukopenia (<4 × 10^9 WBC/L), n (%)	0 (0)	96 (2.9)	0.104
Platelets count ($\times 10^9$ cell/L), median (IQR)	260.0 (175.0–346.0)	237.0 (184.0–302.0)	0.250
Thrombocytopenia (<100 × 10^9 cell/L), n (%)	0 (0)	54 (2.7)	0.212
$SatO_2$<92% in room air, n (%)	21 (40.4)	655 (33.5)	0.522
PaO_2/FIO_2, median (IQR)	273.0 (238.1–309.5)	285.7 (242.9–333.3)	0.232
PaO_2/FIO_2 <250, n (%)	21 (37.5)	665 (28.0)	**0.118**

Abbreviations: IQR = interquartile range; SD = standard deviation; PaO_2/FIO_2 = arterial oxygen tension to inspired oxygen fraction ratio; PSI = pneumonia severity index; $SatO_2$ = oxygen saturation; WBC = white blood cells.
Percentages calculated on non-missing data.
Variables with p-values<0.05 are in bold.
[a] Chi-square test, Fisher's exact test, Student's *t*-test or Mann–Whitney *U* test, as appropriate. Median of C-RP values was used as cut-off value.

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Table 2 Severity and clinical outcomes of patients with (n, 90) and without Non-CF Bronchiectasis (n = 3405).

	NCFBE-CAP (n = 90)	CAP (n = 3405)	p-Value[a]
PSI classes IV-V, n (%)	50 (55.6)	1672 (49.1)	0.227
CURB-65 classes 3-5, n (%)	8 (11.0)	524 (19.4)	0.071
Bacteraemia, n (%)	4 (4.4)	297 (8.7)	0.153
Multilobar infiltration, n (%)	17 (22.4)	628 (21.5)	0.859
Pleural effusion, n (%)	14 (13.5)	452 (13.5)	0.511
ARDS criteria, n (%)	1 (1.2)	93 (3.1)	0.336
Site of care			**0.055**
Outpatients	7 (7.8)	551 (16.2)	**0.017**
Ward	63 (70.0)	2297 (67.5)	0.351
ICU admission, n (%)	20 (22.2)	557 (16.4)	0.094
Mechanical ventilation, n (%)	5 (5.6)	214 (6.3)	0.778
Septic shock, n (%)	4 (4.4)	179 (5.3)	0.708
Acute renal failure, n (%)	19 (21.1)	793 (24.0)	0.527
Length of hospital stay (days), median (IQR)	7.0 (5.0—9.5)	6.0 (3.0—10.0)	0.158
30-day mortality, n (%)	4 (4.4)	246 (7.2)	0.312

Abbreviations: ARDS = acute respiratory distress syndrome; CURB-65 = confusion, blood-urea nitrogen, respiratory rate, blood pressure, age; ICU = intensive care unit; IQR = interquartile range.
Percentages calculated on non-missing data.
Variables with p-values<0.05 are in bold.
[a] Chi-square test, Fisher's exact test or Mann—Whitney *U* test, as appropriate.

However, we performed multivariate analyses for ICU admission, prolonged LOS (>7 days, median LOS of overall population) and 30-day mortality, but none of them showed NCFBE to be an independent associated factor, even after adjustments for NCFBE and potential confounding factors such as previous comorbidities, vaccinations, smoking habits, alcohol consumption and age (online supplement, Tables 2b,3b,4b).

Table 3 Distribution of the causative microorganisms in patients with a defined pneumonia aetiology (n = 1444).

Microorganism	NCFBE-CAP (n = 45)	CAP (n = 1399)	p-Value[a]
Streptococcus pneumoniae	20 (44.4)	598 (42.7)	0.821
Respiratory virus	4 (8.9)	206 (14.7)	0.274
Mixed	8 (17.8)	180 (12.9)	0.335
Atypical bacteria	2 (4.4)	115 (8.2)	0.576
Mycoplasma pneumoniae	1 (2.2)	54 (3.9)	1.000
Chlamydophila pneumoniae	1 (2.2)	39 (2.8)	1.000
Coxiella burnetii	0 (0)	22 (1.6)	1.000
Legionella pneumophila	1 (2.2)	100 (7.1)	0.163
Pseudomona aeruginosa[b]	1 (2.2)	26 (1.9)	0.578
Enterobacteriaceae			
Escherichia coli	2 (4.4)	123 (0.9)	0.068
Klebsiella pneumoniae	0 (0)	6 (0.4)	0.827
Proteus mirabilis	0 (0)	1 (0.1)	0.969
Providencia stuartii	0 (0)	1 (0.1)	1.000
Haemophilus influenzae	2 (4.4)	43 (3.1)	0.413
Moraxella catarrhalis	0 (0)	5 (0.4)	0.853
Haemophilus parainfluenzae	0 (0)	1 (0.1)	0.969
Staphylococcus aureus	3 (6.7)	28 (2.0)	0.069
Others *Streptococcus* species	2 (4.4)	16 (1.0)	0.106
Streptococcus constellatus	1 (2.2)	2 (0.1)	0.091
Streptococcus viridans	1 (2.2)	9 (0.6)	0.272
Streptococcus pyogenes	0 (0)	5 (0.4)	1.000
Others	0 (0.0)	61 (4.4)	0.139

Data are expressed as n (%).
[a] Chi-square test or Fisher's exact test, as appropriate.
[b] *P. aeruginosa* when isolated alone.

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Table 4 Overall frequencies of main isolated microorganisms (monomicrobial and mixed infections).

	NCFBE-CAP n, %		CAP n, %		p-value
Streptococcus pneumoniae	24	53.3%	714	51.0%	0.885
Pseudomonas aeruginosa	7	15.5%	40	2.9%	**<0.001**
Haemophilus influenzae	4	8.8%	83	5.9%	0.618
Respiratory viruses	6	13.3%	290	20.7%	0.308
Atypical pathogens	2	4.4%	149	10.7%	0.279
Enterobacteriaceae	4	8.8%	33	2.4%	**0.025**
Staphylococcus aureus	4	8.8%	50	3.6%	0.157
Legionella pneumophila	1	2.2%	111	7.9%	0.266

Note: Percentages refer to cases with known microbial etiology (NCFBE-CAP: 45, CAP: 1399).
Atypical pathogens include: *Mycoplasma pneumoniae*, *Coxiella burnetii*, *Chlamydia pneumoniae*.
Enterobacteriaceae include: *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Providencia stuartii*.
Variables with p-values<0.05 are in bold.

Discussion

The main findings of this study were the following:

- Despite an older age and more comorbidities, NCFBE patients showed a similar clinical presentation at admission and similar severity scores (PSI, CURB-65).
- Moreover NCFBE patients also showed similar outcomes (mortality, MV, LOS, etc.) in comparison to the general CAP population.
- The microbiological investigation showed that *S. pneumoniae* was the most frequent isolate in both groups, but in the NCFBE-CAP patients there was an overall (monomicrobial and polymicrobial infections) increased rate of *P. aeruginosa* and *Enterobacteriaceae* compared to CAP.
- The NCFBE-CAP group showed a lower rate of adequate empiric antibiotic therapy according to guidelines[18] in comparison with CAP.

This is the first study in the literature analyzing a large CAP series to investigate demographics, clinical characteristics and microbial etiology of pneumonia in NCFBE patients. This study clearly shows that NCFBE-CAP patients in Spain differ from the general CAP population in different aspects. In particular, NCFBE-CAP patients showed older age, more comorbidities and, consequently, increased vaccination rates (pneumococcal and influenza) and more inhaled (ICs) and systemic corticosteroids and previous antibiotic use than CAP population.

Our NCFBE-CAP population, did not show worse clinical outcomes (mortality, LOS etc.) in comparison with CAP albeit older age and more comorbidities. Therefore, it is questionable whether previous antibiotics, steroids and vaccinations could play a protective role in modulating pneumonia severity or whether the usual heterogeneity of NCFBE etiology and severity could also influence overall clinical presentation of pneumonia. Nevertheless it is important to consider that patients with an underlying chronic disease (respiratory or not) might seek health care earlier and with milder infections than previously healthy patients that might prefer home care or attend a hospital on a later stage. Indeed, there are limited studies in the literature describing outcomes for hospitalized NCFBE patients: in 2 studies on ICU patients the reported mortality rates were 40—60% at 1—4 yrs but no specific data are reported about the role of CAP in these patients[22,23]; on the other hand Seitz et al.[24] described an in-hospital mortality rate of 4.6% for NCFBE hospitalizations recorded in USA between 1993 and 2006, being pneumonia and influenza the main cause of death (31%).

Interestingly, despite a greater prevalence of ICs among our NCFBE-CAP patients, their use did not show any association with main outcomes (mortality, LOS, etc.), but only with the risk of hospitalization (not ICU). However, both ICs and systemic steroids have demonstrated some protective role in general CAP by reducing its severity and the frequency of complications.[25—33] Chronic ICs are largely used in NCFBE patients but their role in infections (exacerbations, pneumonia and chronic infections) should be surely further investigated.

The microbiological investigation showed that the majority of NCFBE-CAP are properly covered by current antimicrobial recommendations (CAP guidelines) but a greater prevalence of *P. aeruginosa* and *Enterobacteriaceae* was described in this population. These findings show that microbiological investigation is particularly important in NCFBE patients with pneumonia independently of initial severity to reduce the risk of treatment failure but surely more investigation is needed for the future to provide specific recommendations for clinical management of acute infections in NCFBE. In fact, accordingly to the literature, it is likely that in an NCFBE cohort (and not a CAP cohort) the prevalence of *P. aeruginosa* could be even higher and influence outcomes more consistently, as it has been demonstrated for chronic *P. aeruginosa* infection on lung function, exacerbations and mortality of NCFBE (ref), but the prognostic role of this pathogen in acute infections has to be better defined yet.

Concordantly, the lower proportion of adequate therapy in NCFBE-CAP (compared to CAP) and the increased rate of empiric antibiotic therapy directed at covering potential MDR pathogens could be possibly interpreted on the base of reported risk of *P. aeruginosa* and MDR pathogens in this population[6,11,12] and because of the lack specific recommendations for NCFBE. Nonetheless, mortality rates were similar in both groups indicating that no significant

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consequences were reported in our NCFBE population likely due to prompt antibiotic changes when needed.

Different guidelines for CAP and low respiratory tract infections[13,14,34] describe a number of risk factors for *P. aeruginosa* infection (tobacco, alcohol, malnutrition, recent hospitalization, frequent hospitalization, frequent or recent use of antibiotics, FEV%<30%, oral steroids) but no specific information is provided for NCFBE patients that are considered themselves at risk for this infection[34] independently of their huge etiological and clinical heterogeneity. Only the series of 155 NCFBE patients from Mc Donnell et al. showed that low FEV_1% and polymicrobial colonization are associated conditions with *P. aeruginosa* infection and that it occurs across all strata of lung function impairment.[35] Arancibia et al. showed that the main risk factors for *P. aeruginosa* in CAP where pulmonary comorbidities (OR: 5.8) and a previous hospital admission (OR: 3.8) but no specific mention is given for NCFBE.[36] Unfortunately no other data are currently available in the literature about risk factors for *P. aeruginosa* in NCFBE and particularly in CAP. For all these reasons further investigation is surely needed in NCFBE in order 1) to assess specific risk factors for *P. aeruginosa* and worse outcomes, 2) to guide antimicrobial therapy in both pneumonia and exacerbations.

Potential limitations of this study are: only one center was involved in the study which may not be representative of other regions, particularly considering the varied geographical distribution of NCFBE prevalence around the world; this is a retrospective analysis of a prospective data collection of CAP cases that was not primarily designed to investigate NCFBE therefore we are probably underestimating NCFBE prevalence since CT scan is usually not performed in all CAP patients. Moreover, the observational nature of this work intrinsically implies the risk of some risk of selection bias of the patients described in the study (such as the presence of comorbidities and related treatments, the ease of access to health facilities, local healthcare organization, etc.). Similarly, since our database was initially designed for CAP, HCAP cases are not included in our analysis with the exception of haemodialysis (when immunocompetent) and nursing home patients, that in our country have been demonstrated to have similar etiology to CAP.[37] In particular patients with previous hospitalizations were considered affected by nosocomial infections and therefore excluded, while unfortunately the variables "home infusion therapy", "wound care" and "contact with a family member with known MDR pathogen" were not recorded in our database.

In summary:

- The NCFBE-CAP patients from our population were older and had more comorbidities but showed similar presentation and similar outcomes compared to the general CAP population; nevertheless an extrapolation of these results to the general NCFBE patients cannot be done without the support of further longitudinal studies based on NCFBE cohorts.
- The microbial etiology of NCBE-CAP was similar to CAP, *S. pneumoniae* being the most frequent isolate; nonetheless bronchiectatic patients showed more *P. aeruginosa* and *Enterobacteriaceae* than CAP.
- Consequently, we suggest a wide microbiological investigation should be always performed in NCFBE-CAP independently of initial severity, in order to reduce the risk of treatment failure and to avoid overuse of broad-spectrum antibiotics.
- Pneumococcal vaccination should be widely recommended in bronchiectatic patients considering the prevalence of this microorganism in CAP and chronic bronchial infection.

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Appendix A. Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.jinf.2015.03.009.

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