LETTER TO THE EDITOR

Streptococcus pneumoniae coinfection in hospitalised patients with COVID-19

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To the Editor,

We would like to share our experience of a series of COVID-19 patients coinfected with pneumococcal pneumonia in a district hospital in Barcelona. Bacterial coinfections in patients with COVID-19 are uncommon [1] including those caused by *Streptococcus pneumoniae* [2], especially when compared with other seasonal respiratory viruses [3]. However, the evidence on bacterial pneumonia in COVID-19 is still limited and diagnosis remains a challenge, as both diseases are associated with a similar clinical presentation, high inflammatory markers and radiological changes. Given the high mortality associated with *S. pneumoniae* infection, missing the diagnosis may pose a risk to already vulnerable COVID-19 patients. As such, we describe the prevalence, clinical characteristics and outcomes of pneumococcal infection in COVID-19 patients.

We reviewed all microbiology results for patients admitted to Hospital Sant Joan Despí Moises Broggi (Barcelona, Spain) with PCR-confirmed COVID-19 on nasopharyngeal swabs between March 4, 2020, and November 4, 2020. Our hospital serves a population of 425.000, of which one-quarter are foreign-born, mainly Latin-American. Hospital guidelines for patients admitted with COVID-19 pneumonia recommend blood culture, pneumococcal and legionella urinary antigen tests based on clinical severity and at the clinician's discretion. Clinical samples were tested for pneumococcal antigen using a fluorescence immunoassay, SD Biosensor *S. pneumoniae* urinary antigen test (Republic of Korea), in accordance with the manufacturer's instructions. Two different kits were used to detect SARS-CoV-2 from nasopharyngeal samples: Multiplex PCR, Cepheid, PCR SARS-CoV-2 GeneXpert (USA) and Multiplex PCR, Diasorin, PCR SARS-CoV-2 Simplexa (USA). The treatment of COVID-19 infection was based on hydroxychloroquine and azithromycin from March to June 2020 and dexamethasone with or without remdesivir (according to local protocol) from July to November 2020. Antibiotic treatment used to treat pneumococcal pneumonia was ceftriaxone in the great majority of cases.

Eighty-seven (3%) patients of a total of 2782 who tested positive for COVID-19 and 9% of 917 patients specifically tested for pneumococcal antigen had a pneumococcal coinfection. Of those 87 coinfected patients, 50 (57%) were females, mean age was 68 years (range, 27–92), and 22 (25%) were foreign-born, mainly from Latin-America (17%). Hypertension 47%, diabetes 33%, obesity 22%, malignancy 15% and chronic lung disease 11% were the main comorbidities. Chest X-ray showed bilateral infiltrates in 73 (84%) cases and consolidation was obvious in only 14 (16%) cases. Thirty-day mortality was 17% (15/87). COVID-19 and pneumococcal pneumonia coinfected patients compared with COVID-19 individuals with a negative pneumococcal testing were mostly female (57% vs 34%, $p < 0.001$). No differences in age, comorbidities, ethnicity, length of stay, admission to intensive care unit or 30-day mortality were found between groups. Patient demographics, clinical characteristics and outcomes are shown in Table 1.

Despite the low prevalence of pneumococcal pneumonia in COVID-19 patients (3%), this was higher than the one reported in other studies that varied from 1.2 to 2.5% [4] [2]. The higher prevalence of *S. pneumoniae* and SARS-CoV2 coinfection may be due to a sub-optimal pneumococcal vaccination rates in Spain, ranging from 35% in high-risk population aged < 65 years to 63% in older adults ≥ 65 years [5]. This vaccination coverage rate is below the 90% target set by public health immunisation goals. In addition, lower pneumococcal vaccination rates have also been found among different

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Table 1 Patient demographics, clinical characteristics and outcomes of COVID-19-infected patients with positive and negative pneumococcal urinary antigen. Descriptive statistics are summarised using frequencies and percentages or medians and interquartile ranges (IQR). p values were calculated using χ^2 for categorical and Mann-Whitney U test for continuous variables using SPSS v.26. p values < 0.05 were considered significant

	Pneumococcal Ag positive, $n = 87$		Pneumococcal Ag negative, $n = 830$		p value
Age (years) median (range)	68	(27–92)	65	(21–97)	0.090
Gender (%)					
Female	50	(57%)	285	(34%)	< 0.001
Ethnicity (%)					
Spanish	65	(75%)	625	(75%)	0.897
Foreign-born	22	(25%)	205	(25%)	0.108
Latin-American	15	(17%)	178	(21%)	0.409
Indian/ Pakistan	5	(6%)	5	(1%)	0.001
Moroccans	3	(3%)	23	(3%)	0.730
Comorbidities (%)	63	(72%)	535	(65%)	0.156
Hypertension	41	(47%)	411	(50%)	0.736
Diabetes mellitus	29	(33%)	210	(25%)	0.123
Obesity	19	(22%)	143	(17%)	0.301
Malignancy	13	(15%)	74	(9%)	0.082
Chronic lung disease	10	(11%)	96	(12%)	0.949
Laboratory results, median (range)					
White cell count (10×9/L)	8	(1–30)	7	(1.3–3.3)	0.982
Lymphocytes (10×9/L)	1.1	(0.3–3.7)	1.05	(0.1–3.1)	0.352
CRP (mg/L)	111	(7–434)	87	(1–594)	0.396
D-Dimer (ng/mL)	1020	(250–5100)	860	(3–20000)	0.279
Clinical outcomes					
Length of stay (days), median (range)	9	(1–35)	9	(1–90)	0.982
Intensive care unit admission (%)	8	(9%)	132	(16%)	0.117
30-day mortality (%)	15	(17%)	129	(16%)	0.644
Radiological findings (chest X ray) (%)					
Bilateral infiltrates	73	(84%)	741	(89%)	0.105
Consolidation	14	(16%)	24	(3%)	0.001
No infiltrates/interstitial changes	0	(0%)	62	(8%)	0.001

ethnic minorities [6], which may have further contributed to higher *S. pneumoniae* coinfections in our population. Given the nature of this retrospective study, the diagnostic tests for pneumococcal infection were performed and interpreted by the attending physician based on clinical details, and consequently possible false positive results were not taken into consideration. Although pneumococcal urinary antigen specificity has been shown to be as high as 94–97%, false positive results may occur in patients with recent pneumococcal infection or immunisation [7].

Diagnosis of pneumococcal pneumonia is likely to be missed due to non-specific clinical features and lack of laboratory and radiological specific findings for bacterial pneumonia in patients affected by COVID-19. Therefore, coinfection with *S. pneumoniae* should be suspected in COVID-19 patients and traditional microbiology techniques such as urinary antigen test should be routinely performed. Further understanding of the pathogenesis of pneumococcal pneumonia in COVID-19 may be useful to better characterise patients at risk of coinfection, particularly in populations with low pneumococcal vaccination rates. Additional studies of COVID-19 patients coinfected with *S. pneumoniae* are needed to further investigate if there exist any gender disparities in susceptibility to bacterial coinfection in COVID-19. Finally, reinforcing pneumococcal vaccination during all healthcare encounters is highly recommended to increase coverage rates and prevent *S. pneumoniae* disease in COVID-19 patients.

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