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Factors associated with inflammatory cytokine patterns in community-acquired pneumonia

R. Martínez*,#, R. Menéndez*,#, S. Reyes*, E. Polverino¶, C. Cillóniz¶, A. Martínez*, C. Esquinas¶, X. Filella+, P. Ramírez#,§ and A. Torres#,¶,f

ABSTRACT: Raised systemic levels of interleukin (IL)-6 and IL-10 cytokines have been associated with poorer outcome in community-acquired pneumonia. The aim of our study was to identify potential associated factors with increased levels of IL-6, IL-10, or both cytokines.

We performed a prospective study of 685 patients admitted to hospital with community-acquired pneumonia. IL-6 and IL-10 were measured in blood in the first 24 h.

30-day mortality increased from 4.8% to 11.4% ($p=0.003$) when both cytokines were higher than the median. Independent associated factors with an excess of IL-6 were neurologic disease, confusion, serum sodium <130 mEq·L^{-1}, pleural effusion, and bacteraemia. The associated factors for an excess of IL-10 were respiratory rate $\geqslant 30$ breaths·min^{-1}, systolic blood pressure <90 mmHg and glycaemia $\geqslant 250$ mg·dL^{-1}. The independent associated factors for an excess of both cytokines were confusion, systolic blood pressure <90 mmHg, pleural effusion and bacteraemia. Protective factors were prior antibiotic treatment and pneumococcal vaccination.

Different independent factors are related to an excess of IL-6 and IL-10. Confusion, hypotension, pleural effusion and bacteraemia were associated with the inflammatory profile with the highest mortality rate, whereas anti-pneumococcal vaccination and previous antibiotic treatment appeared to be protective factors.

KEYWORDS: Associated factors, cytokine excess in community-acquired pneumonia, interleukin-6, interleukin-10, mortality

Community-acquired pneumonia (CAP) remains the most frequent cause of death due to infection in developed countries [1], despite advances in antimicrobial therapy and improved management of this disease. The estimated incidence of community-acquired pneumonia is between 3 and 5 cases per 1,000 inhabitants per year, and it is more frequent early and late in life [2]. About one-third of patients with CAP will require hospitalisation.

An inflammatory response of the host to the causal microorganisms occurs in CAP, with the release of pro- and anti-inflammatory cytokines. Although this cytokine production is necessary for the defence function, an excessive response can cause a deleterious effect. In recent years, there has been increased interest concerning the inflammatory response to infections and its relation to outcome. An excess of pro-inflammatory cytokines [3, 4] has proven to be a strong predictor of treatment failure and mortality in CAP and sepsis. In a study performed in hospitalised patients with CAP [5], we found that initial increases in interleukin (IL)-6 and/or IL-8 and their persistence 72 h after treatment correlated with antibiotic treatment failure. KELLUM *et al.* [6], in a large study in CAP patients with or without sepsis, found that mortality in CAP is higher when both levels of IL-6 (pro-inflammatory) and IL-10 (anti-inflammatory) cytokines are raised. This article illustrates the heterogeneity in the inflammatory response in CAP, with different activation patterns of cytokines; this may reflect the implication of different factors in the synthesis of each cytokine.

Our hypothesis is that the excess of systemic levels of cytokines like IL-6 and IL-10 is associated with different factors, whose identification may contribute to a better understanding of the host response to infection. The aim of our study was to measure the systemic cytokine response to infection in hospitalised CAP patients in order to evaluate different inflammatory profiles or patterns (increase in IL-6, IL-10 or both), and to

AFFILIATIONS
*Servicio de Neumología. University Hospital La Fe,
§Unidad de Cuidados Intensivos. University Hospital La Fe, Valencia,
¶Servicio de Neumología, Hospital Clinic, IDIBAPS,
+Servicio de Bioquímica, Hospital Clinic, IDIBAPS,
fUniversidad de Barcelona, Barcelona, and
#Researcher of Ciber de enfermedades respiratorias (CIBERES), Spain.

CORRESPONDENCE
R. Martínez
Servicio de Neumología
Hospital Universitario La Fe
Avda. de Campanar 21
46009 Valencia
Spain
E-mail: rasmartinez@hotmail.com

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identify potential factors of the host and/or the infection associated with those patterns.

METHODS

A prospective longitudinal study was performed in patients with CAP who were consecutively hospitalised in two tertiary-care hospitals. The inclusion criteria were a new radiographic infiltrate and at least two compatible clinical symptoms (*e.g.* temperature >38°C, productive cough, chest pain, shortness of breath, crackles on auscultation). Exclusion criteria were admission within the previous 15 days, immunosuppressive and/or corticosteroid (>15 mg·day^{-1}) treatment, leukopenia <1,000 cells·mm^{-3} or neutropenia <500 cells·mm^{-3} (except where attributable to CAP). The study was approved by the ethics committees of both hospitals, and the patients signed an informed consent form.

Data collection

Data were collected on age, sex, smoking and alcohol habits (>80 g·day^{-1}), comorbidity diseases, such as chronic obstructive pulmonary disease (COPD), cardiac, liver, renal or central nervous system (CNS) disorders, prior influenza and/or anti-pneumococcal vaccination, inhaled or oral corticosteroid treatment, and previous use of antibiotics defined by use of antibiotic therapy for the actual episode before admission in the hospital. Recorded clinical signs and symptoms wereas follows: cough, expectoration, pleuritic chest pain, dyspnoea, acute confusion, temperature, respiratory and heart rates, systolic and diastolic blood pressure, and the presence of crackles. Time in days from onset of symptoms was also recorded. The following analytical data were collected: leukocyte count, glucose, serum sodium, potassium, proteins and albumin, serum creatinine or serum blood urea nitrogen (BUN), bilirubin, aspartate aminotransferase/alanine aminotransferase (AST/ALT), haematocrit, and arterial blood gas analysis. The radiologic findings recorded were multilobar involvement and pleural effusion. Bacteraemia was defined as the presence of any microorganism in blood culture. We monitored survival after discharge by means of a follow-up consultation after 30 days and a telephone call after 90 days.

Cytokines determinations

Blood samples were drawn within the first 24 h after admission when patient is in floor and during the office hours, that is from 09:00 h to 11:00 h. Our patients received the first antibiotic dose in emergency room. The blood was centrifuged and frozen at -80°C. The determination of IL-6 and IL-10 was performed with a commercial enzyme immunoassay technique (Biosurce, Nivelles, Belgium). The detection limits were 2 pg·mL^{-1} for IL-6 and 1 pg·mL^{-1} for IL-10.

Statistical analysis

The dependent variables were the levels of IL-6, IL-10 or both. These variables were dichotomised as excess IL-6 (yes/no), excess IL-10 (yes/no) and excess of both (yes/no), if their levels were above their medians (87 and 5 pg·mL^{-1}, respectively). Separate univariate statistical analyses were performed on all the demographic, clinical, analytic and radiologic variables for the dependent variables. The Chi-squared test was used for categorical variables, and the unpaired t-test or the Mann–Whitney tests were used for continuous variables.

Three multivariate analyses were performed, one for each of the dependent variables. The independent variables were those found in the univariate study to have a significance of $p<0.1$ and the variables considered clinically relevant (influenza vaccine and prior treatment with oral corticoids). The continuous independent variables were dichotomised as present or not using the following cut-off points: tachypnoea for respiratory rate ⩾30 breaths·min^{-1}, hypotension for systolic blood pressure <90 mmHg, hyperglycaemia for glycaemia ⩾250 mg·dL^{-1}, BUN ⩾30 mg·dL^{-1} or creatinine ⩾1.4 mg·dL^{-1} and hyponatraemia for serum sodium <130 mmol·L^{-1}.

The statistical analysis was performed with the SPSS statistical software package, version15.0 (SPSS, Chicago, IL, USA). Results were considered significant for values of $p<0.05$.

RESULTS

Patient population

We studied 685 patients with a mean±SD age of 66.5±17.4 yrs; demographic data, toxic habits, associated diseases, vaccinations, and prior antibiotic treatment are shown in table 1. The median (interquartile range) from onset of symptoms was 4 (3–7) days.

233 (34%) patients had received previous antibiotic treatment during a median of 4.0 days. The antibiotic type received was as follows: 112 (48.0%) β-lactams; 42 (18.0%) quinolones; 39 (16.7%) macrolides; and 40 (17.2%) unknown.

The aetiologic diagnosis was reached in 295 (43.5%) patients. The principal aetiologic agents were as follows: 118 (40%) *Streptococcus pneumoniae*; 24 (8.1%) *Legionella pneumophila*;

TABLE 1 Demographic characteristics, toxic habits, comorbidity, vaccination and prior empirical treatment

Characteristics	Value
Patients n	685
Age yrs	66.5±17.4
Sex F/M n	240/445 (35/65)
Current smoker	161 (23.6)
Alcohol excess	65 (9.5)
Comorbidity	
COPD	135 (19.7)
CNS disorder	141 (20.7)
Diabetes	129 (18.9)
Heart failure	123 (18)
Renal failure	36 (5.3)
Liver disease	23 (3.4)
Prior vaccination	
Influenza	299 (43.6)
Anti-pneumococcal	111 (16.2)
Prior antibiotic treatment	233 (34.1)

Data are presented as mean± SD or n (%), unless otherwise indicated. F: female; M: male; COPD: chronic obstructive pulmonary disease; CNS: central nervous system.

TABLE 2 Levels of interleukin (IL)-6 and IL-10 according to outcome

	In-hospital mortality		30-day mortality		90-day mortality	
	Median (IQR)	p-value#	Median (IQR)	p-value#	Median (IQR)	p-value#
IL-6						
Survival	83 (29–221)	<0.001	82 (29–219)	<0.001	83 (30–221)	0.006
Death	199 (79–1481)		197 (78–1151)		165 (36–811)	
IL-10						
Survival	5 (0–16)	0.158	5 (0–16)	0.117	5 (0–16)	0.024
Death	9 (0–60)		9 (0–39)		9 (0–40)	

IQR: interquartile range. #: determined by Mann–Whitney U-test.

18 (6.1%) *Pseudomonas aeruginosa*; and 14 (4.7%) *Haemophilus influenzae*. Other microorganisms included Enterobacteriaceae, *Staphylococcus aureus*, *Mycoplasma* spp. and *Coxiella pneumoniae*, *Enterococcus* spp. and virus. Bacteraemia was found in 48 (7%) patients: 34 (70.8%) *S. pneumoniae*; 5 (10.4%) *Escherichia coli*; 2 (4.2%) *S. aureus*; 2 (4.2%) *H. influenzae*; 1 (2.1%) *P. aeruginosa*; 1 (2.1%) *Streptococcus pyogenes*; and 3 (6.3%) others. 111 patients had received pneumococcal vaccination, and CAP due to *S. pneumoniae* was less common in vaccinated compared with nonvaccinated patients (13.5% *versus* 17.9%, espectively), although without reaching statistical significance (p=0.258).

38 (5.6%) patients died during hospitalisation. After 30 and 90 days, mortality increased to 6.4% (44 patients) and 8.2% (56 patients), respectively.

Univariate statistical analyses

Levels of IL-6 were significantly lower in patients who survived, whereas this clear pattern was not found for IL-10. Values of IL-6 and IL-10 cytokines according to outcome (survival/death) are shown in table 2.

When there is an excess of IL-6, in-hospital mortality rises from 2.9 to 8.3% (p=0.003), from 3.5 to 9.6% (p=0.002) at 30 days, and from 6.3 to 10.6% (p=0.057) at 90 days. In the case of excess of IL-10, the in-hospital mortality rate increases from 4.7 to 6.5% (p=0.343), from 5.1 to 8.1% (p=0.127) at 30 days, and from 6.3 to 10.7% (p=0.051) at 90 days. When levels of both cytokines are raised, in-hospital mortality rises from 4.1 to 9.6% (p=0.009), from 4.8 to 11.4% (p=0.003) at 30 days, and at 90 days, it increases from 6.8 to 13.3% (p=0.010).

TABLE 3 Univariate study: levels of interleukin (IL)-6 and IL-10 according to the presence of the described variables

Variable	IL-6			IL-10		
	No	Yes	p-value#	No	Yes	p-value#
Associated disorders						
COPD	93 (36–237)	56 (15–171)	0.004	5 (0–19)	5 (0–12)	0.148
CNS disorder	79 (25–223)	119 (47–273)	0.003	6 (0–18)	5 (0–13)	0.456
Previous antibiotic treatment	96 (33–278)	74 (28–192)	0.028	7 (0–20)	3 (0–10)	<0.001
Anti-pneumococcal vaccination	92 (30–240)	76 (31–178)	0.253	6 (0–18)	3 (0–10)	0.032
Prior inhaled corticosteroids	93 (35–235)	66 (18–194)	0.023	5 (0–19)	5 (0–13)	0.184
Physical examination						
Confusion	80 (28–210)	157 (61–552)	<0.001	5 (0–16)	7 (0–34)	0.189
Respiratory rate ⩾30 breaths·min^{-1}	86 (33–225)	98 (22–275)	0.791	5 (0–15)	8 (2–28)	0.001
Systolic blood pressure <90 mmHg	85 (29–225)	215 (66–819)	0.019	5 (0–17)	12 (6–21)	0.066
Arterial oxygen saturation <90%	78 (30–187)	105 (30–297)	0.037	5 (0–15)	7 (1–20)	0.007
Analytical parameters						
Glycaemia ⩾250 mg·dL^{-1}	84 (29–227)	105 (41–299)	0.229	5 (0–16)	11 (1–37)	0.021
BUN ⩾30 or creatinine ⩾1.4 mg·dL^{-1}	79 (29–205)	112 (38–322)	0.016	5 (0–17)	7 (0–19)	0.249
Serum sodium <130 mmol·L^{-1}	83 (28–218)	138 (58–332)	0.003	5 (0–17)	5 (0–18)	0.533
Radiology						
Multilobar involvement	79 (29–213)	143 (47–364)	0.001	5 (0–16)	5 (0–19)	0.535
Pleural effusion	79 (29–221)	127 (43–300)	0.026	5 (0–16)	6 (0–20)	0.433
Bacteraemia	81 (29–210)	218 (84–616)	<0.001	5 (0–17)	12 (1–36)	0.049

Data are presented as median (interquartile range), unless otherwise stated. COPD: chronic obstructive pulmonary disease; CNS: central nervous system; BUN: serum blood urea nitrogen. #: determined by Mann–Whitney U-test.

TABLE 4 Univariate study: number of patients with statistically significant associated factors according to the presence or absence of an excess of both interleukin (IL)-6 and IL-10

Characteristic	Excess of IL-6 and IL-10		p-value#
	Yes	No	
Patients	167 (26.6)	460 (73.4)	
Associated diseases			
CNS disorder	45 (26.9)	86 (18.8)	0.027
Previous antibiotics	43 (25.7)	173 (37.7)	0.005
Prior inhaled corticosteroids	25 (15.1)	104 (22.7)	0.038
Anti-pneumococcal vaccination	19 (11.4)	83 (18.0)	0.046
Physical examination			
Confusion	35 (21)	53 (11.6)	0.003
Respiratory rate $\geqslant$30 breaths·min^{-1}	49 (29.5)	94 (20.8)	0.024
Systolic blood pressure <90 mmHg	9 (5.5)	9 (2.0)	0.022
Analytic parameters			
BUN $\geqslant$30 or creatinine $\geqslant$1.4 mg·dL^{-1}	52 (31.3)	102 (22.2)	0.020
Radiology			
Pleural effusion	34 (20.4)	65 (14.1)	0.059
Bacteraemia	21 (12.6)	23 (5.0)	0.001

Data are presented as n (%), unless otherwise stated. CNS: central nervous system; BUN: serum blood urea nitrogen. #: determined using the Chi-squared test.

Table 3 shows the variables associated with excess of either IL-6 or IL-10. The other variables, not included in the table, were not statistically significant.

Table 4 shows the variables associated with the simultaneous excess of IL-6 and IL-10. These factors were CNS disorder, confusion, respiratory rate $\geqslant$30 breaths·min^{-1}, hypotension, impaired renal function, pleural effusion and bacteraemia. Prior use of antibiotics, prior use of inhaled corticosteroids and anti-pneumococcal vaccination were protective against excess IL-6 and IL-10.

Levels of IL-6 and IL-10 differed in patients who had received previous antibiotic treatment depending on antibiotic type (table 5). In the subset treated with β-lactams, IL-10 was significantly lower whereas in the subset treated with quinolones or macrolides, IL-6 was significantly lower while no statistical difference was found for IL-10.

Time from onset of symptoms was analysed comparing their values and levels of IL-6 and IL-10 respect to the median (4 days). A trend for lower levels of IL-6 and IL-10 was found in patients with more than 4 days of symptoms: IL-6 (77 *versus* 100, p=0.057) and IL-10 (5 *versus* 6, p=0.2). However, if the analysis is performed stratifying patients with previous antibiotic or not, a significant reduction of levels of both IL-6 and IL-10 was found; IL-6 (69 *versus* 94, p=0.03 and IL-10: 3 *versus* 8, p=0.001).

Multivariate statistical analyses

The results of the three multivariate analyses are shown in table 6.

In the first model, with excess IL-6 as the dependent variable, the independent predictor variables were CNS disorder, confusion, hyponatraemia, pleural effusion and bacteraemia, whereas previous use of antibiotics was identified as a protective factor.

In the second model, excess IL-10, the protective variables were previous antibiotic treatment and pneumococcal vaccination; and the predictive variables of excess IL-10 were respiratory rate $\geqslant$30 breaths·min^{-1}, systolic blood pressure <90 mmHg and glycaemia $\geqslant$250 mg·dL^{-1}.

TABLE 5 Previous antibiotic type and cytokine levels

	Previous antibiotic treatment			Previous β-lactams			Previous quinolone or macrolides		
	Yes	Non	p-value	Yes	Non	p-value	Yes	Non	p-value
IL-6	74 (28–172)	96 (33–278)	0.028	81 (28–210)	91 (31–237)	0.548	55 (24–161)	92 (30–243)	0.015
IL-10	3 (0–10)	7 (0–20)	0.001	2 (0–9)	6 (0–19)	0.001	5 (0–12)	6 (0–18)	0.282

Data are presented as median (interquartile range), unless otherwise stated. IL: interleukin. p-values were determined by Mann–Whitney U-test.

TABLE 6 Independent variables related to an excess of interleukin (IL)-6, IL-10 and of both

Characteristic	IL-6		IL-10		IL-6 and IL-10	
	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value
CNS disorder	1.8 (1.2–2.8)	0.007				
Previous antibiotic treatment	0.6 (0.5–0.9)	0.015	0.4 (0.3–0.7)	<0.001	0.6 (0.4–0.9)	0.016
Anti-pneumococcal vaccination			0.5 (0.3–0.9)	0.012	0.5 (0.3–0.9)	0.027
Confusion	1.7 (1.0–2.8)	0.046			2.0 (1.2–3.3)	0.006
Respiratory rate ⩾30 breaths·min^{-1}			1.9 (1.3–3.0)	0.001		-
Systolic blood pressure <90 mmHg			4.8 (1.3–17.6)	0.018	2.7 (1.0–7.2)	0.050
Glycaemia ⩾250 mg·dL^{-1}			1.8 (1.0–3.1)	0.049		
Serum sodium <130 mmol·L^{-1}	1.9 (1.1–3.3)	0.015				
Pleural effusion	2.1 (1.3–3.3)	0.002			1.8 (1.1–3.0)	0.013
Bacteraemia	2.5 (1.3–4.7)	0.004			2.3 (1.2–4.3)	0.008

CNS: central nervous system.

In the third multivariate analysis, with excess of both cytokines (IL-6 and IL-10) as the dependent variable, the protective variables were also previous use of antibiotics and pneumococcal vaccination. The predictive variables for excess of both IL-6 and IL-10 were confusion, hypotension, pleural effusion and bacteraemia.

DISCUSSION

The most important findings of our study are the following: 1) different independent factors are associated with an excess of IL-6 and with an excess of IL-10; 2) associated factors related to an excess of both cytokines are confusion, hypotension, pleural effusion and bacteraemia; 3) previous use of antibiotics is independent protective factor for excess IL-6 and/or IL-10, and pneumococcal vaccination is a protective factor for excess IL-10 and of IL-6 and IL-10; 4) mortality (in-hospital mortality, 30-day mortality and 90-day mortality) is higher in patients with an excess of both cytokines.

This study has shown the systemic increase in pro-inflammatory (IL-6) and anti-inflammatory (IL-10) cytokines in CAP, as reported in previous studies, and its association with a worse prognosis [7–10]. KELLUM *et al.* [6] found that several combinations of cytokine activation with high or medium concentrations of IL-6 and IL-10 were associated with higher mortality, and the pattern of high IL-6/high IL-10 together was associated with the highest mortality (hazard ratio 20.5). In our study, we identify some factors that are associated with initial high levels of IL-6 and/or IL-10 in CAP. When levels of both cytokines are raised, the combination of associated factors is different (two factors related to the increase in IL-6 and two others related to the increase in IL-10). Even more interestingly, we found that previous use of antibiotics was an independent protective factor against an excess of cytokines (both IL-6 and IL-10).

The associated factors for an increase in both cytokines (IL-6 and IL-10) that determine a worse scenario [6] for prognosis were confusion, arterial hypotension, pleural effusion and bacteraemia. In fact, when these four variables are analysed, the first two, confusion and hypotension, are two of the variables in the CURB65 [11], the prognostic scale that identifies severity. Interestingly, confusion is an associated factor with increased levels of the pro-inflammatory cytokine IL-6, while arterial hypotension has a stronger association with increased levels of the anti-inflammatory cytokine IL-10. Moreover, in patients with severe sepsis or septic shock, increased IL-10 levels in blood were associated with a poorer prognosis [12–15]. Hyponatraemia and hyperglycaemia were associated with increased levels of different cytokines: hyponatraemia with IL-6, and hyperglycaemia with IL-10. However, other initial analytic deviations included in the pneumonia severity index (PSI) [16] were not found to be significant independent factors for excess levels of either cytokine. In an experimental animal model, it was demonstrated that hyperglycaemia and hyperinsulinaemia increased synthesis of IL-10 [17]. In patients with severe sepsis, LEONIDOU *et al.* [18] analysed the glycaemic profile and the profile of pro- and anti-inflammatory cytokines in the first 24 h. They reported that IL-10 levels in blood, age, and hyperglycemia were independent prognostic factors of in-hospital mortality, whereas the sepsis-related organ failure assessment (SOFA) score was not. The authors hypothesised that stress hyperglycaemia occurred mainly during the anti-inflammatory phase of the disease and is therefore associated with elevated levels of IL-10 and a poorer prognosis.

The others associated factors found for the raised IL 6 and IL 10 profile were pleural effusion and bacteraemia. Pleural effusion, in addition to being a variable included in the PSI [16], is a risk factor associated for treatment failure [19], as it represents local spread of infection and inflammation. Bacteraemia represents the spread of infection from the pulmonary compartment to the systemic level, and has been traditionally associated with a higher risk of mortality in CAP [20]. In a large prospective cohort of hospitalised patients with CAP, pneumococcal bacteraemia was an independent risk factor related to early mortality (within the first 48 h of hospitalisation) [21]. Interestingly, in patients who had received pneumococcal vaccination, a trend for lower IL-6 and IL-10 was found although without reaching statistical significance probably due

to the lower number of cases. Moreover, we found that levels of IL-6 and IL-10 were also higher in bacteraemia caused by other microorganisms although the low figures in some of them preclude us to perform statistical comparisons.

The two protective factors against excessive inflammation are the previous use of antibiotics (OR 0.6) and anti-pneumococcal vaccination (OR 0.5).

Time from onset of symptoms emerged as a protective factor of high levels of IL-6; that is lower levels in those patients with >4 days of symptoms. Host inflammatory response is an evolutionary process over time that varies depending on number of days and many other factors. CALBO *et al.* [22] reported that in severe pneumococcal CAP levels of pro-inflammatory cytokines were lower within the first hours in patients and higher in those with >48 h not receiving antibiotic treatment. Interestingly, we found some differences concerning previous antibiotic type and cytokine profile. Prior treatment with quinolones or macrolides was associated with lower IL-6 while prior treatment with β-lactams was associated with lower IL-10. The immunomodulatory effect of macrolides is well known [23–25] mainly reducing tumour necrosis factor (TNF)-α and pro-inflammatory cytokines. CALBO *et al.* [26] also reported that fluoroquinolone treatment compared with β-lactams significantly reduce levels of TNF-α in pneumococcal CAP. Alternatively, β-lactams may promote an increase in cytokine production due to the release of cell wall components of bacteria. Curiously, we found significant lower levels of IL-10 in those treated with β-lactams while no differences in IL-6 were detected. Our findings confirm the importance of early initiation of antibiotic treatment, unanimous recommendation of guidelines for the management of CAP [27–29], probably because a rapid antibiotic action can reduce or prevent excessive local and systemic inflammation. Similarly, MENENDEZ *et al.* [30] found that patients who had received antibiotic treatment prior to hospitalisation achieved clinical stability 1 day earlier.

The second protective factor related with excessive inflammation is anti-pneumococcal vaccination. In our study, pneumococcal pneumonia was less common in vaccinated patients with pneumococcal vaccine compared with nonvaccinated patients (13.5 *versus* 17.9%) although without reaching statistical significance. It is well-known that the pneumococcal polysaccharide vaccine reduces the incidence of bacteraemic pneumococcal disease in adults [31, 32], and it reduces the rate of mortality or ICU (intensive care unit) admission in CAP [33]. Additionally, prior pneumococcal vaccination appears to be associated with a faster resolution of symptoms and a shorter hospital stay in adults with pneumococcal pneumonia [34, 35]. This could be explained, at least partially, by the reduced systemic inflammation. In fact, in our study a trend for lower IL6 was found in vaccinated patients with bacteraemic pneumococcal CAP.

In conclusion, our study identifies different clinical factors associated with an excess of initial pro-inflammatory and anti-inflammatory cytokines in CAP. Confusion, hypotension, pleural effusion and bacteraemia, as independent associated factors to an increase in IL-6 and IL-10, should alert clinicians to the need for closer monitoring or more aggressive management in order to reduce the morbidity and mortality associated with this inflammatory profile. Anti-pneumococcal vaccination and prior antibiotic treatment appear as protective factors against overproduction of cytokines.

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STATEMENT OF INTEREST

None declared.

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I. Arribas, an independent statistician, performed the statistical analyses.

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