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Usefulness of consecutive C-reactive protein measurements in follow-up of severe community-acquired pneumonia

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ABSTRACT: Despite the introduction of new inflammatory markers, C-reactive protein (CRP) remains commonly used in patients hospitalised with severe infections. However, evidence on the usefulness of consecutive CRP measurements is still unclear. The clinical relevance of consecutive CRP measurements was studied in follow-up of antibiotic treatment in patients with severe community-acquired pneumonia (CAP).

In a prospective multicentre trial, CRP levels were measured on admission, and on days 3 and 7. Patients were followed clinically for 28 days.

Aetiology could be determined in 137 (47.4%) out of the 289 patients included. In 122 (38.8%) patients, initial antibiotic therapy was appropriate. A decline of <60% in CRP levels in 3 days and a decline of <90% in CRP levels in 7 days were both associated with an increased risk of having recieved inapproriate empiric antibiotic treatment (day 0–3, odds ratio (OR) 6.98, 95% confidence interval (CI) 1.56–31.33 and day 0–7, OR 3.74, 95% CI 1.12–13.77).

In conclusion, consecutive C-reactive protein measurements are useful in the first week in follow-up of antibiotic treatment for severe community-acquired pneumonia when taking the causative microorganism and use of steroids into account. A delayed normalisation of C-reactive protein levels is associated with a higher risk of having received inappropriate antibiotic treatment.

KEYWORDS: Antibiotic treatment, community-acquired pneumonia, C-reactive protein, follow-up

Community-acquired pneumonia (CAP) is the major cause of death due to infectious diseases in the western world and accounts for an increasing figure of ⩾20 admissions per 1,000 inhabitants annually [1]. Current guidelines advise combination therapy with β-lactam and macrolide antibiotics for initial treatment of severe CAP [2, 3]. Consequently, management of severe CAP accounts for high utilisation of healthcare resources and antibiotic consumption, leading to a risk of emerging resistance. In the USA, annual estimated costs for treating CAP exceed US$12 billon and in several countries an increase in macrolide-resistant strains has been observed [4, 5].

Once aetiology of CAP has been established, pathogen-directed antibiotic therapy can be initiated and a test indicative of aetiology early in the course of disease would be a worthwhile target for the reduction of antibiotic consumption. Unfortunately, thus far no biomarker has been found to have sufficient sensitivity and specificity to guide initial therapy, and protocols for guidance of empirical antibiotic treatment must be relied on [2, 3]. However, an alert for an unfavourable response to treatment early in follow-up, as an increased inflammatory response, suboptimal drug levels, or inappropriate empirical treatment, could help in optimising treatment for CAP patients. Before aetiology has been established, or when aetiology cannot be established, an indicator of the appropriateness of empirical antibiotic therapy may contribute to a more tailored approach in antibiotic treatment early in the course of the disease. Furthermore, such an indicator might help in continuing tailored antibiotic therapy, determining the length of antimicrobial treatment, and guiding a switch from intravenous to oral antibiotic therapy [6]. Hypothetically, these strategies may contribute to a reduction in antibiotic consumption.

The determination of the serum concentration of C-reactive protein (CRP) is a rapid, simple and inexpensive procedure and consecutive CRP measurements have become routine clinical practice in the follow-up of patients hospitalised

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with severe infections [7]. However, despite its frequent use, evidence on the usefulness of consecutive CRP measurements for follow-up of antibiotic treatment for severe CAP is lacking. Few studies have addressed CRP kinetics in the follow-up of CAP previously, and these are on a relatively small scale and have not taken aetiology into account [8, 9]. A recent study has pointed out that high serum levels of CRP, interleukin (IL)-6 or, procalcitonin (PCT) are associated with a higher risk of any treatment failure [10]. However, the introduction of newer inflammatory markers, such as PCT, IL-6 and neopterin emphasises the need to clarify the position of the older and less costly markers, such as CRP [11]. To determine the clinical relevance of consecutive CRP measurements in follow-up of antibiotic treatment in patients with severe CAP, the present study examined the predictive value of delayed normalisation of CRP levels for the risk of having received inappropriate empirical antibiotic therapy or developing an unfavourable outcome.

MATERIALS AND METHODS

Setting and study population

The current study is a retrospective analysis of data derived from a multicentre, prospective randomised controlled trial on the cost effectiveness of an early switch from *i.v.* to oral antibiotic therapy for severe CAP [12]. The trial was conducted in five teaching hospitals (Meander Medical Centre (Amsterfoort), Diakonessen Hospital (Utrecht), Rijnstate Hospital (Arnhem), St Antonius Hospital (Nieuwegein) and Jeroen Bosch Hospital (s-Hertogenbosch)) and two university medical centres (Academic Medical Centre Amsterdam (Amsterdam) and University Medical Centre Utrecht (Utrecht)) in the Netherlands from July 2000 to June 2003. All adult patients (age $\geqslant$18 yrs) admitted to one of the participating hospitals due to CAP were eligible for inclusion. CAP was defined as present in cases with at least two symptoms of acute lower respiratory tract infection with onset before hospital admission and a new or progressive pulmonary infiltrate on chest radiograph. Severe CAP was defined as a Pneumonia Severity Index (PSI) score >90 or according to the American Thoracic Society definitions [13, 14]. All patients gave written informed consent prior to enrolment and the study was approved by the medical ethics committees of all participating hospitals. Patients with interstitial pneumonia, cystic fibrosis, a history of colonisation with Gram-negative bacteria due to structural damage to the respiratory tract, a life expectancy of <1 month because of an underling disease, severe neutropenia ($<0.5\times10^9$ neutrophils·L^{-1}) or HIV infection with a CD4 count <200 cells·mm^{-3}, infections other than pneumonia necessitating treatment with *i.v.* antibiotics, and patients admitted directly to an intensive care unit (ICU) were excluded.

Data collection and CRP assay

On admission, demographic data and clinical signs and symptoms were recorded. Severity of disease was determined by PSI score and Acute Physiology and Chronic Health Evaluation (APACHE) II score [14, 15]. Laboratory tests, microbiological tests and a chest radiograph were obtained before empirical antibiotic treatment was instituted. Patients were followed for a maximum of 28 days. Serum samples to quantify the serum CRP concentration were obtained on admission in the emergency department and on days 3 and 7 of hospitalisation. Serum concentrations of CRP were measured by monoclonal immunoassay using a VITROS analyser (Ortho-Clinical Diagnostics, Johnson and Johnson, Amersham, UK) The normal reference range for this assay is <10 mg·L^{-1}.

Microbiological evaluation

Sputum samples (when available) and blood samples were collected, cultured and evaluated according to standard procedures [12]. Sputum samples were considered adequate and subsequently cultured if $\geqslant$25 polymorphonuclear neutrophils and <10 epithelial cells were present in each high-power field. Urinary antigen tests (Binax Inc., Portland, ME, USA) were used to detect antigens of *Streptococcus pneumoniae* and *Legionella pneumophila*. Acute and convalescent sera were collected and tested for *Mycoplasma pneumoniae*, *L. pneumophila* and *Chlamydia pneumoniae*. The following results were considered indicative of infection: for *M. pneumoniae*, a four-fold or greater increase in titre in paired sera or a single titre of 1:40 or greater (immune fluorescence agglutination, Serodia-MycoII; Fujirebio, Malvern, PA, USA) [16]; for *L. pneumophila*, a four-fold increase in the antibody titre to 1:128 or greater, or single titres of 1:256 or more [17]; and for *C. pneumoniae*, detection of immunoglobulin (Ig)M above established values, seroconversion of IgG between acute and convalescence samples, high amounts of IgG in single titres, or a combination of these (ELISA; Savyon Diagnostics, Ashdad, Israel). Pathogenic microorganisms cultured from blood or sputum, detected by urinary antigen test or a seroconversion were considered the cause of the episode of CAP.

Definitions

Appropriate antibiotic treatment was defined as at least one antibiotic covering all of the causative pathogens identified, as determined by the sensitivity pattern in the antibiogram. Guidelines of the Dutch antimicrobial committee (SWAB) were used to determine the appropriateness of antibiotic therapy for each aetiology [18].

Early treatment failure was defined as clinical instability (respiratory rate >25 breaths·min^{-1}; oxygen saturation <90% as measured by pulse oximetry; P_{a,O_2} <7.3 kPa (<55 mmHg); haemodynamic instability or acute alterations in mental state), ICU admission or mortality in the first 3 days of admission [19]. Late treatment failure was defined as clinical deterioration or complications including mortality, the need for mechanical ventilation, readministration of *i.v.* antibiotics after a switch to oral therapy, readmission for pulmonary infection after discharge, or an increase in body temperature after initial improvement in the follow-up period [20]. The per cent decline in CRP levels reflects the relative changes in CRP concentrations in the course of time, calculated in relation to the day 0 CRP concentrations. Delayed normalisation of CRP was defined as a decline of <60% in CRP levels in 3 days and a decline of <90% in CRP levels in 7 days.

Analytical approach

In order to investigate the clinical relevance of consecutive CRP measurements in the follow-up of antibiotic treatment for severe CAP, the relationships between baseline CRP levels and patients' demographics, comorbidity, medication use and

aetiology were initially explored. Subsequently, among patients with established aetiology, the association between the decline in CRP levels and appropriateness of empirical antibiotic treatment was studied. Furthermore, the predictive value of a delayed normalisation of CRP for the risk of having received inappropriate antibiotic treatment or an unfavourable clinical outcome, such as mortality, early treatment failure and late treatment failure, was studied by means of multivariable models.

Statistical methods

Continuous variables were tested by Mann–Whitney U-tests or paired t-test, where appropriate, and categorical variables were compared using the Chi-squared test. ANOVA was used for comparisons between more than two groups. The rate of decline in CRP levels was dichotomised: the cut-off values of a 60% decline on day 3 and a 90% decline on day 7 were determined in line with previous published data and the 75th percentiles of CRP levels on day 3 and 7, after rounding [8]. The association of a delayed decline in CRP levels and the appropriateness of initial antibiotic treatment and clinical outcome was compared by estimation of the odds ratio (OR) with corresponding 95% confidence intervals (CIs). Correction for patient characteristics, pneumonia severity, and symptoms and signs of pneumonia on admission was performed by multivariate assessment. A p-value of <0.10 in univariable analysis or any clinically relevant parameter was used as an entry criterion for multivariate analysis. A p-value of <0.05 was considered statistically significant.

RESULTS

Baseline characteristics

A total of 289 patients with severe CAP were enrolled in the trial. The patients' mean$\pm$SD age was 69.7$\pm$13.8 yrs. The mean PSI and APACHE II scores in the study population were 112.9$\pm$25.7 and 13.8$\pm$4.6, respectively. Of the study patients, 180 (62.3%) had a risk-elevating medical condition congestive heart failure, neoplasm, cerebrovascular disease, chronic renal failure, liver disease or chronic obstructive pulmonary disease. Overall, the median serum CRP concentration on admission was 174 mg·L^{-1} (interquartile range 147–390 mg·L^{-1}; table 1). Slightly lower baseline CRP levels were observed in patients who had recieved outpatient antibiotic treatment (135.0 mg·L^{-1} *versus* 184.0 mg·L^{-1}; p=0.07) or outpatient treatment with inhalation steriods (146.0 mg·L^{-1} *versus* 185.5 mg·L^{-1}; p=0.09). No significant association between baseline CRP levels and demographic characteristics or the presence of comorbidity was observed ($p>0.25$). A total of 232 (80.3%) patients enrolled in the study received β-lactam monotherapy as empirical antibiotic treatment, which is a recommended initial regimen in the Netherlands for CAP patients not necessitating ICU admission and with a negative Legionella urinary antigen test, and 47 (16.3%) patients received combination therapy with β-lactam and macrolide antibiotics [18]. In total, 10 (3.5%) patients received a different empirical antibiotic therapy. Of those, four (0.6%) patients were initially treated with doxycyclin or erythromycin monotherapy because of suspicion of an atypical cause of pneumonia on admission. In one (0.3%) patient, combination therapy with erythromycin and rifampicin was initiated because of a strong suspicion for an *L. pneumophila* infection.

In 122 (89.1%) out of 137 patients with established aetiology, empirical antibiotic treatment was considered appropriate. A total of 20 (6.9%) patients had died by day 28 and nine (3.1%) patients required ICU admission during follow-up (table 1).

Aetiology and CRP levels

An aetiological diagnosis could be established in 137 (47.4 %) patients. *S. pneumoniae* was the most frequently indentified pathogen in 55 (19.0%) cases. Median (interquartile range) baseline CRP concentrations were the highest in patients with a *S. pneumoniae* infection (278 (147–390) mg·L^{-1}),

TABLE 1 Characteristics of the study cohort of 289 patients with severe community-acquired pneumonia

Age yrs	69.7$\pm$13.8
Females	99 (34.3)
PSI score	112.9$\pm$25.7
Class IV	198 (68.5)
Class V	52 (18.0)
APACHE II score	13.8$\pm$4.6
Comorbidity	180 (62.3)
Congestive heart failure	36 (12.5)
Neoplasm	65 (22.5)
Liver disease	3.0 (1.0)
Cerebrovascular disease	25 (8.7)
Chronic renal disease	27 (9.3)
COPD	88 (30.4)
Clinical features	
Temperature °C	38.5$\pm$1.2
Respiratory rate breaths·min^{-1}	26.7$\pm$8.7
Laboratory data	
CRP mg·L^{-1}	174 (147–390)
White blood cell count 10^9·L^{-1}	16.5$\pm$9.2
Antibiotic therapy	
β-lactam	232 (80.3)
Amoxicillin $\pm$ clavulanic acid	169 (58.5)
Cephalosporin (2nd or 3rd generation)	60 (20.7)
Cephtriaxone	47 (16.2)
Cephtazidime	12 (4.2)
Cephotaxime	1 (0.3)
Penicillin	3 (1.0)
β-lactam/macrolide combination	47 (16.3)
Amoxicillin $\pm$ clavulanic acid and macrolide	32 (11.1)
Cephalosporin (2nd or 3rd generation) and macrolide	14 (4.8)
Cephtriaxone and macrolide	11 (3.8)
Cephtazidime and macrolide	2 (0.7)
Other[#]	10 (3.5)
Outcome	
ICU admissions during hospitalisation	9 (3.1)
28-day mortality	20 (6.9)

Data are presented as mean$\pm$SD, n (%) or median (interquartile range). PSI: Pneunomia Severity Index; APACHE: Acute Physiology and Chronic Health Evaluation; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; ICU: intensive care unit. [#]: other antibiotics include: cotrimoxazole (n=2; 0.7%); β-lactam and ciprofloxacin (n=2; 0.7%); doxycyclin (n=2; 0.7%); erytromycin and rifampicin (n=1; 0.3%); levofloxacin (n=1; 0.3%); and erythromycin (n=2; 0.6%).

TABLE 2 Median baseline C-reactive protein (CRP) values according to aetiology in patients with severe community-acquired pneumonia

	Subjects	Median CRP level	Size of range	Interquartile range
Streptococcus pneumoniae [#]	55 (19.0)	278.0	686	147–390
Haemophilus influenzae	9 (3.1)	214.0	278	168–313
Staphylococcus aureus [¶]	8 (2.8)	187.0	299	115–330
Chlamydia pneumoniae	10 (3.5)	115.5	328	57–317
Mycoplasma pneumoniae	5 (1.7)	49.0	299	27–228
Legionella pneumophila [+]	7 (2.4)	247.0	286	176–421
Enterobacteriaciae [§]	15 (5.2)	129.0	452	53–272
Moraxella catarrhalis	5 (1.7)	64.0	197	49–165
Other pathogens [ƒ]	11 (3.8)	185.0	403	117–231
Multiple bacterial pathogens	12 (4.2)	213.0	672	83–404
Unknown aetiology	152 (52.6)	140.5	576	56–293

[#]: determined by sputum culture (n=19), blood culture (n=24) or urinary antigen test (n=20), in eight cases *S. pneumoniae* was determined by multiple tests; [¶]: determined by sputum culture (n=6) or blood culture (n=2); [+]: all determined by both serology and urinary antigen test (n=7); [§]: Enterobacteriaciae include: *Eschericia Coli* (n=6; 2.1%); *Klebsiella pneumoniae* (n=4; 1.4%); *Proteus mirabilis*. (n=1; 0.3%); Enterobacter spp. (n=2; 0.7%); Citrobacter spp. (n=2; 0,7%); [ƒ]:other pathogens include: *P. aeruginosa* (n=2; 0.7%); *Streptococcus agalactiae* (n= 3; 1.0%); *H. parainfluenzae* (n=2; 0.7%); *Staphylococcus hominis* (n=1; 0.3%); *Proprionibacter acnes* (n=1; 0.3%); Gram-positive spp. (n=2; 0.7%).

followed by *L. pneumophila* (247 (147–390) mg·L^{-1}), *Haemophilus influenzae* (214 (168–313) mg·L^{-1}), *Saphylococcus aureus* (187 (115–330) mg·L^{-1}), Enterobacteriaciae (129.0 (53–272) mg·L^{-1}), *Chlamydia pneumoniae* (115.5 (57–317) mg·L^{-1}), *Moraxella catarrhalis* (64.0 (49–165) mg·L^{-1}) and *M. pneumoniae* infections (49 (27–228) mg·L^{-1}; table 2). Patients with multiple identified bacterial pathogens had median admission CRP levels of 213.0 mg·L^{-1}. The aetiology of these 12 cases is specified in table 3. The median baseline CRP levels were significantly different among the causative pathogens ($p<0.01$, ANOVA). Patients with unknown aetiology had a significantly lower median CRP concentration on admission than patients with established aetiological diagnosis (140.5 mg·L^{-1} *versus* 209.0 mg·L^{-1}; $p<0.01$). Patients with *L. pneumophila* infection had a slower, but not statistically significant, normalisation of CRP within the first 3 days of follow-up as compared with patients with other aetiological diagnosis. The decline in CRP levels on days 0–3 was 32.9% in patients with *L. pneumophila* infection, as compared with 38.6% in patients with pneumonia of other aetiology (mean difference 5.7%; $p=0.58$). However, in the second part of the first week of follow-up, the decrease in CRP levels was larger in patients with *L. pneumophila* infection (48.5%) compared with others (28.5%; mean difference 20.0; $p<0.01$).

TABLE 3 Aetiology of the 12 cases with multiple bacterial pathogens specified

Subject	Aetiology	
	Pathogen 1	Pathogen 2
1	*Streptococcus pneumoniae* [#]	*Haemophilus influenzae* [¶]
2	*Streptococcus pneumoniae* [+]	Enterobacter spp [¶]
3	*Streptococcus pneumoniae* [¶]	*Eschericia coli* [¶]
4	*Streptococcus pneumoniae* [#, ¶]	*Chlamydia pneumoniae*
5	*Streptococcus pneumoniae* [#, +]	*Chlamydia pneumoniae*
6	*Haemophilus influenzae* [¶]	*Chlamydia pneumoniae*
7	*Haemophilus influenzae* [¶]	*Legionella pneumophila*
8	*Haemophilus influenzae* [¶]	*Staphylococcus hominis* [#]
9	*Mycoplasma pneumoniae*	*Eschericia coli* [¶]
10	*Chlamydia pneumoniae*	*Staphylococcus aureus* [¶]
11	*Legionella pneumophila*	*Corynebacterium difteria* [#]
12	*Legionella pneumophila*	Streptococcus group B [#]

[#]: determined by blood culture; [¶]: determined by sputum; [+]: determined by urinary antigen test.

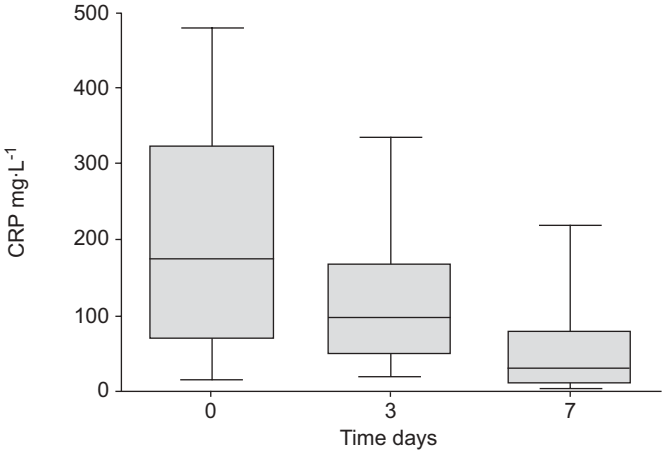

FIGURE 1. Patterns of normalisation of C-reactive protein (CRP) levels for the 289 study patients with severe community-acquired pneumonia. Horizontal lines represent the median; boxes, the interquartile range; and whiskers, the highest and lowest non-outlier values.

TABLE 4 Appropriateness of empirical antibiotic treatment and normalisation patterns of C-reactive protein (CRP)

	Unknown aetiology	Patients with established aetiology			
		Received appropriate antibiotic treatment	Received inappropriate antibiotic treatment	Mean difference# (95% CI)	p-value
Subjects	152 (52.6)	112 (38.8)	25 (8.7)		
Median CRP values					
Day 0	140.5 (56–293)	233.0 (131–358)	152 (63–243)		
Day 3	90.0 (23–153)	98.0 (30–168)	108.5 (55–215)		
Day 7	29.0 (12–79)	36.0 (18–75)	29 (15–92)		
Mean decline in CRP					
Day 0–3	36.3±30.4	44.5±30.5	25.2±24.4	19.3 (6.1–32.5)	<0.001
Day 0–7	63.1±34.6	75.5±24.7	60.4±32.3	15.1 (1.8–28.5)	0.03

Data are presented as n (%), median (interquartile range) or mean±SD, unless otherwise stated. CI: confidence interval. #: the mean difference (95% CI) in per cent decline in CRP among patients with appropriate and inappropriate antibiotic treatment (established aetiology) is displayed.

The value of consecutive CRP measurements in follow-up of antibiotic treatment

CRP measurements were performed in all patients on admission, in 264 (91.3%) patients on day 3 and in 210 (72.6%) patients on day 7 of hospitalisation. The median (range) CRP concentration was 97.5 (51–163) mg·L^{-1} on day 3 and 31.0 (13–78) mg·L^{-1} on day 7 of follow-up. Patterns of normalisation of CRP are displayed in figure 1. The mean decline in CRP levels was 38.4% (interquartile range 5.3–65.5%) within the first 3 days and 80.9% (interquartile range 54.2%–92.0%) within the first week of follow-up. In univariate analysis, patients treated with inappropriate empirical antibiotics had significantly slower normalisation of CRP levels as measured in the first 3 days (mean difference 19.3%; 95% CI 6.1–32.5%) and in the first week of hospitalisation (mean difference 15.1%; 95% CI 1.8–28.5%; table 4). In multivariate analysis, a decline of <60% in CRP levels in 3 days and a decline of <90% in CRP levels in 7 days were both associated with an increased risk of having received inappropriate empirical antibiotic treatment (day 0–3, OR 6.98, 95% CI 1.56–31.33) and (day 0–7; OR 3.74, 95% CI 1.12–13.77; table 5).

TABLE 5 Multivariate analysis of delayed normalisation of C-reactive protein (CRP) and the risk of having received inappropriate antibiotic treatment

	Received inappropriate antibiotic treatment	
	OR (95% CI)#	p-value
Day 0–3 CRP decline <60%	6.98 (1.56–31.33)	0.004
Day 0–7 CRP decline <90%	3.74 (1.12–13.77)	0.04

Multivariate analysis was conducted among the 137 patients with established aetiology. OR: odds ratio; CI: confidence interval. #: the displayed ORs are adjusted for patient characteristics (age, sex and comorbid illnesses), Pneumonia Severity Index score, symptoms and signs of pneumonia (cough, sputum production, sore throat, dyspnoea, chest pain, haemoptoe, confusion, blood pressure, respiratory rate, pulse and oxygen saturation).

Patients with delayed normalisation of CRP levels in the first week had a trend towards an increased risk of mortality (OR 3.73, 95% CI 0.46–30.52; p=0.06); however when corrected for pneumonia severity, patients' charactecteristics, and symptoms or signs of pneumonia on admission, this was not statistically significant. In addition, patients with delayed normalisation of CRP in the first 3 days had a slightly increased risk of developing early or late treatment failure, but again this was not statistically significant (table 6).

DISCUSSION

The results of the present study show that consecutive measurements of CRP in follow-up of antibiotic treatment for severe CAP are useful. Delayed normalisation of CRP within the first 3–7 days of follow-up is suggestive of inappropriate empirical antibiotic therapy. Patients with a decline of <60% in CRP levels in 3 days or a decline of <90% in 7 days had a four- to seven-fold increased risk of having received inappropriate antibiotic treatment. Since there is limited evidence on the relevance of consecutive CRP measurements, the main findings of the present study may have clinical implications.

The results of the few previous studies concerning the usefulness of consecutive CRP measurements in follow-up of CAP are in line with the present findings [8–10]. SMITH *et al.* [9] studied the usefulness of CRP as marker in 28 patients who had no obvious response to treatment. They concluded that CRP could be of aid to clinicians. Another study in 53 patients with severe CAP admitted to the ICU also showed that identification of CRP patterns may be of value in follow-up of treatment [8]. Recently, MENENDEZ *et al.* [10] have demonstrated that a persistently high CRP level on days 1 and 3 in follow-up of patients with mild-to-severe pneumonia was independently associated with a higher risk of treatment failure. In the present cohort, patients with an inadequate decline in CRP also had a higher risk of treatment failure; however, this was not statistically significant. These different results may be explained by differences in pneumonia severity of both study populations and addressing absolute CRP values at days 1 and 3 as compared with relative changes in CRP measured on days 3 and 7 in the present study.

TABLE 6 Multivariate analysis of delayed normalisation of C-reactive protein (CRP) and the risk for having an unfavorable outcome

	Mortality (within 28 day)		Early (within 3 days) treatment failure		Late (within 28 days) treatment failure	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Day 0–3 CRP decline <60%	1.09 (0.32–3.73)	0.89	1.57 (0.85–2.92)	0.16	1.29 (0.62–2.68)	0.50
Day 0–7 CRP decline <90%	1.23 (0.45–2.99)	1.00			0.87 (0.39–1.94)	0.74

The displayed odds ratios (ORs) are adjusted for patient characteristics (age, sex and comorbid illnesses), Pneumonia Severity Index score, symptoms and signs of pneumonia (cough, sputum production, sore throat, dyspnoea, chest pain, hemoptoe, confusion, blood pressure, respiratory rate, pulse and oxygen saturation). CI: confidence interval.

In univariable assessment, a delayed decline in CRP levels was associated with a trend towards increased risk for mortality. However, after correction for pneumonia severity, patients' characteristics and clinical variables at baseline, a statistically significant relationship could not be established. A recent study has shown that failure of CRP to decrease leads to an increased risk of mortality [21].

Interestingly, baseline CRP levels appeared to be influenced by the causative pathogen, antibiotic use prior to hospitalisation and the use of inhalation steroids. Theoretically, baseline CRP levels could be of use in determining aetiology of severe CAP, but the ability of CRP to differentiate in aetiology of severe CAP is low [22]. As indicated by the results of the present study and others, CRP levels are influenced by the use of steroids. Moreover, it has been reported that treatment with steroids leads to suppression of CRP production [23]. A study by PERREN *et al.* [24] demonstrated that corticosteroids did not influence the time-dependent decline of CRP levels. However, according to the present results, the use of steroids needs to be considered in order to interpret CRP levels in follow-up correctly. Concerning the influence of the causative pathogen on the decay of CRP, a slower decline in CRP levels was observed in the first 3 days of follow-up in *L. pneumophila* than in other pathogens. This may be due to inappropriate empirical treatment; however, all patients had Legionella antigen test performed within 12 h and patients with a positive Legionella antigen test received treatment for Legionella infection within 12 h. Another explanation may be that *L. pneumophila*, as an intracellular pathogen, causes a different host response to infection, characterised by prolonged and greater increases of CRP [25, 26]. According to these results, the causative pathogens need to be taken into account in order to interpret CRP levels in follow-up correctly. For example, in case of an established *L. pneumophila* infection, persistent high CRP levels should not be the sole reason for antibiotic switch or additional invasive diagnostic procedures. The results of the present study indicate that a delayed decline in CRP levels is related to inappropriate empirical antibiotic treatment. Conversely, CRP levels returning to normal ranges might indicate that duration of antibiotic treatment has been sufficient, allowing earlier discontinuation of antibiotics or a switch to oral antibiotics. Such a CRP-based management strategy could potentially help in reducing antibiotic usage, costs, toxicity, length of hospital stay and the risk of emerging resistance [8]. However, this concept needs to be addressed in further studies.

The present study has three important limitations. First, focus was placed on episodes of severe CAP in patients without the primary need for ICU admission. Because acute phase proteins, such as CRP, reflect the intensity of inflammation, generalisibility to patients with less severe pneumonia can be questioned [27]. Secondly, appropriate treatment was defined as ''at least one antibiotic covering all of the causative pathogens identified''. However, the causative role in CAP can be debated for some of the isolated bacteria. When these isolates only represent colonisation of the respiratory tract, the association of a delayed decline and the risk of having received inappropriate therapy may be overestimated. Thirdly, daily CRP measurements could have added more information to the study. However, the study was designed in accordance with a previous study taking clinically relevant time-points after admission [21].

In conclusion, consecutive C-reactive protein measurements are useful in the first week in follow-up of antibiotic treatment for severe community-acquired pneumonia, when taking the causative microorganism and use of steroids into account. A delayed decline in C-reactive protein levels is associated with a higher risk of having received inappropriate antibiotic treatment.

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