



Original article

C-reactive protein for discriminating treatment failure from slow responding pneumonia

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ABSTRACT

Background: The management of patients with community-acquired pneumonia (CAP) who fail to improve constitutes a challenge for clinicians. This study investigated the usefulness of C-reactive protein (CRP) changes in discriminating true treatment failure from slow response to treatment.

Methods: This prospective multicenter observational study investigated the behavior of plasma CRP levels on days 1 and 4 in hospitalized patients with CAP. We identified non-responding patients as those who had not reached clinical stability by day 4. Among them, true treatment failure and slow response situations were defined when initial therapy had to be changed or not after day 4 by attending clinicians, respectively.

Results: By day 4, 78 (27.4%) out of 285 patients had not reached clinical stability. Among them, 56 (71.8%) patients were cured without changes in initial therapy (mortality 0.0%), and in 22 (28.2%) patients, the initial empirical therapy needed to be changed (mortality 40.9%). By day 4, CRP levels fell in 52 (92.9%) slow responding and only in 7 (31.8%) late treatment failure patients ($p < 0.001$). A model developed including CRP behavior and respiratory rate at day 4 identified treatment failure patients with an area under the Receiver Operating Characteristic curve of 0.87 (CI 95%, 0.78–0.96).

Conclusion: Changes in CRP levels are useful to discriminate between true treatment failure and slow response to treatment and can help clinicians in management decisions when CAP patients fail to improve.

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1. Introduction

Community-acquired pneumonia (CAP) is considered the primary cause of mortality from infection in developed countries [1]. However, several issues regarding its management are not fully clarified. One of these issues constitutes the management of patients who do not respond adequately to initial antibiotic treatment. Although difficult to define, non-responding CAP seems fairly common. Between 6 and 28% of hospitalized CAP patients have been included as non-responding in previous studies, and derived mortality is increased nearly fivefold [2–5].

Recent guidelines have addressed the management of non-responding patients extensively and definition, causes and management have been proposed [6]. At this point however, clinicians often have difficulties in distinguishing between true treatment failure from slow response to treatment. Although some predictors of delay in clinical improvement have been identified in previous studies (i.e., older age, comorbidity, high grade of severity, multilobar involvement, and bacteremia [7–10]), their operating characteristics are unknown. The British Thoracic Society (BTS) guidelines stated that CRP levels that do not fall by 50% within 4 days suggest failure of treatment or the development of complications, although further prospective studies were recommended [11].

C-reactive protein (CRP) has provided promising results as a marker of resolution in selected populations with severe CAP [12]. The aim of our study was to further understand the usefulness of CRP changes in distinguishing true treatment failure from slow response in unselected hospitalized patients with CAP.

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2. Materials and methods

2.1. Setting and study design

From October 2005 to April 2006, a multicenter observational prospective study was carried out in five Spanish hospitals. The study cohort was comprised of adult patients (>18 years of age) hospitalized with CAP. Inclusion criteria were a clinical picture compatible with CAP with at least two clinical symptoms and a new radiographic infiltrate. Exclusion criteria included patients admitted within the previous 15 days, immunosuppression (including corticosteroids >15 mg/day of prednisone or its equivalent, neutropenia <500/mm not attributable to CAP, and HIV infection with a CD4 count <100), patients who were discharged within the first 72 h of treatment, and patients who died or were transferred to the ICU because of respiratory failure or hemodynamic instability within 72 h of admission (early failure) [6].

2.2. Study protocol

The study protocol was approved by each institution's ethical committee, and informed verbal consent was obtained from each patient. At the initial visit to the emergency department (day 1), demographic, clinical and physical information were collected from each patient. In addition to initial blood tests, a plasma sample was obtained to perform CRP. Microbiological studies included blood cultures and collection of a sputum sample for Gram stain and culture when possible. In some Spanish hospitals *Streptococcus pneumoniae* and *Legionella pneumophila* antigen detection tests in urine samples, as well as standard serology to identify *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Coxiella burnetii*, were included as an initial microbiological work-up. To stratify severity in patients, we used a validated prediction rule, which was calculated according to the Pneumonia Severity Index (PSI) [13]. Antibiotic therapy was administered in the emergency department in accordance to clinician's judgement, although Spanish guidelines recommend the administration of a β -lactam agent plus a macrolide or a third-generation quinolone alone [14].

All patients were monitored daily during their hospital stay. After 72 h of antibiotic treatment (day 4), a blood sample was collected and stored to perform a second CRP test. By day 4, patients were classified as responding or non-responding. Non-responding patients were identified if they met at least one of the following conditions: temperature >37.2 °C, heart rate >100 beats/min, respiratory rate >24 breaths/min, systolic blood pressure <90 mm Hg, oxygen saturation <90% or arterial oxygen partial pressure <60 mm Hg [8] (Table 1). We considered patients with oxygen therapy at home to be stabilized when the need for oxygen was the same as that before hospital admission. Responsible clinicians were blinded to the second CRP value, and subsequent management of CAP was made according to their own judgement. At the end of the process, non-responding patients were classified as having a) *true treatment failure*, when changes in the initial antibiotic treatment and/or invasive procedures for therapeutic purposes (i.e., chest tube drainage) were performed; or b) *slow response*, when clinical stability was achieved without

changes in the initial empiric antibiotic treatment. To narrow the initial empiric treatment because of the identification of a causative microorganism was not considered a change in initial empiric therapy.

Blood samples for CRP were analyzed by a particle-enhanced turbidimetric assay marketed as Tina-quant®, following the indications of the manufacturer (Roche Diagnostics, Mannheim, Germany). The range of detection of CRP was from 1 to 800 mg/L.

2.3. Statistical analysis

Results are reported as means (SD) or medians (quartiles) as needed. Comparisons between groups were performed with the χ^2 and Fisher exact tests for categorical variables, and the nonparametric Kruskal–Wallis and Mann–Whitney tests were used for continuous variables. All statistical comparisons were two-sided and carried out at the 0.05 significance level. Sensitivity, specificity, positive and negative predictive values (with confidence intervals based on exact binomial distribution), as well as the area under the receiver operating characteristic (ROC) curve, were used for comparison of predictive tests. Data were analyzed with R, a language and environment for statistical computing (version 2.9.0).

3. Results

During the study period, 327 patients were eligible for inclusion. However, 6 patients were excluded because they had been discharged within 15 days, 8 were immunosuppressed, 20 were discharged within 72 h of treatment, and 18 patients died or transferred to the ICU because of respiratory failure or hemodynamic instability within 72 h of admission.

The final study population was 285 patients. Of them, 171 (60.0%) were older than 65 years, and the male/female ratio was 2.2:1. According to the PSI severity score, patients were classified in I (28 patients), II (64 patients), III (69 patients), IV (105 patients) and V (19 patients) risk classes. A microorganism was identified in 99 (34.7%) patients as follows: 63 with *S. pneumoniae*, 12 with *L. pneumophila*, 8 with *C. pneumoniae*, 5 with *Pseudomonas aeruginosa*, 4 with enteric Gram-negative bacilli, 3 with *M. pneumoniae*, 2 with *C. burnetii*, 1 with *Haemophilus influenzae*, and 1 with *Klebsiella pneumoniae*.

By day 4, 207 (72.6%) and 78 (27.4%) patients had and had not reached clinical stability, respectively. Among patients with early response (clinical stability by day 4), there were 109 (52.6%) patients with an age older than 65 years, 74 (35.7%) were females, and 113 (54.0%) had a PSI score higher >3. The CRP values at day 1 are shown in Fig. 1. The characteristics of patients with clinical instability are shown in Table 2. Among 78 patients who failed to improve by day 4, 56 (71.8%) were cured without changes in initial therapy (slow responding patients), and in 22 (28.2%) patients, the initial empirical therapy needed to be changed (true treatment failure patients). Comparison between both groups is shown in Table 2. The two groups did not differ in age, gender, severity or CRP levels at presentation. However, differences were found in plasma CRP behavior between days 1 and 4, as well as the presence of tachypnea and hypoxemia by day 4. The two groups did not differ between the number of complementary explorations performed after day 4. Days to reach clinical stability, hospitalization and mortality were higher in the true treatment failure group, as Table 2 shows. The cause of true treatment failure was identified in 10 (45.4%) patients: 6 patients had a microorganism that was not initially covered by empirical treatment (*P. aeruginosa* (2), enteric Gram-negative bacilli (2), *L. pneumophila* (1), and *C. burnetii* (1)); 2 patients developed empyema and a chest tube was inserted; and in 1 patient, a final diagnosis of cryptogenic organizing pneumonia was made.

A comparison of plasma CRP values among study groups is shown in Figs. 1 (day 1) and 2 (day 4). On day 1, plasma CRP values in

Table 1

Parameters obtained from patients who failed to improve by day 4.

Parameter	Present, n = 78 (%)
Fever (temperature >37.2 °C)	49 (62.8)
Tachycardia (heart rate >100 beats/min)	30 (38.5)
Tachypnea (respiratory rate >24 breaths/min)	34 (43.6)
Hypotension (systolic blood pressure <90 mm Hg)	8 (10.3)
Hypoxemia (oxygen saturation <90%) ^a	31 (39.7)
All 5 present	4 (5.1)

^aArterial oxygen partial pressure \leq 60 mm Hg when blood gas oxymetry was performed.

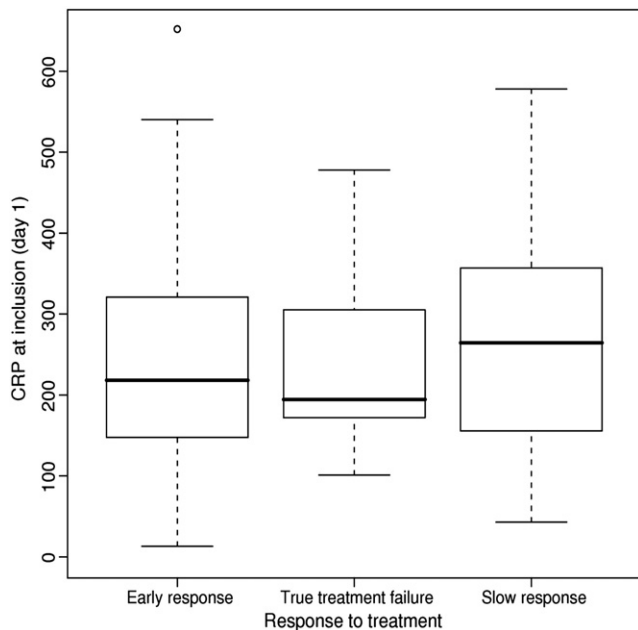


Fig. 1. Distribution (median, quartiles, and range) of plasma C-reactive protein (CRP) levels at admission (day 1) among the study groups. Outliers are plotted separately (open circles) and included in the analysis, and CRP values are given in mg/L. CRP values in patients with early response (218.0 mg/L, Interquartile range, IQR 147.5–321.0), true treatment failure (194.5 mg/L, IQR 175.8–291.3) and slow response (264.5 mg/L, IQR 156.3–352.5) did not differ ($p=0.2785$).

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Table 2

Comparison between slow response and true treatment failure patients with community-acquired pneumonia.

	Slow response n (%) (n = 56)	True treatment failure n (%) (n = 22)	p-value
Parameters present by day 1			
Age older than 65 years	35 (62.5)	16 (72.7)	0.440
Female	17 (30.4)	9 (40.9)	0.429
Pneumonia severity index > 3	28 (50.0)	16 (72.7)	0.081
CRP level at day 1 (mg/L) ^a	264.5 (156.2–352.5)	194.5 (175.8–291.2)	0.408
Parameters present by day 4 ^b			
Fever	34 (60.7)	15 (68.2)	0.610
Tachycardia	20 (35.7)	10 (45.5)	0.449
Tachypnea	19 (33.9)	15 (68.2)	0.010
Hypotension	6 (10.7)	2 (9.1)	1.000
Hypoxemia	17 (30.4)	14 (63.6)	0.010
CRP decreased	52 (92.9)	8 (36.4)	<0.001
Complementary explorations			
Computer tomography	14 (25.0)	10 (45.5)	0.093
Bronchoscopy	4 (7.1)	3 (13.6)	0.379
Microbiological study ^c	49 (87.5)	17 (77.2)	0.262
Chest tube insertion	0 (0.0)	1 (4.5)	0.098
Transthoracic needle aspiration	0 (0.0)	1 (4.5)	0.098
Thoracentesis alone	10 (17.9)	2 (9.1)	0.718
Outcome parameters			
Days to reach stability ^a	5 (5–6.3)	7 (6–9)	0.006
Days of hospitalization ^a	10 (7–14)	12.5 (9.3–20.8)	0.06
Mortality	0 (0.0)	9 (40.9)	<0.001

^a Values are given as median (Interquartile range, IQR 25–75).

^b Cut-off points for physical signs are shown in the Materials and methods section.

^c Blood cultures and sputum if available.

however, plasma CRP values in true treatment failure patients (242.0 mg/L, IQR 154.5–267.5) were higher than those found in early response (50.0 mg/L, IQR 28.0–85.0) and slow response (107.0 mg/L, IQR 71.8–187.0) patients ($p<0.0001$).

After 72 h of treatment (day 4), CRP levels fell in 204 (98.5%) early responding, in 52 (92.9%) slow responding and only in 7 (31.8%) late treatment failure patients. To identify patients with true treatment failure, the operating characteristics of an increase in CRP plasma levels between days 1 and 4 were the following: sensitivity 68.2% (CI 95%, 45.1–86.1), specificity 92.9% (CI 95%, 82.7–98.0), positive predictive value 88.1% (CI 95%, 77.1–95.1), and negative predictive value 78.9% (CI 95%, 54.4–93.9). The area under the ROC curve obtained with this model was 0.80 (CI 95%, 0.78–0.96). To increase the operating characteristics of CRP, a prediction model was constructed by adding the variable “tachypnea” (presence or absence of respiratory rate of >24 breaths/min at day 4). In this model, an increase in CRP values between days 1 and 4, or a decrease in CRP values but in the presence of tachypnea, identified patients with true treatment failure with a sensitivity 90.9% (CI 95%, 70.8–98.9), specificity 58.9% (CI 95%, 45.0–71.9), positive predictive value 46.5% (CI 95%, 31.2–62.3), and negative predictive value 94.3% (CI 95%, 80.8–99.3). The area under the ROC curve obtained with this model was 0.87 (CI 95%, 0.780–0.966). In Table 3 the operating characteristics of models are shown along with that recommended by the British Thoracic Society.

By using this model, we could speculate that approximately half of the complementary explorations performed in non-responding patients could be prevented.

4. Discussion

Non-responding patients with CAP usually require important management decisions: transfer of the patient to a higher level of care, further diagnostic testing, and/or changes on initial antibiotic treatment [6]. However, a lack of prospective studies addressing the management of non-responding CAP patients makes such decisions

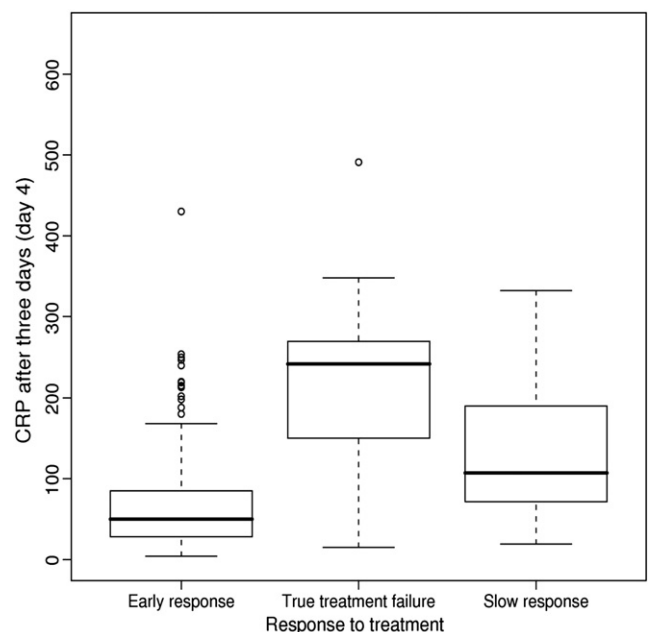


Fig. 2. Distribution (median, quartiles, and range) of plasma C-reactive protein (CRP) levels at day 4 among the study groups. Outliers are plotted separately (open circles), and included in the analysis, and CRP values are given in mg/L. CRP values in true treatment failure patients (242.0 mg/L, Interquartile range, IQR 154.5–267.5) were higher than those found in early response (50.0 mg/L, IQR 28.0–85.0) and slow response (107.0 mg/L, IQR 71.8–187.0) patients ($p<0.0001$).

Table 3

Operating characteristics of different models of C-reactive protein (CRP) changes alone, respiratory rate alone, or the combination of both to identify true treatment failure patients with CAP.

Day 4	Positive predictive value % (CI 95%)	Negative predictive value % (CI 95%)	Sensitivity % (CI 95%)	Specificity % (CI 95%)	AUC % (CI 95%)
CRP not decreased by >50% (in comparison with day 1 CRP) ^a	42.6 (28.3–57.8)	93.5 (78.6–99.2)	90.9 (70.8–98.9)	51.8 (38.8–65.3)	71.3 (62.3–80.4)
CRP increased (in comparison with day 1 CRP)	78.9 (54.4–93.9)	88.1 (77.1–95.1)	68.2 (45.1–86.1)	92.9 (82.7–98.0)	80.5 (70.1–91.0)
Tachypnea ^b alone	44.1 (28.8–60.5)	84.0 (70.6–92.0)	68.1 (47.3–83.6)	66.0 (53.0–77.0)	71.8 (64.1–79.4)
CRP increased or any decrease with tachypnea at day 4 (in comparison with day 1 CRP)	46.5 (31.2–62.3)	94.3 (80.8–99.3)	90.9 (70.8–98.9)	58.9 (45.0–71.9)	87.3 (78.0–96.6)

^a Model suggested by the British Thoracic Society [12].

^b Tachypnea >24 breaths/min.

difficult to perform. This study has provided a tool for clinicians to discriminate slow response from true treatment failure when a patient fails to improve after 72 h of antibiotic treatment. We observed that an increase in CRP plasma values between days 1 and 4 achieved a good discriminatory power to identify patients with treatment failure.

The CRP constitutes a biomarker that has been studied in respiratory infections with different objectives. In a study of 168 patients with acute cough performed in the primary setting, a CRP > 100 mg/L could identify patients with pneumonia with an ROC curve of 0.83 [15]. In another study performed in the emergency ward with 284 patients with respiratory infections (208 of them with pneumonia), only the CRP could discriminate in a multivariate analysis between pneumonia and other respiratory conditions in comparison with other variables (erythrocyte sedimentation rate, leukocyte count and temperature) [16].

The CRP has also been used as a double determination. In a study performed on 73 patients with CAP, the median time for a 50% decrease of CRP was 3.3 days [16,17]. Based on these results, the BTS guidelines suggested that physicians be aware when CRP levels do not fall by 50% within 4 days of initial treatment, although further prospective studies were recommended [12]. Few approaches have been performed since that date. In a study published by Chalmers et al. [18], the CRP performed at days 1 and 4 was used to identify the prognosis of pneumonia in a cohort of 570 patients with CAP. They found that a failure to decrease the CRP levels by 50% between both days was independently associated with an increase in 30-day mortality (OR 24.5), need for mechanical ventilation or inotropic support (OR 7.1), and complicated pneumonia (OR 15.4). Although these findings are interesting, some aspects should be addressed: If the primary outcome was the severity assessment of CAP, it could not be applied for patients who died, were admitted to the ICU or discharged within 4 days of admission (43.6% of the study population). In addition, the secondary outcome included the identification of complicated pneumonia, defined by the authors as the development of pleural effusion or lung abscess. If these complications can be easily identified by a chest radiograph, a need for two consecutive CRP determinations is likely superfluous.

Recently, the behaviour of several cytokines (IL1, IL6, IL8, and IL10), as well as CRP and procalcitonin (PCT), was studied in a cohort of 453 patients with CAP; 84 (18%) of them were identified as having treatment failure [19]. The authors found that a CRP \geq 219 mg/L on day 1 had independent predictive value to identify treatment failure. After 72 h of treatment, the authors also found differences in CRP medians (45 mg/L vs 121 mg/L) between patients that had or had not stabilized. However, no attempt was done to discriminate patients with slow response to treatment from those with true treatment failure. Finally, a recent study published by Bruns et al. [20], was carried out in 289 patients with severe CAP. The authors found that a decline of <60% in CRP levels between admission and day 3 of treatment was associated with an increased risk of having received inappropriate empiric antibiotic treatment, with an odds ratio of 6.98. Although interesting, clinicians are also interested in identifying other

causes of treatment failure such as parapneumonic effusions, infectious embolism or diseases other than lung infection.

The present study has incorporated a novel utility for CRP. The management of patients who fail to improve after 72 h of initial treatment constitutes a challenge for clinicians, and clinical guidelines that consider the information on such issues are scarce and mainly retrospective [6]. Although no randomized studies have compared the utility of invasive versus non-invasive strategies in the CAP population with non-response, many patients undergo bronchoscopy and chest computer tomography to rule out infections not covered by initial antibiotic therapy, complications of infections, such as empyema, or non-infectious conditions that can mimic pneumonia. As a consequence, morbidity, hospital stay, and derived costs increase without clear evidence of the benefit. As a result, discrimination between patients with a slow response to initial treatment from those with true treatment failure constitutes an important issue and could help clinicians decrease the number of patients who undergo invasive strategies. In this situation, our study can help clinicians in their decision-making processes. The results of the study show that in patients with slow response to treatment, the CRP tends to fall over days, as it does in patients with an early response to treatment. However, in patients with true treatment failure, the CRP levels tend to increase. The objective of the model developed from the present study was to identify patients with true treatment failure, because of the high mortality found in this group. The addition of the clinical variable (tachypnea) increased the accuracy of the model in identifying the true treatment failure group. In practical terms, the most useful parameter of the model was its high negative predictive value. Indeed, a patient who fails to improve after initial antibiotic treatment but a decrease of CRP levels or an absence of tachypnea by day 4 is observed, the probability of having a slow response to treatment is 94.3%.

Potential drawbacks of the study should be addressed. The rate of patients who failed to improve by day 4 was 27.4%. This proportion is quite high in comparison with previous studies. A reason could be the strict selection criteria used in our study. Indeed, of the 5 proposals made by Halm and colleagues to define clinical stability, we decided to use the one closest to our clinical practice [9]. As previous studies performed in a similar setting [21], a temperature threshold of 37.2 °C instead of 37.8 °C was more commonly used in clinical practice as a determining factor to define clinical stability. Furthermore, the observational design of the study makes the clinician's judgement as the gold standard to classify patients into slow responding or true treatment failure groups. Therefore, it is possible that some patients assigned to the treatment failure group were due to changes in initial antibiotic treatment rather than unfavourable evolution of the disease. Although it cannot be proven, we think this explanation is improbable because of the high rate of mortality found in the true treatment failure group (40.9%), similar to previous studies performed in this population [2]. In any case, a satisfactory correction for the bias introduced by such an imperfect gold standard does not exist.

In summary, the results of the present study confirm that serial CRP measurements could help clinicians to discriminate CAP patients with slow response to treatment from those with true treatment

failure. Further studies are needed to confirm that a strategy based on CRP changes may be safe for patients and allows a reduction of additional tests.

Learning points

- Approximately 20% of patients with community-acquired pneumonia do not respond adequately to initial antibiotics. Most of them are finally cured without changes but 30% of patients are considered as true treatment failure. In this study, we have provided a tool for clinicians to discriminate between both groups. An increase in C-reactive protein plasma values between days 1 and 4 achieved a high discriminatory power to identify patients with true treatment failure.

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