ERJ Express. Published on May 28, 2008 as doi: 10.1183/09031936.00003608

Usefulness of consecutive CRP measurements in follow-up of treatment for severe CAP

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Word count: 3149
References: 27
Tables: 4
Figures: 1
Keywords: Community-acquired pneumonia; C-reactive protein; Antibiotic treatment; Follow-up
Short running title: Consecutive CRP measurements in severe CAP

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 usefullness of consecutive CRP measurements is still unclear. We therefore studied the clinical relevance of consecutive CRP measurements in follow-up of antibiotic treatment in patients with severe community-acquired pneumonia (CAP).

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

Etiology could be determined in 137 (47.4%) 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 CRP measurements are useful in the first week in follow-up of antibiotic treatment for severe CAP when taking the causative micro-organism and use of steroids into account. A delayed normalisation of CRP levels is associated with a higher risk of having received inappropriate antibiotic treatment.

Introduction

Community-acquired pneumonia (CAP) is the major cause of death due to infectious diseases in the western world and accounts with an increasing figure for at least 20 admissions per 1000 inhabitants annually [1]. Current guidelines advise combination therapy with beta-lactam and macrolide antibiotics for initial treatment of severe CAP [2, 3]. Consequently, management of severe CAP accounts for high utilization of healthcare resources and antibiotic consumption, leading to a risk of emerging resistance. In the United States, annual estimated costs for treating CAP exceed $12 billon and in several countries an increase in macrolide resistant strains has been observed [4, 5].

Once etiology of CAP is established, pathogen directed antibiotic therapy can be initiated and a test indicative of etiology early in course of disease would be a worthfull target to reduce antibiotic consumption. Unfortunately, untill now no biomarker has acceptable sensitivity and specificity to guide initial therapy and we must relay on protocols for guidance of empiric antibiotic treatment [2, 3]. However, an alert for an unfavorable response to treatment early in follow-up; as an increased inflammatory response, suboptimal drug-levels, or inappropriate empiric treatment could help in optimizing treatment for CAP patients. Before an etiology has been established or when etiology can not be established, an indicator of the appropriateness of empiric antibiotic therapy may contribute to a more tailored approach in antibiotic treatment early in the course of the disease. Furthermore, it might help in continuing tailored antibiotic therapy, determining the length of antimicrobial treatment, and guiding a switch from IV 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 the use of consecutive CRP measurements has become routine clinical practice in follow-up of patients hospitalised with severe infections [7]. However,

despite its frequent use, evidence on the usefullness of consecutive CRP measurements in follow-up of antibiotic treatment for severe CAP is lacking. Few studies have adressed CRP kinetics in follow-up of CAP before, but these are relatively small scale studies without etiology taken into account [8, 9]. A recent study pointed out that high serum levels of CRP, IL-6 or, PCT are associated with a higher risk of any treatment failure [10]. Yet, the introduction of newer inflammatory markers such as procalcitonin, Il-6, and neopterin stresses the need for clarifying the position of the older and less costly markers such as CRP even more [11]. To determine the clinical relevance of consecutive CRP measurements in follow-up of antibiotic treatment in patients with severe CAP, we studied the predictive value of delayed normalisation of CRP levels for the risk of having received inappropriate empiric antibiotic therapy or developing an unfavorable outcome.

Material and methods

Setting and study population

The current study is a retrospective analysis of data derived from a multi-center, prospective randomised controlled trial on the cost-effectiveness of an early switch from parental to oral therapy for severe CAP [12]. The trial was conducted in five teaching hospitals and two university medical centres in the Netherlands from July 2000 to June 2003. All adult patients (age 18 or above) admitted to one of the participating hospitals because of CAP were eligible for inclusion. CAP was defined as 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 of > 90 or according to the ATS definitions [13, 14]. All patients gave written informed consent prior to enrollment 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 less then 1 month because of an underling disease, severe neutropenia (<0,5x 109/l) or HIV infection with a CD4 count <200/mm3, infections other than pneumonia necessitating treatment with antibiotics intravenously, and patients admitted directly to an intensive care unit (ICU) were excluded.

Data collection and CRP assay

On admission, demographic data, clinical signs and symptoms were recorded. Severity of disease was determined by PSI score and 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 day 3 and 7 of hospitalisation. Serum concentrations of CRP were measured by monoclonal immunoassay using a VITROS analyser (Ortho-Clinical Diagnostics Johnson&Johnson, Amersham, U.K.) The normal reference range for this assay is <10mg/l.

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 25 or more polymorphonuclear neutrophils and fewer than 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*. We considered the following results indicative of infection: for *M pneumoniae*, a fourfold or greater increase in titre in paired sera or a single titre of 1:40 or greater (immune fluorescence agglutination, Serodia-MycoII, Fujirebio) [16]; for *L pneumophila*, a fourfold 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 IgM above established values, seroconversion of IgG between acute and convalescence samples, high amounts of IgG in single titres, or a combination of these (enzyme linked immunosorbent assay, Savyon Diagnostics). Pathogenic micro-organisms 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 etiology [18].

Early treatment failure was defined as clinical instability (respiratory rate >25/min; oxygen saturation <90% as measured by pulse oximetry; Pa02 <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, re-administration of intravenous 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 decline in CRP levels in percentages reflects the relative changes in CRP concentrations in course of time, calculated in relation with 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

To investigate the clinical relevancy of consecutive CRP measurements in follow-up of antibiotic treatment for severe CAP, we first explored the relations between baseline CRP levels and patients' characterisics as demographics, comorbidity, medication use, and etiology. Subsequently, among patients with established etiology, we studied the association between the decline in CRP levels and appropriateness of empiric antibiotic treatment. Furthermore, the predictive value of a delayed normalisation of CRP for the risk of having received inappropriate antibiotic treatment or an unfavorable 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 Student's T test, where appropriate and categorical variables were compared using the chi-square test. ANOVA analysis of variance was used for comparisons between more than two groups. The rate of decline in CRP levels was dichotomized: the cut-off values of a 60% decline on day 3 and a 90% decline on day 7 were determined in line 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 (CI). Correction for patients' characteristics, pneumonia severity, and symptoms and signs of pneumonia on admission was performed by multivariate assesment. 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. All statistical analyses were performed with the statistical software package SPSS 15.0. for windows (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

We enrolled 289 patients with severe CAP in the trial. The patients' mean age was 69.7 (±13.8 SD) years. The mean PSI score and APACHE II score in the study population were 112.9 (±25.7SD) and 13.8 (±4.6SD), respectively. Of all study patients, 180 (62.3%) patients had a risk-elevating medical condition as congestive heart failure, neoplasm, cerebrovascular disease, chronic renal failure, liver disease, or chronic obstructive pulmonary disease (COPD). Overall, the median serum CRP concentration on admission was 174 mg/l (interquartile range 147-390) (table 1). Slightly lower baseline CRP levels were observed in patients who had recieved outhospital antibiotic treatment (135.0 mg/l versus 184.0 mg/l; p=0.07) or outhospital treatment with inhalation steriods (146.0 mg/l versus 185.5 mg/l; p=0.09). No significant association between baseline CRP levels and demographic characteristics or the presence of comorbidity was observed (p>0.25). 232 (80.3%) of patients enrolled in the study received beta-lactam monotherapy as empiric 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 beta-lactam and macrolide antibiotics [18]. 10 (3.5%) patients received another empiric antibiotic therapy. Of those, 4 (0.6%) patients were initially treated with doxycyclin or erythromycin monotherapy because of suspicion for an atypical cause of pneumonia on admission. In 1 (0.3%) patient combination therapy with erythromycin and rifampicin was initiated because of a strong suspicion for a *L. pneumophila* infection.

In 122 (89.1%) of 137 patients with established etiology, empiric antibiotic treatment was considered appropriate. 20 (6.9%) patients had died by day 28 and 9 (3.1%) patients needed ICU admission during follow-up (table 1).

Etiology and CRP levels

An etiological diagnosis could be established in 137 (47.4 %) patients. *S. pneumoniae* was the most frequently indentified pathogen in 55 (19.0%) cases. Median baseline CRP concentrations were the highest in patients with a *S. pneumoniae* infection (278 mg/l; interquartile range 147-390), followed by *L. pneumophila* (247 mg/l;179-421), *H. influenzae* (214 mg/l; 168-313), *S. aureus* (187 mg/l; 115-330), Enterobacteriaciae (129.0 mg/l; 53-272), *C. pneumoniae* (115.5 mg/l; 57-317), *M. catharralis* 64.0 mg/; 49-165) and *M. pneumoniae* infections (49 mg/l; 27-228) (table 2a). Patients with multiple bacterial pathogens indentified had median admission CRP levels of 213.0mg/l. The etiology of these 12 cases is specified in table 2b. The median baseline CRP levels were significantly different among the causative pathogens ($p<0.01$ ANOVA). Patients with unknown etiology had a significantly lower median CRP concentration on admission than patients with established etiological diagnosis (140.5 mg/l versus 209.0 mg/l; $p<0.01$). 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 to patients with other etiologic diagnosis. The decline in CRP levels in day 0-3 was 38.6% in patients with *L. pneumophila* infection as compared to 32.9 % in patients with pneumonia of other etiology (mean difference 5.7%; $p=0.58$). However, in the second part of the first week of follow-up the decay in CRP was larger in patients with *L. pneumophila* infection (48.5%) as compared to others (28.5%) (mean difference 20.0, $p<0.01$).

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 the 3th day and in 210 (72.6%) patients on the 7th day of hospitalisation. The median CRP concentration was 97.5 mg/l (51-163) on day 3 and 31.0 mg/l (13-78) 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% (25^{th}-75^{th} percentile 5.3% - 65.5 %) within the first 3 days and 80.9% (25^{th}-75^{th} percentile 54.2% - 92.0%) within the first week of follow-up. In univariate analysis, patients treated with inappropriate empiric 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) (tabel 3a). 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 recieved inapproriate empiric 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 3b). 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 to develop early or late treatment failure but not statistically significant (table 4).

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 to 7 days of follow-up is suggestive of inappropriate empiric antibiotic therapy. Patients with a decline of <60% in CRP levels in 3 days or a decline of <90% in 7 days had about an four- to sevenfold increased risk of having recieved inapproriate antibiotic treatment. Since the limited evicence 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 measurement in follow-up of CAP are in line with the present findings [8-10]. Smith et al. studied the usefullness 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 ICU also showed that indentification of CRP patterns may be of value in follow-up of treatment [8]. Recently, Menendez et al. demonstrated that a persistent high CRP level on day 1 and 3 in follow-up of patients with mild to severe pneumonia was independently associated with a higher risk of treatment failure [10]. In our cohort, patients with an indequate decline in CRP had a higher risk of treatment failure too, however this was not statistically significant. These different results may be explained by differences in pneumonia severity of both study populations and adressing absolute CRP values at day 1 and 3 as compared to relative changes in CRP measured on day 3 and 7 in the present study.

In univariable assesment, a delayed decline in CRP levels was associated with a trend towards increased risk for mortality. However, after correction for pneumonia severity, patients' characteritics and clinical variables at baseline, a statiscal significant relation could not be established. A recent study did show 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 help in determing etiology of severe CAP, but the ability of CRP to differentiate in etiology of severe CAP is low [22]. As indicated by others and our results, 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. demonstrated that corticosteroids did not influence the time-depent decline of CRP levels [24]. However, according to our results, the use of steroids needs to be considered to interpret CRP levels in follow-up correctly. Concerning the influence of the causative pathogen on the decay of CRP, we observed a slower decline in CRP levels in the first three days of follow-up in *L. pneumophila* as compared to other pathogens. This may be due to inappropriate empirical treatment, however, all patients had legionella antigen test performed within 12 hours and patients with a positive Legionella antigen test received treatment for Legionella infection within 12 hours. Another explanation may be that *L. pneumophila,* as intracellular pathogen, causes a different host response to infection, characterized by prolonged and greater increases of CRP [25, 26]. According to these results, the causative pathogens needs to be taken into account 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. Results of the present study indicate that a delayed decline in CRP levels is related to inappropriate empiric antibiotic treatment. On the other hand, hypothetically 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.

Our study has two important limitations. First, the present study focused 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]. Second, we defined appropriate treatment as "at least one antibiotic covering all of the causative pathogens identified". However, the causative role in CAP of some bacteria isolated can be debated. When these isolates only represent colonisation of the respiratory tract, the association of a delayed decline and the risk of having received inappropriat therapy may be overestimated. Third, daily CRP measurements could have added some more information to our study. However, we designed our study in accordance with a previous study taking clinically relevant time points after admission [21].

In conclusion, consecutive CRP measurements are useful in the first week in follow-up of antibiotic treatment for severe CAP when taking the causative micro-organism and use of steroids into account. A delayed decline in CRP levels is associated with a higher risk of having received inappropriate antibiotic treatment.

Acknowledgment

Conflicts of interests: All authors no conflicts of interest.

Financial interests: None of the authors had financial relationships and affiliations relevant to the subject of this manuscript.

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Tables and figures

TABLE 1	Descriptive characteristics of the studycohort of 289 patients with severe community-acquired pneumonia*
Age (y)	69.7 ±13.8
Female	99 (34.3)
Pneumonia Severity Index (PSI) score	112.9 ±25.7
PSI class IV	198 (68.5)
PSI class V	52 (18.0)
APACHE II score	13.8 ±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 ±1,2
Respiratory rate (p/min)	26.7 ±8,7
Laboratory data	
Median C-reactive protein (mg/l) (interquantile range)	174 (147-390)
White blood cell count (109/l)	16.5 ±9.2
Antibiotic therapy	
Beta-lactam	232 (80.3)
Amoxicillin ± clavulanic acid	169 (58.5)
Cefalosporin (2^{nd} or 3^{rd} generation)	60 (20.7)
Ceftriaxone	47 (16.2)
Ceftazidime	12 (4.2)
Cefotaxime	1 (0.3)
Penicillin	3 (1.0)
Beta-lactam/ macrolide combination	47 (16.3)
Amoxicillin ± clavulanic acid + macrolide	32 (11.1)
Cefalosporin (2^{nd} or 3^{rd} generation) + macrolide	14 (4.8)
Ceftriaxone + macrolide	11 (3.8)
Ceftazidime + macrolide	2 (0.7)
Other	10 (3.5)
Outcome	
IC admissions during hospitalisation	9 (3.1)
28 day mortality	20 (6.9)

* Data are presented as mean SD or n (%), unless otherwise stated.
† Other antibiotics include cotrimoxazole (n=2, 0.7%); beta-lactam and ciprofloxacin (n=2, 0.7%); doxycyclin (n=2, 0.7%); erytromycin and rifampicin (n=1, 0.3%); levofloxacin (n=1, 0.3%); erythromycin (n=2, 0.6%)

TABLE 2a **Median baseline CRP values according to etiology in patients with severe community-acquired pneumonia**

	No	%	Median CRP level	Range	Inter-quartile 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 catharralis	5	1.7	64.0	197	49-165
Other pathogens◊	11	3.8	185.0	403	117-231
Multiple bacterial pathogens	12	4.2	213.0	672	83-404
Unknown etiology	152	52.6	140.5	576	56-293

* determined by sputum culture (n=19), bloodculture (n=24) or urinary antigen test (n=20), in 8 cases *S.pneumoniae* was determined by multiple tests.
† determined by sputum culture (n=6) or bloodculture (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%)
◊ Other pathogens include: *Pseudomonas aeruginosa* (n=2, 0.7%)*; Streptococcus agalactiae* (n= 3, 1.0%); *Haemophilus parainfluenzae* (n=2, 0.7%); *Staphylococcus hominis* (n=1, 0.3%); *Proprionibacter acnes* (n=1, 0.3%); Gram positive spp (n=2, 0.7%).

TABLE 2b **Etiology of the 12 cases with multiple bacterial pathogens specified**

No	Etiology pathogen 1	pathogen 2
1	*Streptococcus pneumoniae* (blood)	*Haemophilus influenzae* (sputum)
2	*Streptococcus pneumoniae* (UAT)	*Enterobacter spp* (sputum)
3	*Streptococcus pneumoniae* (sputum)	*Eschericia Coli* (sputum)
4	*Streptococcus pneumoniae* (sputum, blood)	*Chlamydia pneumoniae*
5	*Streptococcus pneumoniae* (blood, UAT)	*Chlamydia pneumoniae*
6	*Haemophilus influenzae* (sputum)	*Chlamydia pneumoniae*
7	*Haemophilus influenzae* (sputum)	*Legionella pneumophila*
8	*Haemophilus influenzae* (sputum)	*Staphylococcus hominis* (blood)
9	*Mycoplasma pneumoniae*	*Eschericia Coli* (sputum)
10	*Chlamydia pneumoniae*	*Staphylococcus aureus* (sputum)
11	*Legionella pneumophila*	*Corynebacterium difteria* (blood)
12	*Legionella pneumophila*	*Streptococcus group B* (blood)

* UAT= urinary antigen test

TABLE 3a **Appropriateness of empiric antibiotic treatment and normalisation patterns of CRP**

	Unknown etiology n=152 (52.6%)	Patients with established etiology n=136 (47.4%)			
		Received appropriate antibiotic treatment n=112 (38.8%)	Received inappropriate antibiotic treatment n=25 (8.7%)	Mean difference* (95%CI)	P value
Median CRP values (interquartile range)					
Day 0 (baseline)	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(±SD)					
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

* The mean difference (95% CI) in percentage decline in CRP among patients with appropriate and inappropriate antibiotic treatment (estblished etiolgy) is displayed.

TABLE 3b **Multivariate analysis of delayed normalisation of CRP and the risk for 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 etiology

#The displayed odds ratio's are adjusted for patient characteristics (age, gender, co-morbid illnesses), pneumonia severity index score, symptoms and signs of pneumonia (cough, sputum production, sore throat, dyspnea, chest pain, hemoptoe, confusion, blood pressure, respiratory rate, pulse, oxygen saturation)

TABLE 4 **Multivariate analysis of delayed normalisation of 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 ratio's are adjusted for patient characteristics (age, gender, co-morbid illnesses), pneumonia severity index score, symptoms and signs of pneumonia (cough, sputum production, sore throat, dyspnea, chest pain, hemoptoe, confusion, blood pressure, respiratory rate, pulse, oxygen saturation)

Figure1