

## Procalcitonin-Guidance of Antibiotic Therapy in Community-

### Acquired Pneumonia - A Randomized Trial

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## **ABSTRACT**

**Rationale:** In patients with community-acquired pneumonia, guidelines recommend antibiotic treatment for 7 to 21 days. Procalcitonin is elevated in bacterial infections, and its dynamics have prognostic implications.

**Objective:** To assess procalcitonin guidance for the initiation and duration of antibiotic therapy in community-acquired pneumonia.

**Methods:** In a randomized intervention trial, 302 consecutive patients with suspected community-acquired pneumonia were included. Data were assessed at baseline, at days 4, 6 and 8 and after 6 weeks. The control group (n=151) received antibiotics according to usual practice. In the procalcitonin group (n=151), antibiotic treatment was based on serum procalcitonin concentrations as follows: strongly discouraged <0.1 µg/L; discouraged <0.25; µg/L; encouraged >0.25 µg/L; strongly encouraged >0.5 µg/L. Primary endpoint was antibiotic use; secondary endpoints were measures of clinical, laboratory and radiographic outcome.

**Results:** At baseline, both groups were similar with regards to clinical, laboratory and microbiology characteristics, and Pneumonia Severity Index (PSI). Procalcitonin-guidance reduced total antibiotic exposure (relative risk, 0.52; 95 % confidence interval [CI] 0.48-0.55; P<0.001), antibiotic prescriptions on admission (85 versus 99 %; P<0.001) and antibiotic treatment duration (median, 5 versus 12 days; P<0.001) compared to patients treated according to guidelines. After adjustment for PSI, the hazard ratio of antibiotic discontinuation was higher in the procalcitonin group than in the control group (3.2, 95 % CI 2.5 to 4.2). Outcome was similar in both groups with an overall success rate of 83 %.

**Conclusions:** Procalcitonin-guidance substantially reduces antibiotic use in community-acquired pneumonia. These findings may have important clinical and public-health implications.

**Key words:** community-acquired pneumonia, antibiotic therapy, procalcitonin

**Word count:** 247

## INTRODUCTION

Community-acquired pneumonia (CAP) is the major infection-related cause of death in developed countries (1, 2). Approximately 10 to 20 % of hospitalized patients with CAP have to be admitted to the intensive care unit (ICU), where 20 to 50 % of them will ultimately die (3, 4).

CAP is characterized by recently acquired respiratory symptoms and by an infiltrate on chest radiograph, signs which are unspecific. In CAP respiratory symptoms can be ambiguous, and especially elderly patients may present without fever (5). The differential diagnosis of clinically suspected CAP includes infectious (bacterial and non-bacterial) and non-infectious causes.

In bacterial CAP, prompt initiation of antibiotic therapy is pivotal, as a delay of more than 4 hours can be associated with an increased mortality (6). The optimal duration of antibiotic therapy in CAP is unknown (7). Most likely, it varies from patient to patient. Current guidelines recommend antibiotic courses of 7 to 21 days, depending on illness severity and type of pathogen (2, 8, 9). However, adherence to guidelines is variable (10, 11) and physicians tend to treat longer, especially in elderly patients with comorbidities and patients with severe CAP (12, 13). Duration of antibiotic therapy can be guided by clinical signs such as defervescence, decrease of sputum production and coughing, or improvement of general condition. However, the interpretation of the clinical response lacks standardization and validation and is prone to interobserver variability (14).

A novel approach to estimate the presence of an infection and its treatment response is the use of biomarkers (15, 16). Circulating levels of calcitonin precursors, including procalcitonin, are elevated in bacterial infections (17, 18). As a prototype of a “hormokine” mediator, procalcitonin can follow either a classical hormonal expression pathway or, alternatively, in the presence of an infection, a cytokine-like expression pathway (18, 19). The ubiquitous release of procalcitonin during infections is induced either directly by microbial toxins (e.g. endotoxin) and / or indirectly by humoral factors (e.g. interleukin-1 $\beta$ , tumor necrosis factor- $\alpha$ , interleukin-6) or the cell-mediated host response (19). This induction can be attenuated by cytokines released during viral infections (e.g. interferon- $\gamma$ ) (16, 19). Importantly,

procalcitonin is a pivotal mediator in systemic infections and immunoneutralization of hyperprocalcitoninemia improves survival in several animal models of sepsis (18-23).

As diagnostic marker, procalcitonin guidance markedly and safely reduced antibiotic prescriptions in a mixed population with lower respiratory tract infections using a sensitive assay (13). The dynamics of procalcitonin levels have prognostic implications, as persistently elevated levels are associated with adverse outcome (24). Conversely, decreasing procalcitonin levels suggest a favorable outcome, usually showing a log-linear drop-off and a half life of 20 to 24 hours (18). In this randomized intervention trial, we assessed the capability of procalcitonin-guidance to shorten antibiotic duration in patients with all severity levels of CAP admitted to the emergency department. We hypothesized that procalcitonin guidance could significantly shorten antibiotic duration with a similar clinical and laboratory outcome (25, 26).

## **METHODS** (word count 1114)

### **Setting and Study Population**

This is a randomized, controlled open intervention trial in patients with all severities of CAP admitted to the emergency department (27). We compared antibiotic therapy in patients treated according to usual practice (control group) with patients in whom antibiotic treatment was guided by serum procalcitonin levels (procalcitonin group). The study was approved by the institutional review board and registered in the Current Controlled Trials Database as “ProCAP”-Study [ISRCTN04176397]. Written informed consent was obtained from all included patients or their legal representatives. All data were held and analyzed by the authors.

All patients with suspicion of CAP admitted from November 2003 through February 2005 to the University Hospital, Basel, Switzerland, a 950-bed tertiary care hospital, were assessed for eligibility (**Figure 1**). Included were adult (>18 years) patients with CAP as principal diagnosis on admission, defined by a new infiltrate on chest radiograph and the presence of one or several of the following acute respiratory sign or symptom, cough, sputum production, dyspnea, core body temperature >38.0° C, auscultatory findings of abnormal breath sounds and rales and leukocyte count >10 or <4 x 10<sup>9</sup> cells L<sup>-1</sup> (2). Excluded were patients with cystic fibrosis or active pulmonary tuberculosis; hospital-acquired pneumonia and severely immunocompromised patients.

Patients were examined on presentation to the emergency department by a resident supervised by a board-certified specialist in internal medicine. Baseline assessment included clinical data and vital signs, comorbid conditions, and routine blood tests. A senior radiologist, blinded to group assignment and laboratory findings, reviewed all chest radiographs. The procalcitonin level was communicated to the physician in charge with corresponding protocol-derived recommendations regarding antibiotic use in the procalcitonin group. The Pneumonia Severity Index (PSI) was calculated (28). The patients' functional status was assessed using a visual analogue scale, ranging from 0 (feeling extremely ill) to 100 (feeling completely healthy), and by a quality of life questionnaire for patients with respiratory illnesses (13).

## Measurement of Serum Procalcitonin

Measurements were done using a time-resolved amplified cryptate emission (TRACE) technology assay (Kryptor<sup>®</sup> PCT, Brahms AG, Hennigsdorf, Germany) (13) with a functional assay sensitivity of 0.06 µg/L, about four-fold above mean normal levels (29). Assay time is less than 20 minutes and results were routinely available within one hour. According to the manufacturer, the prize per procalcitonin measurement in Switzerland is approximately 15\$ and 30\$ including reagents, technicians' time for processing specimens, and purchase and maintenance of durable lab equipment, respectively. A fee of around around 50\$ is currently reimbursed by Swiss health insurances and sickness funds.

## Antibiotic Treatment

On admission, patients were randomly assigned to one of the two treatment assignments by sealed, opaque envelopes. In the control group, antibiotic therapy was chosen based on usual practice-guidelines (2, 8, 9). The treating physician was unaware of serum procalcitonin levels (9, 30).

In the procalcitonin group, the antibiotic treatment was guided by serum procalcitonin levels. Thereafter, the physician in charge was advised to classify the patients into four groups, according to the probability of bacterial infection. This classification and the cut-offs used were derived by calculating multilevel likelihood-ratios and validated in a previous study (13). A procalcitonin level of <0.1 µg/L suggested the absence of bacterial infection and the initiation or continuation of antibiotics was strongly discouraged. A procalcitonin level between 0.1 and 0.25 µg/L indicated that bacterial infection was unlikely, and the initiation or continuation of antibiotics was discouraged. A procalcitonin level from 0.25 to 0.5 µg/L was considered to indicate a possible bacterial infection and the initiation or continuation of antibiotic therapy, respectively, was encouraged. A procalcitonin level of >0.5 µg/L strongly suggested the presence of bacterial infection and antibiotic treatment and continuation was strongly encouraged. Reevaluation of the clinical status and measurement of serum procalcitonin levels was recommended after 6–24 h in all patients in whom antibiotics were withheld. Procalcitonin levels were reassessed on days 4,

6 and 8. Antibiotics were discontinued using the procalcitonin cut-offs defined above. In patients with a very high procalcitonin value on admission (e.g.,  $>10 \mu\text{g/L}$ ), discontinuation of antibiotics was already encouraged if levels decreased to levels  $< 10\%$  of the initial value (e.g.  $1 \mu\text{g/L}$ , instead of  $<0.25 \mu\text{g/L}$ ).

## **Outcome Measures**

The primary endpoint was total antibiotic use (i.e. antibiotic prescription [percentage] and duration [patient days]). The incidence density ratio of antibiotic exposure was calculated as total antibiotic exposure time divided by total follow-up time, until week 6 [expressed as relative risk (RR)].

Appropriateness of initial antibiotic therapy was defined as previously described (31). Secondary endpoints were measures of laboratory and clinical outcome.

Primary and secondary endpoints were recorded on days 4, 6, and 8 and at follow-up after 6 weeks, respectively. At the follow-up visit after 6 weeks, the outcome was evaluated by clinical, laboratory, radiographic and microbiological criteria. Cure was defined as resolution of clinical, laboratory and radiographic signs of CAP. Improvement was defined as reduction of clinical signs and symptoms, improvement of laboratory findings and the reduction of the number or intensity of radiographic signs of CAP. Treatment success represented the sum of the rates for cure and improvement. Treatment failure included death, recurrence, relapse or persistence of clinical, laboratory and radiological signs of CAP, and patients lost to follow-up.

## **Statistical Analysis**

Discrete variables are expressed as counts (percentage) and continuous variables as means  $\pm$  standard deviation (SD). Endpoints were predefined and analyzed on the basis of intention-to-treat. A study sample of 150 patients in each group gave the study a power of 95 % to detect a 30 % reduction in antibiotic exposure from 10 to 7 days per patient assuming a two-tailed test, a 1 % level of significance and a SD of 6 days in both groups. This sample size gave the study a power of 74 % to detect a 10 % increase in the combined treatment failure and complication rate (from 10 to 20 %) using the

procalcitonin algorithm with a one-sided alpha-value of 0.05. Comparability of the control group and the procalcitonin group was analyzed by  $\chi^2$  test and non-parametric Mann-Whitney U test. The time to discontinuation of antibiotic treatment was compared between the two study groups by use of the log-rank test. Using Cox proportional hazards regression analysis, we estimated the rate of antibiotic treatment discontinuation, after adjustment for the PSI class. We performed crude cost and sensitivity analyses to estimate direct costs associated with changes of repeated measurements of procalcitonin and antibiotic therapy. Indirect costs (e.g. adverse events, emergence of antibiotic resistance and need of high-priced second-line antibiotics for future treatment) were not considered. The economic analysis was conducted in Swiss Francs and then converted to US\$ using the average actual currency conversion rate during the trial period.

## RESULTS

### Baseline characteristics of the patients

During the study period, 404 consecutive patients with CAP were screened for eligibility. Of these, 302 were eligible and randomized into the procalcitonin group (n=151) or into the control group (n=151) (**Figure 1**). Baseline characteristics on admission were similar in both groups (**Table 1**). In both groups, fever  $>38^{\circ}\text{C}$  was present in 60% of CAP patients overall and in 55% in those with positive blood cultures. The temperature was not higher in CAP patients with positive cultures ( $38.4^{\circ}\text{C}$  [37.7-38.9]) as compared to patients with negative blood cultures ( $38.4^{\circ}\text{C}$  [37.7-39.2]  $P=0.6$ ). The classic triad of cough, fever and dyspnea, as reported by the patients, was present in 58 % of cases of both groups. One fifth of the patients had already received antibiotics at the time of randomization, without a significant difference between the groups. Overall, 87 % of patients (87 % in the control and 88 % in the procalcitonin group;  $P = 0.73$ ) had relevant co-morbidities. After diagnosis of CAP, 3 % of all patients were discharged on the same day. On the day of admission, serum procalcitonin levels were  $<0.1 \mu\text{g/L}$  in 28 patients (17 in the control group and 11 in the procalcitonin group;  $P = 0.23$ ),  $0.1$  to  $0.249 \mu\text{g/L}$  in 60 patients (28 and 32;  $P = 0.56$ ),  $0.25$  to  $0.49 \mu\text{g/L}$  in 55 patients (27 and 28;  $P = 0.88$ ), and  $\geq 0.5 \mu\text{g/L}$  in 159 patients (79 and 80;  $P = 0.91$ ). Compiling both groups, 86 of 302 patients (28%) had procalcitonin levels  $<0.25\mu\text{g/L}$  on admission, 125 of 265 (47%) on day 4, 146 of 240 (61%) on day 6 and 123 of 176 on day 8 (70%). In 5 (10%) of the patients with without antibiotic therapy based on an initial procalcitonin level  $<0.25\mu\text{g/L}$ , antibiotics were started when procalcitonin levels increased to  $>0.25 \mu\text{g/L}$  at the follow-up after 6 hours. Only in 2% of these patients, procalcitonin at the follow-up measurement after 6 hours increased to  $>0.5\mu\text{g/L}$ . All patients in whom antibiotics were withheld on admission based on low procalcitonin levels had ultimately a favorable outcome. Median (interquartile range) procalcitonin levels in patients pretreated with antibiotics was 0.5 (0.2-1.6), which was not significantly different from patients without antibiotic pretreatment (0.5 (0.2-2.4)).

## Microbiology

In patients with CAP a causative microorganism was identified in 80 patients (28 %). The rate of positive cultures was similar in the control group as compared to the procalcitonin group (25 % vs. 28 %). In both groups the most frequently isolated microorganism was *Streptococcus pneumoniae* (14 % in both groups), followed by *Pseudomonas aeruginosa* (3 % in both groups), *Haemophilus influenzae* (1 % vs. 3 %), *Klebsiella pneumoniae* (1 % vs. 3 %), and *Legionella pneumophila* (2 % vs. 1 %).

## Primary Endpoint - Antibiotic use

In 15 % of the patients in the procalcitonin group and in 1 % in the control group, antibiotics were withheld on admission ( $P < 0.001$ , **Figure 2 A**). After adjustment for the PSI class, the rate of antibiotic discontinuation was significantly higher in the procalcitonin group than in the control group (hazard ratio, 3.2, 95 % confidence interval [CI], 2.5 to 4.2) (**Figure 2 B**). Consequently, the total rate of antibiotic exposure decreased in patients with procalcitonin guidance (relative risk, 0.52; 95 % CI, 0.48-0.55;  $P < 0.001$ ).

As compared to the control group, antibiotic duration was reduced by 55% in the procalcitonin group (median, 12 versus 5 days,  $P < 0.001$ , **Figure 3**). Procalcitonin levels increased with increasing severity of CAP, as defined by the PSI score ( $p < 0.001$ ). Patients with a mild CAP, as defined by a PSI score I-III had significantly lower ProCT levels (median 0.3, interquartile range 0.1-1.1) as compared to patients with CAP and a PSI score IV and V (0.7, 0.3-3.3,  $p < 0.001$ ). Only in the procalcitonin group but not in the control group, patients with a high PSI class IV and V had a significantly longer duration of antibiotic treatment as compared to patients with a low PSI class I to III (**Figure 3**). Equally, only in the procalcitonin group mean antibiotic duration in patients with positive blood cultures was significantly longer as compared to patients with negative blood cultures (**Figure 3**). Duration of antibiotic therapy was similar in patients with bacteremia in the control and the procalcitonin group (**Table 2**). Antibiotic duration was influenced by a positive culture from respiratory specimens in the control group ( $17.7 \pm 10.7$  and  $12.3 \pm 5.6$  days,  $P = 0.03$ ), in contrast to the procalcitonin group ( $6.2 \pm 5.8$  and  $4.8 \pm 3.6$  days,  $P = 0.52$ ).

Initial empiric antibiotic therapy was appropriate in 97 %, similar in both groups (**Table 2**), based on microbiology results and local resistance patterns. Combination therapy with two or more antibiotics was used in 34%, similar in both groups. Administered antibiotics included amoxicillin-clavulanate (control group 122 [82 %], procalcitonin group 102 [80 %]), clarithromycin (55 [37 %], 44 [35 %]), ceftriaxone (37 [25 %], 20 [16 %]), and other agents (49 [33 %], 42 [33 %]), with a similar distribution in both groups.

Procalcitonin levels in patients pretreated with antibiotics were 0.5 (0.2-1.6) µg/L, which was not significantly different from patients without antibiotic pretreatment (0.5 (0.2-2.4) µg/L). Antibiotic treatment including macrolides did not affect the change of procalcitonin levels during the course of CAP.

On admission, antibiotics were given to one patient (1 %) with end-stage pulmonary fibrosis and a procalcitonin level <0.1 ng/ml and in 19 patients (13 %) with a procalcitonin level 0.1 to 0.25 µg/L (6, severe chronic obstructive pulmonary disease; 2, end-stage pulmonary fibrosis; 11, other severe comorbidities). Antibiotics were not withdrawn after 4, 6 or 8 days against the recommendation of the algorithm in 8 % of patients (5, severe chronic obstructive pulmonary disease; 4, lack of clinical improvement; 1, persistent fever due to cryptogenic organizing pneumonia; 1, request of the patient; 1, communication error).

Median costs of antibiotics in the procalcitonin group were \$100 per patient, as compared to \$190 per patient in the control group (**Table 3**). In the procalcitonin group, the marker was measured 529 times (151 on admission, 21 at follow-up after 6 to 24h, 139 on day 4, 128 on day 6, 90 on day 8), thus 3.5 times per patient. Thereafter, the use of procalcitonin for antibiotic stewardship in CAP would become cost-effective below 25\$ per analysis.

### **Secondary Endpoints - Clinical and Laboratory Outcome**

In both groups, laboratory and clinical measures of outcome were similar at baseline (**Table 2**), during the early course of the disease (day 4, 6 and 8, data not shown) and at follow-up after a mean of  $6.9 \pm 1.9$  weeks. Of the patients who completed the follow-up visit after 4 to 6 weeks, 91% had a follow-up

measurement on day 4, 84% a follow-up measurement on day 6 and 61% a follow-up measurement on day 8. There was a gradual decline of procalcitonin levels (median [interquartile range]) from admission (0.5 [0.2-2.2]), to day 4 (0.3 [0.1-0.9]), day 6 (0.2 [0.1-0.4]), and day 8 (0.1 [0.09-0.3]), which was similar in both groups.

The final course of CAP (i.e., failure or success) as determined 4-6 weeks after admission was similar in both groups. The percentage and cause of readmission was comparable in both groups. Similarly, the number of patients who received any antibiotics during long term follow-up was comparable in both groups.

On admission, patients who died during the course of the study had significantly higher levels of procalcitonin as compared to patients who survived (median [interquartile range] 0.7 [0.4-3.0] and 0.45 [0.2-2.0], respectively,  $P=0.02$ ), higher mean PSI ratings ( $124.3 \pm 29.2$  and  $95.9 \pm 34.7$ , respectively,  $P<0.001$ ), and a lower visual analogue scale ( $31.1 \pm 18.8$  and  $41.8 \pm 20.4$ , respectively,  $P<0.001$ ). C-reactive protein levels and leukocyte counts were similar in patients who died and patients who survived (153 [93-204] vs 126 [63-211] mg/dl,  $p=0.57$ ). On day 4, both, procalcitonin and CRP levels were higher in non-survivors as compared to survivors (median [interquartile range] 0.72 [0.25-3.29] vs 0.25 [0.11-0.87],  $p=0.002$  and 117 [85-183] vs 60 [30-117] mg/dl,  $p=0.002$ ). Deaths in the two groups were due to respiratory failure (8 in the control group / 5 in the procalcitonin group), cardiac failure (6 / 5), septic shock (2 / 3), tumor (3 / 3), multiorgan failure (0 / 2), and intracerebral hemorrhage (1 / 0). Eighteen of the 20 deceased patients in the control group had procalcitonin levels  $>0.25 \mu\text{g/L}$  at admission and 2 had procalcitonin levels between 0.1 and  $0.25 \mu\text{g/L}$ . All were treated with antibiotics on admission. All 18 patients who died in the procalcitonin group were treated with antibiotics on admission, 17 based on high procalcitonin levels  $>0.25 \mu\text{g/L}$  and one patient with a procalcitonin value of  $0.20 \mu\text{g/L}$ . Initial procalcitonin levels in patients with pleural effusion were (median, [IQ range]) 1.0 [0.2-5.3] as compared to patients with empyema (0.9 [0.2-3.4],  $p=0.4$ ). The clinically and radiologically documented recurrence rate was 2.6 % in both groups.

## DISCUSSION

This is the first randomized trial investigating guidance of antibiotic treatment duration in CAP by a laboratory test. Procalcitonin-stewardship markedly reduced antibiotic exposure in patients with CAP, mainly by individually reducing the duration of antibiotic courses from a median of 12 to 5 days. In the procalcitonin group antibiotic courses were markedly shorter as suggested by current guidelines. Measures of clinical and laboratory outcome were similar in both groups.

The use of procalcitonin improves the accuracy of the clinical diagnosis of sepsis (16, 24). For this purpose it is more helpful than C-reactive protein and other laboratory markers (17, 32). Circulating procalcitonin levels correlate with the clinical course of a systemic infection and its dynamics has prognostic implications (33). Accordingly, in 2005 the Food and Drug Administration approved procalcitonin in conjunction with other laboratory markers to aid in the risk assessment of critically ill patients with sepsis. Limits to the use of procalcitonin as a biomarker have been recently reviewed (16, 34). Clinically apparent infections are a sequel of complex and variable interactions between host immune response, microbes and their toxins. Obviously, any infection is far too complex to be reduced to a single cut-off of any surrogate marker. Therefore, we propagated and validated the use of *cut-off ranges* for antibiotic stewardship (13, 16). This was based on the principle that the likelihood for a bacterial etiology of an infection increases gradually with increasing procalcitonin levels. Conversely, systemic levels of procalcitonin may be less helpful in the diagnosis of the presence or the development of localized infections. Although the overall number of patients with encapsulated empyema in this study was low, several of these patients presented with low procalcitonin level.

Herein we extend the concept of antibiotic stewardship by procalcitonin from a heterogeneous group of patients with lower respiratory tract infections to a larger cohort of patients with suspected CAP (13). These patients may suffer from a severe bacterial infection and are more likely to experience an adverse outcome compared to patients with any type of respiratory tract infection. Procalcitonin appears to be a more reliable measure for individual tailoring and early discontinuation of antibiotic therapy as compared to routinely used clinical and other laboratory parameters. For example, only in the

procalcitonin group duration of antibiotic courses was adapted to the severity of CAP. The presence of fever is an important clinical sign indicating infection. However, defeverescence is of limited value to stop antibiotic therapy in view of the up to 40 % of patients with CAP who present without fever. Similarly, in over 70 % of patients with CAP of presumed bacterial origin the causative microbe cannot be identified (13, 35-37). Therefore, culture results are not considered central to the clinical care of this infection. This wide ambiguity of clinical symptoms and the high rate of negative culture results could explain the reluctance to stop antibiotic therapy early in the control group (35). Conversely, especially in bacteremic patients, CAP is associated with adverse outcome and, thus, longer antibiotic courses are recommended (38-40). Accordingly, in the procalcitonin group antibiotic therapy was longer in bacteremic patients with a median duration of more than ten days.

In bacterial CAP, delayed initiation of antibiotic therapy can be associated with an increased mortality (6). Therefore, in the emergency management of suspected CAP antibiotic therapy is rapidly initiated in all patients. The presence of non-bacterial diseases is usually suspected only after failure of antibiotic therapy, with the ensuing risks related to untreated, potentially life-threatening non-bacterial disease (41). In self-limiting viral infections, cure of CAP under antibiotic therapy may be falsely considered as a proof of bacterial etiology. In the procalcitonin group, antibiotics were withheld in 15 % of the patients with suspected CAP based on low procalcitonin levels, confirming previous findings (13). The uneventful course strongly argues against the presence of a clinically relevant bacterial infection in these patients. If a patient shows an infiltrate on chest radiograph in the presence of acute respiratory symptoms and repetitively low procalcitonin levels, clinicians may consider “watchful waiting” or early discontinuation of antibiotic therapy and actively seek an alternative diagnosis to bacterial pneumonia, including viral pneumonia, pulmonary embolism, malignancy, cryptogenic organizing pneumonia and congestive heart failure, among others (42). Conversely, in patients with diagnostic ambiguities the finding of procalcitonin levels of  $>0.25$  to  $>0.5$   $\mu\text{g/L}$  supports the clinician in his diagnosis of CAP.

Previous attempts to shorten antibiotic therapy in CAP used defined treatment regimens (e.g., 5 versus 10 days) and excluded patients with severe pneumonia and a PSI score  $>130$  (43, 44).

Azithromycin was also used for shorter antibiotic courses in CAP (45, 46). However, a therapy of three to five days with a long-acting macrolide is arguably the equivalent of a longer course for another drug. Furthermore, sustained subinhibitory antibiotic concentrations represent a selective pressure for colonizing, resistant bacteria (47).

Several limitations merit consideration. First, this study was an open intervention trial, where clinicians knew that their treatment decisions were observed. Moreover, the treating physicians may have learned from their experience with procalcitonin testing and improved their clinical judgment. Although we cannot control for these biases, Hawthorne and spill-over effects, if present, would be conservative for outcomes such as the antibiotic prescription rate and the duration of antibiotic therapy and would bias the results towards null.

Second, in our cohort of predominantly elderly CAP patients with a high rate of comorbidities, length of hospitalization was similar in the two groups. One might argue that once antibiotics are discontinued hospital discharge should be safe. However, we did not intervene with patient management besides duration of antibiotic therapy to minimize a potential bias. This assured a similar surveillance for complications during the early course of the infection in both study groups.

Third, due to the sample size, our study had limited powered to proof the safety of the procalcitonin strategy in clinical care and to assess the optimal duration of antibiotic therapy for different types of bacteria, especially atypical pathogens, and resistance patterns, respectively. Overall, the complication rate was similar in both groups and comparable to previous findings (13, 41, 48).

Forth, the mean duration of antibiotic therapy of 13 days in the control group appears rather long, as more recent guidelines recommend a duration of antibiotic therapy in CAP of 7 to 10 days (2, 8, 9). However, we aimed to mirror usual care in clinical routine in the control group. Physicians tend to overtreat patients, and 10 to 14 days is the usual length of treatment, especially in severely sick patients who require admission to the hospital (12). In patients with PSI classes I-III procalcitonin-guidance shortened the duration of antibiotic therapy safely to a mean of 4 days, well below the most recent guideline recommendation.

Fifth, our results mainly refer to hospitalized patients; whether procalcitonin guidance can reduce antibiotic use in the outpatient setting, is currently being investigated (51).

One might argue that antibiotic duration in CAP could also be reduced using stewardship with CRP. To the best of our knowledge, no such a study has been done. CRP is an acute-phase reactant which proved useful in various clinical settings. However, the reliability of CRP for guidance of antimicrobial therapy is hampered by its protracted response with late peak levels, a suboptimal specificity, especially in patients with severe inflammation and infection and a reduced increase in patients with steroid or other immunosuppressive therapies (16, 49, 50). Thus, the routine use of standard laboratory tests like CRP or white blood cell count seems to be motivated more by the low cost, easy availability and historic practice rather than by its diagnostic accuracy. Costs of procalcitonin measurement and potential savings in consumption of hospital resources are to be considered to establish cost-effectiveness in a public health perspective. It could become cost-effective either by reducing the number of measurements, by lowering the costs per analysis, in settings with high costs of antibiotic agents, considering potential effects on hospitalization rate and duration, or including short-term cost for adverse events, such as diarrhea, and long-term cost for a possible increase in antibiotic resistance and its monitoring.

Respiratory tract infections are responsible for more than half of antibiotic prescriptions (52). Thus, if applied on a larger scale a markedly reduced antibiotic use by procalcitonin-guidance might have important public health implications. A trial investigating the impact of procalcitonin guided antibiotic-therapy in acute respiratory tract infections in the primary care setting is ongoing (51). Reduced costs, fewer side effects, improved patient compliance, and, most importantly, a reduced selective pressure for the emergence of resistance favor shorter courses of antibiotic therapy (9, 53, 54).

In conclusion, procalcitonin-guidance leads to a more judicious antibiotic use, mainly by individual tailoring and earlier discontinuation of antibiotic therapy in patients with CAP. The vast majority of eligible patients agreed to participate in this study, assuring applicability of the proposed approach under “real life” conditions. To evaluate the external validity of our concept, larger multi-center intervention trials are encouraged. Thereby, procalcitonin has to be repeatedly measured by a sensitive assay and it

should never be used as a substitute for a careful clinical assessment during the entire course of the disease (29).

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## **LEGENDS TO THE FIGURES**

### **Figure 1 Trial Profile**

Community-acquired pneumonia denotes community-acquired pneumonia, HAP healthcare-associated pneumonia, ITT intention to treat.

### **Figure 2**

#### **A Percentage of Patients on Antibiotic Therapy in the Control and the Procalcitonin Group on Admission and During the Course of the Disease**

AB denotes antibiotics, d days

#### **B Cumulative Frequency Distribution Curve for the Time to Discontinuation in Patients in whom Antibiotic Therapy was Prescribed**

Patients in the procalcitonin group were compared to those in the control group.

### **Figure 3 Antibiotic Duration**

The duration of antibiotic courses in the procalcitonin group and in the control group is given overall (upper panel), in patients classified according to pneumonia severity index risk class (middle panel) and blood culture result (lower panel), respectively. Squares denote mean, boxes SEM and whiskers  $1.96 \times$  SEM. Results of the procalcitonin group are shown in brown, results of the control group in blue.

**Table 1** Baseline Characteristics of the 302 Patients Randomized to Control Group or Procalcitonin group\*

<b>Characteristic</b>	<b>Procalcitonin group (N=151)</b>	<b>Control group (N=151)</b>
<b>Age - years</b>	70 ± 17	70 ± 17
<b>Male sex - no. (%)</b>	94 (62)	93 (62)
<b>Smoking status</b>		
- Current smoker – no. (%)	34 (23)	39 (26)
- Packyears in current and ex-smokers	42 ± 27	38 ± 20
<b>Antibiotic pretreatment (%)</b>	27 (18)	34 (23)
<b>Coexisting illnesses - no. (%)</b>		
- Coronary artery disease	49 (33)	48 (32)
- Hypertensive heart disease	42 (28)	36 (24)
- Congestive heart failure	7 (5)	9 (6)
- Peripheral vascular disease	11 (7)	9 (6)
- Cerebrovascular disease	8 (5)	8 (5)
- Renal dysfunction	36 (24)	45 (30)
- Liver disease	12 (8)	19 (13)
- Diabetes mellitus	32 (21)	29 (19)
- Chronic obstructive pulmonary disease	44 (29)	32 (21)
- Neoplastic disease	25 (17)	23 (15)
<b>History - no. (%)</b>		
- Cough	134 (89)	136 (90)
- Sputum	108 (72)	113 (75)
- Dyspnea	118 (78)	111 (74)
<b>Examination – no. (%)</b>		
- Rales	137 (91)	134 (89)
- Body temperature - °C	38.4 ± 1.1	38.4 ± 1.1
- Oxygen saturation - %	92 ± 5	91 ± 6
- Respiratory rate – per min	24 ± 7	23 ± 7
- Heart rate – per min	96 ± 20	97 ± 19
- Systolic blood pressure – mm Hg	130 ± 26	130 ± 24
<b>Laboratory findings</b>		
- Procalcitonin – µg/L median (IQ range)	0.57 (0.2-2.5)	0.44 (0.2-1.9)
- C-reactive protein (mg/L) median (IQ range)	111 (57-204)	152 (72-212)
- Leukocyte count (x10 <sup>9</sup> /L)	13.7 ± 6.7	13.4 ± 6.6
<b>Quality of Life score – pts †</b>	40 ± 13	39 ± 13
<b>Visual analogue scale - % ‡</b>	43 ± 20	39 ± 21
<b>Imaging – no. (%)</b>		
- Pleural effusion	17 (11)	20 (13)
- Multilobar pneumonia	24 (16)	29 (19)
<b>PSI - points</b>	99.7 ± 36.1	99.2 ± 34.5
<b>PSI class – no. (%)</b>		
- I, II and III	54 (36)	66 (44)
- IV	68 (45)	62 (41)
- V	29 (19)	23 (15)

\*Plus-minus values are means  $\pm$  SD. P values of all comparisons between the control group and the procalcitonin group were not significant as assessed by  $\chi^2$  test or non-parametric Mann-Whitney U test, as appropriate. Because of rounding, percentages may not sum to 100. The conversion factor for procalcitonin is as follows:  $\mu\text{g} / \text{L} \times 0.161 = \text{nmol/l}$ .

no means number, min means minute, mm Hg means millimeter Hg, IQ means interquartile.

† Higher quality of life scores indicate worse quality of life

‡ The visual analogue scale ranged from 0 (feeling extremely ill) to 100 (feeling completely healthy)

**Table 2.** Outcome and Antibiotic use in Patients with community-acquired pneumonia According to the Treatment Algorithm\*

	<b>Procalcitonin group (N=151)</b>	<b>Control group (N=151)</b>	<b>P Value</b>
<b>Procalcitonin</b> – µg/L median (IQ range)	0.03 (0.02-0.08)	0.04 (0.02–0.07)	0.62
- Day 6	0.2 (0.1-0.3)	0.2 (0.1-0.5)	0.98
<b>Primary outcome (Antibiotic use)</b>			
Antibiotics prescribed – no. (%)	128 (85)	149 (99)	<0.001
- initial appropriateness	124 (97)	144 (97)	0.83
- initial combination therapy	40 (31)	55 (37)	0.32
Mean duration of therapy - days	5.8 ± 5.3	12.9 ± 6.5	<0.001
- if prescribed – days†	6.8 ± 5.1	13.1 ± 6.4	<0.001
- if bacteremic -days	13.0 ± 8.9	13.9 ± 4.9	0.29
- Per 1000 days of follow-up (95% CI)	136 (126 – 146)	323 (309 – 338)	<0.001
Antibiotic costs total - US \$	29'428	59'535	<0.001
- per patient (median (IQ range))	100 (33-186)	190 (133-337)	<0.001
<b>Secondary outcomes</b>			
<b>Hospitalization – no. (%)</b>	146 (97)	146 (97)	1.0
Hospitalization - days	12.0 ± 9.1	13.0 ± 9.0	0.35
<b>Complications – no. (%)</b>			
Need for ICU stay	20 (13)	21 (14)	0.87
Microbiological recurrence	1 (1)	0 (0)	0.32
Microbiological relapse	1 (1)	0 (0)	0.32
Clinical and radiological recurrence	4 (3)	4 (3)	1.0
Persistence of pneumonia	1 (1)	3 (2)	0.31
Empyema	4 (3)	7 (5)	0.36
Acute respiratory distress syndrome	1 (1)	1 (1)	1.0
Death	18 (12)	20 (13)	0.73
- pneumonia-related mortality	10 (56)	10 (50)	0.73
<b>Laboratory outcomes</b>			
C-reactive protein - mg/L median (IQ range)	5 (2-11)	4 (2-12)	0.86
- Day 6	26 (13-78)	47 (17-96)	0.1
Leukocyte count - x10 <sup>9</sup> /L ‡	10.4 ± 3.8	10.2 ± 4.7	0.73
- Day 6	10.2 ± 3.7	10.6 ± 5.6	0.44
Body temperature - ° C	36.8 ± 0.4	36.7 ± 0.5	0.93
- Day 6	37.2 ± 0.6	37.3 ± 0.6	0.36
Oxygen saturation - %	96 ± 3	95 ± 3	0.22
Respiratory rate – per min.	17 ± 2	18 ± 3	0.24
Heart rate – per min.	77 ± 12	80 ± 13	0.09
- Day 6	76 ± 13	79 ± 13	0.41
Systolic blood pressure – mm Hg	129 ± 14	129 ± 14	0.42
- Day 6	132 ± 19	131 ± 20	0.84
<b>Quality of life score</b> – pts §	10 ± 10	11 ± 10	0.14
<b>Visual analogue scale</b> - %	79 ± 18	74 ± 20	0.29
<b>Follow-up</b> – no. (%)	149 (99)	151 (100)	0.16
<b>Outcome at follow-up</b> – no. (%)			
Success	127 (84)	124 (82)	0.65
- Cured	108 (85)	105 (85)	
- Improved	19 (15)	19 (15)	
Failure ††	24 (16)	27 (18)	0.65

\*Plus-minus values are means  $\pm$  SD. The conversion factor for procalcitonin is as follows:  $\mu\text{g} / \text{L} \times 0.161$   
= nmol/l.

ICU means intensive care unit, iv intravenous, po per os, IQ interquartile range, no number, CI confidence interval, US \$ US dollars, min means minute, mm Hg means millimeter Hg.

+ “if prescribed” means that mean duration was calculated when only patients were considered in whom antibiotics were prescribed on admission.

‡ Values are given from day 8 of hospital stay. All other follow-up measurements were done after 4 to 6 weeks.

§ Higher quality of life scores indicate worse quality of life

|| The visual analogue scale ranged from 0 (feeling extremely ill) to 100 (feeling completely healthy)

†† Including deaths and lost to follow up

**Table 3.** Sensitivity Analyses: Effect of Changes of Total Costs of Antibiotic Therapy and Procalcitonin (in \$/patient)\*

	<b>Procalcitonin group (N=151)</b>	<b>Control group (N=151)</b>	<b>P Value</b>
<b>As in this trial †</b>			
Costs for antibiotic therapy	100 (33-186)	190 (133-337)	P<0.001
Costs for procalcitonin measurement †	200 (150-200)	0	n.a.
Sum of costs for antibiotics and procalcitonin	290 (212-378)	190 (133-337)	P<0.001
<b>Sum assuming higher antibiotic costs</b>			
- 2-fold	383 (241-544)	379 (266-673)	0.14
- 2.5-fold	432 (250-630)	474 (332-842)	0.007
- 3-fold	481 (250-716)	569 (399-1010)	<0.001
<b>Sum assuming lower procalcitonin costs</b>			
- \$ 30 per measurement	212 (136-292)	190 (133-337)	0.83
- \$ 25 per measurement	192 (121-272)	190 (133-337)	0.14
- \$ 20 per measurement	173 (100-252)	190 (133-337)	0.007
- \$ 15 per measurement	154 (78-232)	190 (133-337)	<0.001
<b>Sum assuming less procalcitonin measurements per patient</b>			
- 3 measurements	250 (183-338)	190 (133-337)	0.001
- 2 measurements	200 (133-288)	190 (133-337)	0.60
- 1 measurement	150 (83-238)	190 (133-337)	<0.001

\* Assuming comparable costs for consummation of other hospital resources in the procalcitonin and the control group based on the similar duration of hospital stay and rate of complications as listed in Table 2 (including ICU admission and mortality). Short-term cost for adverse events of antibiotic therapy, such as diarrhea, and long-term cost for monitoring of antibiotic susceptibility patterns and a possible increase in antibiotic resistance are not considered.

† Considering 3.5 procalcitonin measurement per patient during the course of CAP and the prize of procalcitonin (\$50 per measurement) and antibiotic therapy currently reimbursed by health insurances in Switzerland, respectively.

**Figure 1**

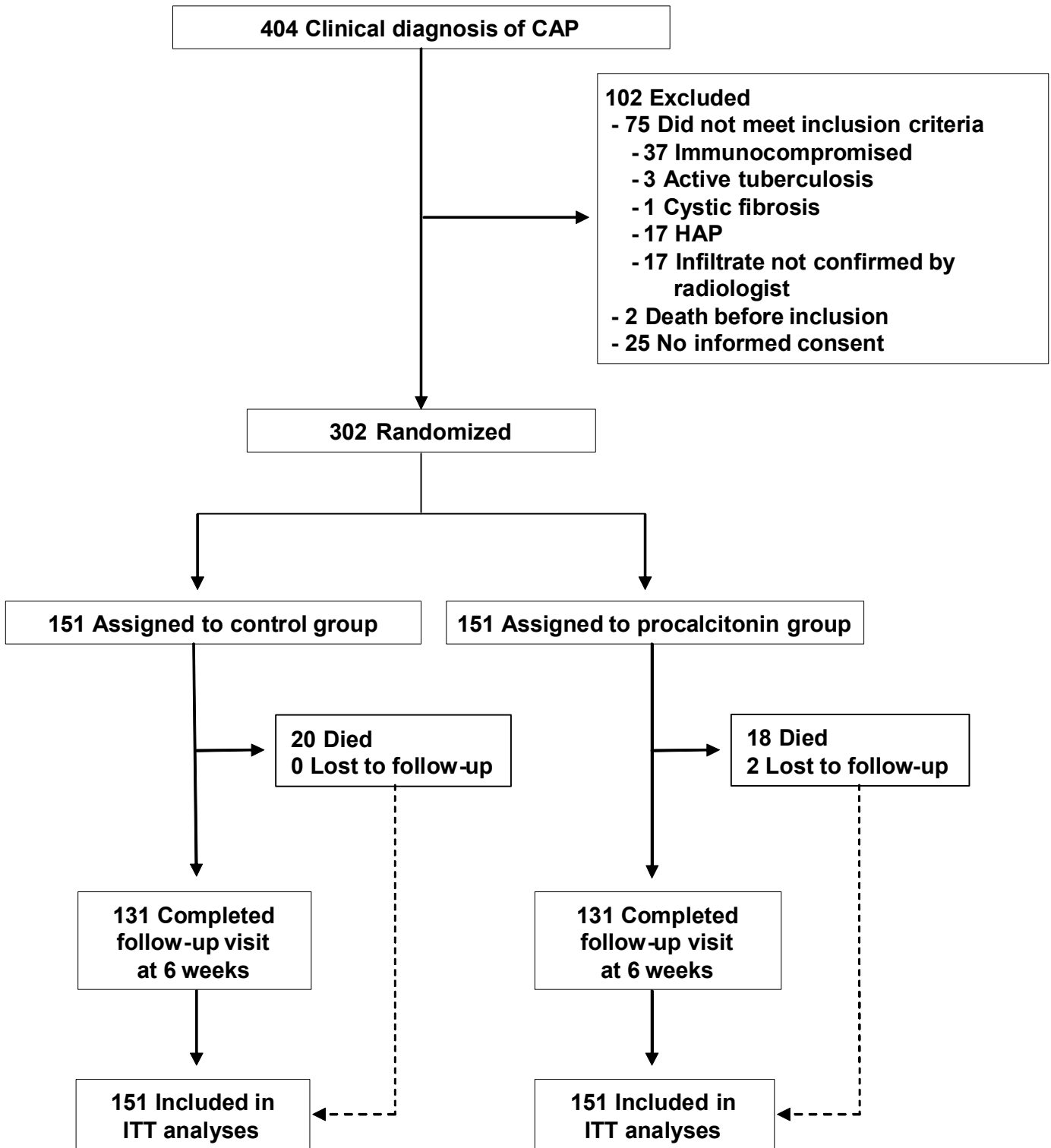
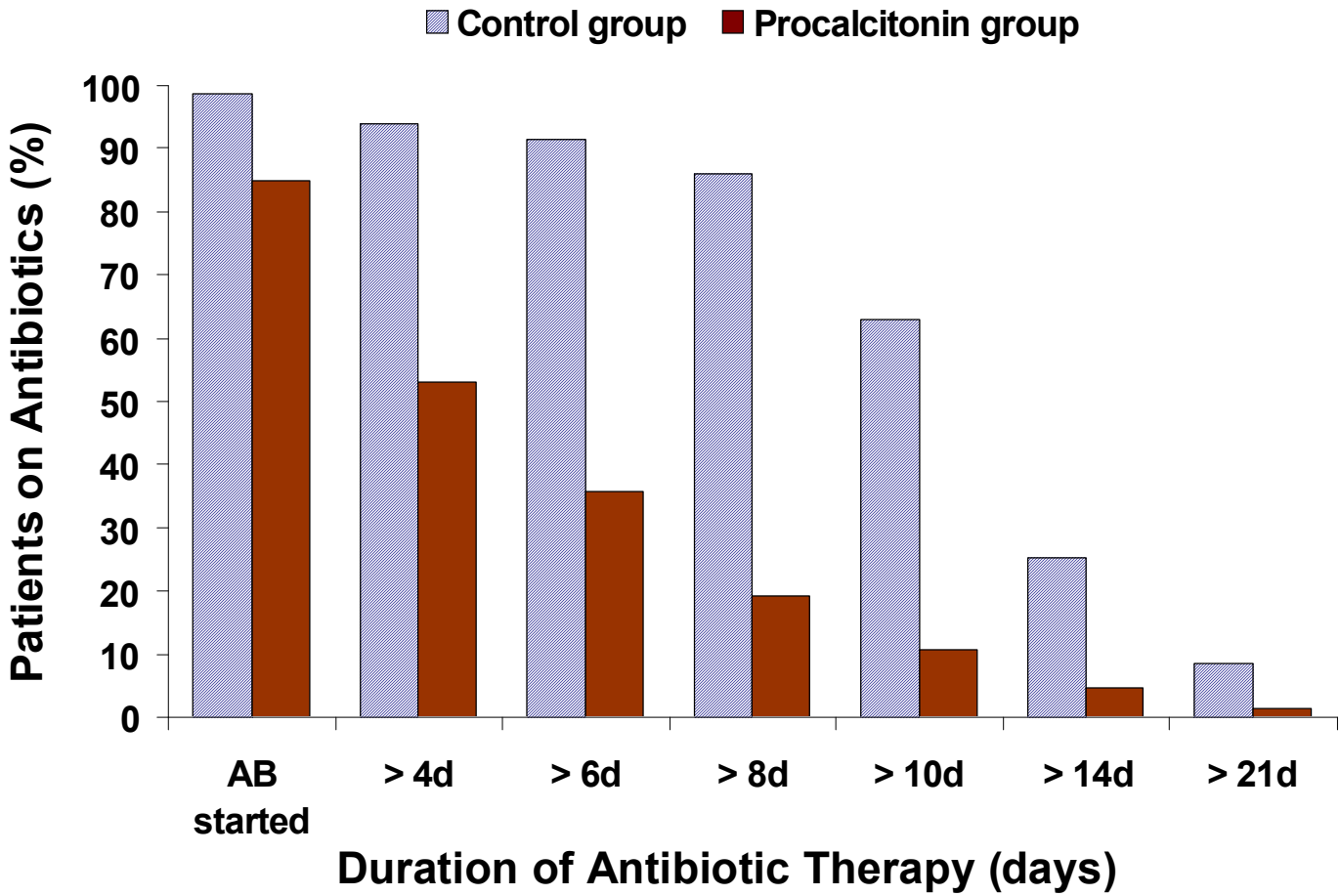


Figure 2

A



B

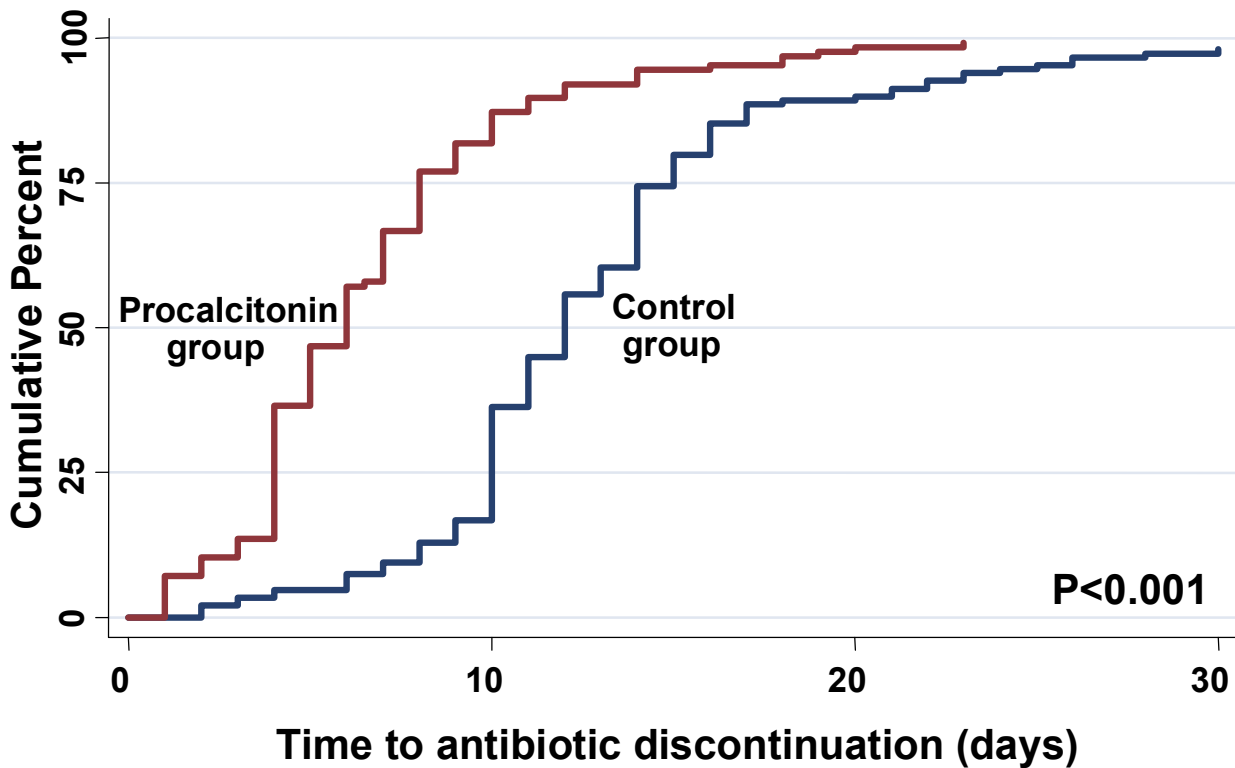
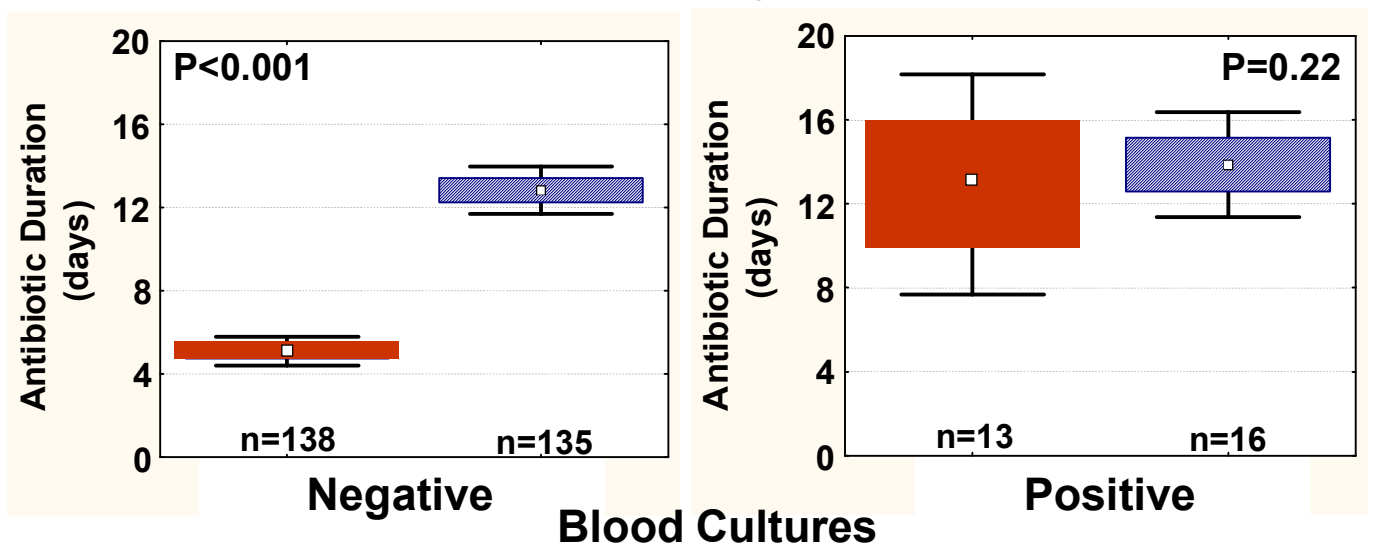
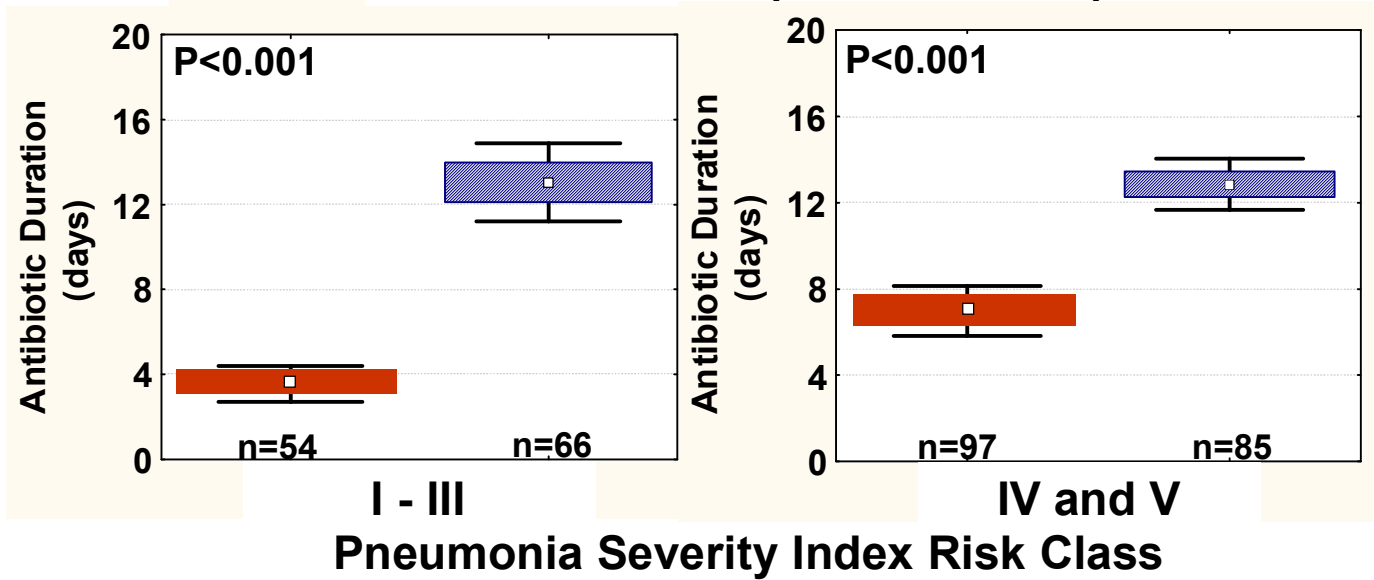
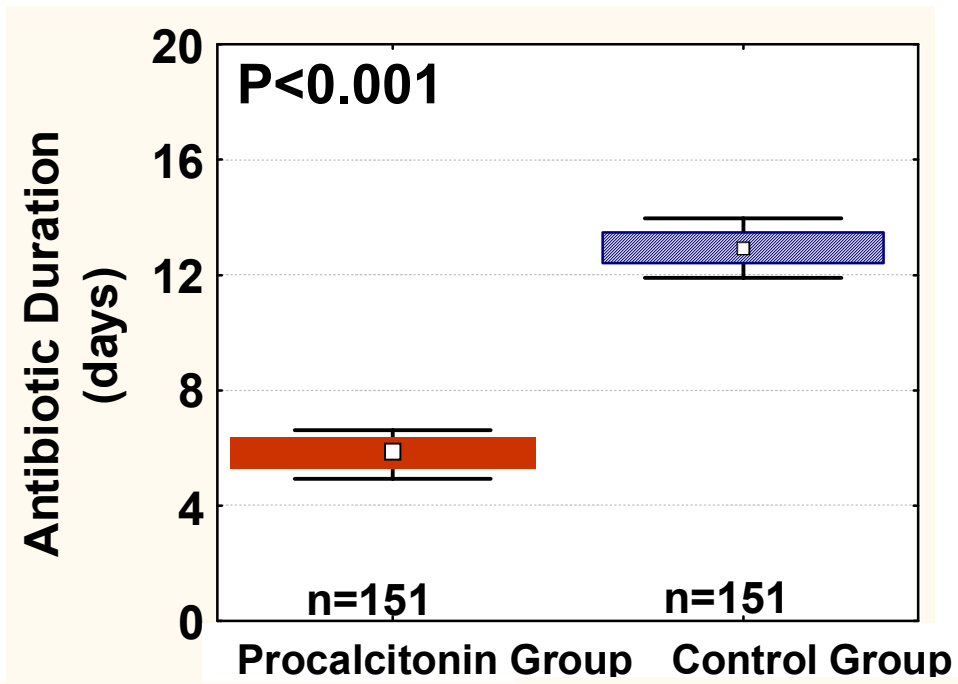


Figure 3



# **Procalcitonin-Guidance of Antibiotic Therapy in Community-Acquired Pneumonia - A Randomized Trial**

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**This is an online supplement**

## METHODS

### Setting and Study Population

This is a randomized, controlled open intervention trial in patients with all severities of community-acquired pneumonia admitted to the emergency department and the results are reported following the Consolidated Standards of Reporting Trials (CONSORT) statement (E1). We compared antibiotic therapy in patients treated according to published guidelines (control group) with patients in whom antibiotic treatment was guided by serum procalcitonin levels (procalcitonin group). The study was approved by the institutional review board and registered in the Current Controlled Trials Database as “ProCAP”-Study [ISRCTN04176397]. Written informed consent was obtained from all included patients or their legal representatives. All data were held and analyzed by the authors.

All patients with suspicion of community-acquired pneumonia admitted from November 2003 through February 2005 to the University Hospital, Basel, Switzerland, a 950-bed tertiary care hospital, were assessed for eligibility (**Figure 1**). Included were adult (>18 years) patients with community-acquired pneumonia as principal diagnosis on admission, defined by a new infiltrate on chest radiograph and the presence of one or several of the following recently acquired respiratory sign or symptom, cough, sputum production, dyspnea, core body temperature >38.0° C, auscultatory findings of abnormal breath sounds and rales and leukocyte count >10 or <4 x 10<sup>9</sup> cells L<sup>-1</sup> (E2). Excluded were patients with cystic fibrosis or active pulmonary tuberculosis; hospital-acquired pneumonia and severely immunocompromised patients.

Patients were examined on admission to the emergency department by a resident supervised by a board-certified specialist in internal medicine. Blood sampling was routinely performed by the emergency department (ED) nurses on admission. Baseline assessment included clinical data and vital signs, comorbid conditions, and routine blood tests. These tests were available after a median time of 60 minutes. Chest radiographs were screened by the physician in charge and were available after a median time of 45 minutes. A senior radiologist, blinded to group assignment and laboratory findings, reviewed all chest radiographs. If the clinical suspicion of CAP was confirmed by an infiltrate on chest X-ray, the

clinician in charge who was not a member of the study staff was required to obtain informed consent from the potentially eligible patient with radiologically confirmed CAP, complete study forms and to immediately inform the study team. After obtaining informed consent, procalcitonin was ordered by telephone from the lab. Therefore, the remainder of the plasma asserved for routine blood chemistry was used.

The clinical management including all decisions regarding initiation or discontinuation of antibiotics was left to the physician in charge. The study staff was not involved in the management of patients. The only influence of the study personal was to communicate the procalcitonin value to the physician in charge and give corresponding protocol-derived recommendations regarding antibiotic use in the procalcitonin group. A patient staying in the ED over midnight was counted as "hospitalized", and 97% of all patients included in our study stayed in a bed on the "emergency ward" for one night.

The next morning, the condition of the patient was reassessed by the routine medical staff (i.e., a nurse, a resident and a board-certified specialist in internal medicine). Thereafter, the routine medical staff decided on further hospitalization and consecutive transfer to the medical or geriatric wards or affiliated hospitals. The study team was neither present nor involved in this routine process.

Randomized patients who were discharged from the ED for home antibiotic treatment remained in the study and were followed-up according to the same algorithm as hospitalized patients.

The Pneumonia Severity Index (PSI) was calculated as described elsewhere (E3). A microorganism was defined as causing agent, if detected in respiratory specimens (sputum or bronchoalveolar lavage fluid), blood, or both, excluding normal skin or mucosal flora. Only purulent sputum samples with >25 white blood cells and <10 squamous cells per field at 100x magnification were considered. We searched for *Legionella pneumophila* antigen in urine (*Legionella* now Binax, Portland, ME, USA), by culture or by polymerase chain reaction (PCR) from bronchoalveolar lavage fluid. The patients' functional status was assessed using a visual analogue scale, ranging from 0 (feeling extremely ill) to 100 (feeling completely healthy), and by a quality of life questionnaire for patients with respiratory illnesses (E4).

## **Measurement of Serum Procalcitonin**

If the suspicion of community-acquired pneumonia was confirmed by an infiltrate on chest X-ray the procalcitonin measurement was ordered by telephone from the lab. The assay time for procalcitonin measurements is less than 20 minutes and procalcitonin results were routinely available within one hour upon ordering (24 hours a day, 7 days per week).

Measurements were done using 20 to 50  $\mu$ L of plasma or serum by a time-resolved amplified cryptate emission (TRACE) technology assay (Kryptor<sup>®</sup> PCT, Brahms AG, Hennigsdorf, Germany), as described (E4). The assay has a functional assay sensitivity of 0.06  $\mu$ g/L, which is about four-fold above mean normal levels (E5). The conversion factor for procalcitonin is as follows:  $\mu$ g /L x 0.161 = nmol/l.

According to the manufacturer, the prize per procalcitonin measurement in Switzerland is approximately 15\$ and 30\$ including reagents, technicians' time for processing specimens, and purchase and maintenance of durable lab equipment, respectively. A fee of around around 50\$ is currently reimbursed by Swiss health insurances and sickness funds.

## **Antibiotic Treatment**

On admission to the emergency department, patients were randomly assigned by the physician in charge to one of the two treatment assignments by sealed, opaque envelopes. Block size was 30 envelopes.

Treating physicians were not aware of envelope contents before randomization. In all patients, the diagnostic procedures, therapeutic regimen and final decision to initiate antimicrobial therapy was left to the discretion of the treating physician.

In the control group, antibiotic therapy was chosen based on current guidelines. The treating physician was unaware of serum procalcitonin levels (E6, E7). In this group, predominantly amoxicillin-clavulanate and / or clarithromycin were prescribed for 7 to 21 days, depending on patient age, suspected pathogen, severity of illness and clinical characteristics, respectively. The antibiotic regimen was

adjusted within 24 to 72 hours based on antibiotic susceptibility patterns of isolated microorganisms, if necessary.

In the procalcitonin group, the antibiotic treatment was guided by serum procalcitonin levels, which were communicated by a fax. Thereafter, the physician in charge was advised to classify the patients into four groups, according to the probability of bacterial infection. This classification and the cut-offs used were derived by calculating multilevel likelihood-ratios and validated in a previous study (E4). A procalcitonin level of  $<0.1 \mu\text{g/L}$  suggested the absence of bacterial infection and the initiation or continuation of antibiotics was strongly discouraged. A procalcitonin level between  $0.1$  and  $0.25 \mu\text{g/L}$  indicated that bacterial infection was unlikely, and the initiation or continuation of antibiotics was discouraged. A procalcitonin level from  $0.25$  to  $0.5 \mu\text{g/L}$  was considered to indicate a possible bacterial infection and the initiation or continuation of antibiotic therapy, respectively, was encouraged. A procalcitonin level of  $>0.5 \mu\text{g/L}$  strongly suggested the presence of bacterial infection and antibiotic treatment and continuation was strongly encouraged. The same cut-offs were used for patients pretreated with antibiotics (i.e. treated with one or more doses of antibiotics prior to admission to the emergency department). Reevaluation of the clinical status and measurement of serum procalcitonin levels was recommended after 6–24 h in all patients in whom antibiotics were withheld. During the course of disease, procalcitonin levels were reassessed on days 4, 6 and 8 in patients with ongoing antibiotic therapy, and in case of worsening or delayed recovery of signs and symptoms. Antibiotics were discontinued using the procalcitonin cut-offs defined above. In successfully treated infections, circulating procalcitonin levels decrease in a log-linear pattern and have a plasma half life of 24 hours (E8). In patients with a very high procalcitonin value on admission (e.g.,  $>10 \mu\text{g/L}$ ), discontinuation of antibiotics was already encouraged if levels decreased below 90% of the initial value (e.g.  $1 \mu\text{g/L}$ , instead of  $<0.25 \mu\text{g/L}$ ). In patients with an initial procalcitonin level  $>10 \mu\text{g/L}$  and lesser reductions during follow-up, continuation of antibiotic treatment was encouraged.

## Outcome Measures

The primary endpoint was total antibiotic use (i.e. antibiotic prescription and duration). The proportion of antibiotic prescriptions was measured in percentage and the duration in patient days and, thereafter, the incidence density ratio of antibiotic exposure was calculated as total antibiotic exposure time divided by total follow-up time, until week 6 [expressed as relative risk (RR)]. Costs of all antibiotics were determined by summing up the costs of all prescribed systemic antibiotics related to community-acquired pneumonia during hospitalization and thereafter. Published average wholesale prices in Switzerland using an exchange rate of 1.20 Swiss francs / US\$ were used. Appropriateness of initial antibiotic therapy was defined as previously described (E9). If no causative microbial agent could be detected, treatment according to internal guidelines was considered as appropriate. Secondary endpoints were measures of laboratory and clinical outcome. These included plasma C-reactive protein levels, blood leukocyte counts, body temperature, hemoglobin oxygen saturation, respiratory rate, pulse rate, blood pressure and quality of life indices. In addition, rate and length of hospitalization, complications during the course of disease, and final outcome of community-acquired pneumonia until follow-up were assessed. We also compared procalcitonin levels in patients who died during the course of the study with levels in patients who did not die.

Primary and secondary endpoints were recorded on days 4, 6, and 8 and at follow-up after 6 weeks, respectively. At the follow-up visit after 6 weeks, the outcome was evaluated by clinical, laboratory, radiographic and microbiological criteria. Cure was defined as resolution of clinical, laboratory and radiographic signs of community-acquired pneumonia. Improvement was defined as reduction of clinical signs and symptoms, improvement of laboratory findings (i.e. C-reactive protein and leukocyte count) and the reduction of the number or intensity of radiographic signs of community-acquired pneumonia. Treatment success represented the sum of the rates for cure and improvement. Treatment failure included death, recurrence, relapse or persistence of clinical, laboratory and radiological signs of community-acquired pneumonia at follow-up, and patients lost to follow-up. Pulmonary reinfection was named recurrent if microbiologically documented by bacterial growth from blood or sputum and was termed

relapse if the initial causative bacterial strain was again isolated. Appropriateness of antibiotic therapy was defined as treatment according the susceptibility pattern of the microorganism if available, or in all other patients according to guidelines based on regular reviews of the susceptibility pattern of respiratory tract pathogens cultured in our hospital and in Switzerland (E10).

## **Statistical Analysis**

Discrete variables are expressed as counts (percentage) and continuous variables as means  $\pm$  standard deviation (SD), unless stated otherwise. The endpoints were predefined and analyzed on the basis of intention-to-treat, i.e. in all recruited patients. A study sample of 150 patients in each group gave the study a power of 95 % to detect a 30 % reduction in antibiotic exposure from 10 to 7 days per patient. Assumptions included the use of a two-tailed test, a 1 % level of significance and a standard deviation of 6 days in both groups. This sample size gave the study a power of 74 % to detect a 10 % increase in the combined treatment failure and complication rate (from 10 to 20 %) using the procalcitonin algorithm with a one-sided alpha-value of 0.05. Comparability of the control group and the procalcitonin group was analyzed by  $\chi^2$  test and non-parametric Mann-Whitney U test. The time to discontinuation of antibiotic treatment was compared between the two study groups by use of the log-rank test. Using Cox proportional hazards regression analysis, we estimated the rate of antibiotic treatment discontinuation, after adjustment for the PSI class. We performed crude cost and sensitivity analyses to estimate direct costs associated with changes of repeated measurements of procalcitonin and antibiotic therapy. Indirect costs (e.g. adverse events, emergence of antibiotic resistance and need of high-priced second-line antibiotics for future treatment) were not considered. The economic analysis was conducted in Swiss Francs and then converted to US\$ using the average actual currency conversion rate during the trial period.

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