

Procalcitonin Guidance of Antibiotic Therapy in Community-acquired Pneumonia

A Randomized Trial

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Rationale: In patients with community-acquired pneumonia, guidelines recommend antibiotic treatment for 7 to 21 d. 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, after 4, 6, and 8 d, and after 6 wk.

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, less than 0.1 µg/L; discouraged, less than 0.25 µg/L; encouraged, greater than 0.25 µg/L; strongly encouraged, greater than 0.5 µg/L. The primary endpoint was antibiotic use; secondary endpoints were measures of clinical, laboratory, and radiographic outcome.

Results: At baseline, both groups were similar regarding clinical, laboratory, and microbiology characteristics, and Pneumonia Severity Index. Procalcitonin guidance reduced total antibiotic exposure (relative risk, 0.52; 95% confidence interval, 0.48–0.55; p < 0.001), antibiotic prescriptions on admission (85 vs. 99%; p < 0.001), and antibiotic treatment duration (median, 5 vs. 12 d; p < 0.001) compared with patients treated according to guidelines. After adjustment for Pneumonia Severity Index, the hazard ratio of antibiotic discontinuation was higher in the procalcitonin group than in the control group (3.2; 95% confidence interval, 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.

Keywords: antibiotic therapy; community-acquired pneumonia; procalcitonin

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 must be admitted to the intensive care unit, 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 that 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 nonbacterial) and noninfectious causes.

In bacterial CAP, prompt initiation of antibiotic therapy is pivotal, as a delay of more than 4 h can be associated with 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 d, 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 in sputum production and coughing, or improvement of general condition. However, 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-1β, tumor necrosis factor-α, and interleukin-6) or the cell-mediated host response (19). This induction can be attenuated by cytokines released during viral infections (e.g., interferon-γ) (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 a 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 h (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

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procalcitonin guidance could significantly shorten antibiotic duration with a similar clinical and laboratory outcome (25, 26).

METHODS

Setting and Study Population

This is a randomized, controlled, open intervention trial involving 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 Procalcitonin-guided Reduction of the Duration of Antibiotic Therapy in Community-acquired Pneumonia (the 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 patients (older than 18 yr of age) 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 signs or symptoms: cough, sputum production, dyspnea, core body temperature exceeding 38.0°C, auscultatory findings of abnormal breath sounds and rales, and leukocyte count greater than 10×10^9 or less than 4×10^9 cells L^{-1} (2). Excluded were patients with cystic fibrosis or active pulmonary tuberculosis, patients with 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 functional status of the patients was assessed with a Visual Analog 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 with a time-resolved amplified cryptate emission technology assay (Kryptor PCT; Brahms AG, Hennigsdorf, Germany) (13) with a functional assay sensitivity of 0.06 $\mu g/L$, about fourfold above mean normal levels (29). Assay time is less than 20 min and results were routinely available within 1 h. According to the manufacturer, the price per procalcitonin measurement in Switzerland is approximately \$15, including (only) assay material, and \$30, including reagents, technicians' time for processing specimens, and purchase and maintenance of durable laboratory equipment, respectively. A fee of about \$50 is currently reimbursed by Swiss health insurance and sickness funds.

Antibiotic Treatment

On admission, patients were randomly assigned to one of the two groups by sealed, opaque envelopes. In the control group, antibiotic therapy was chosen on the basis of 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

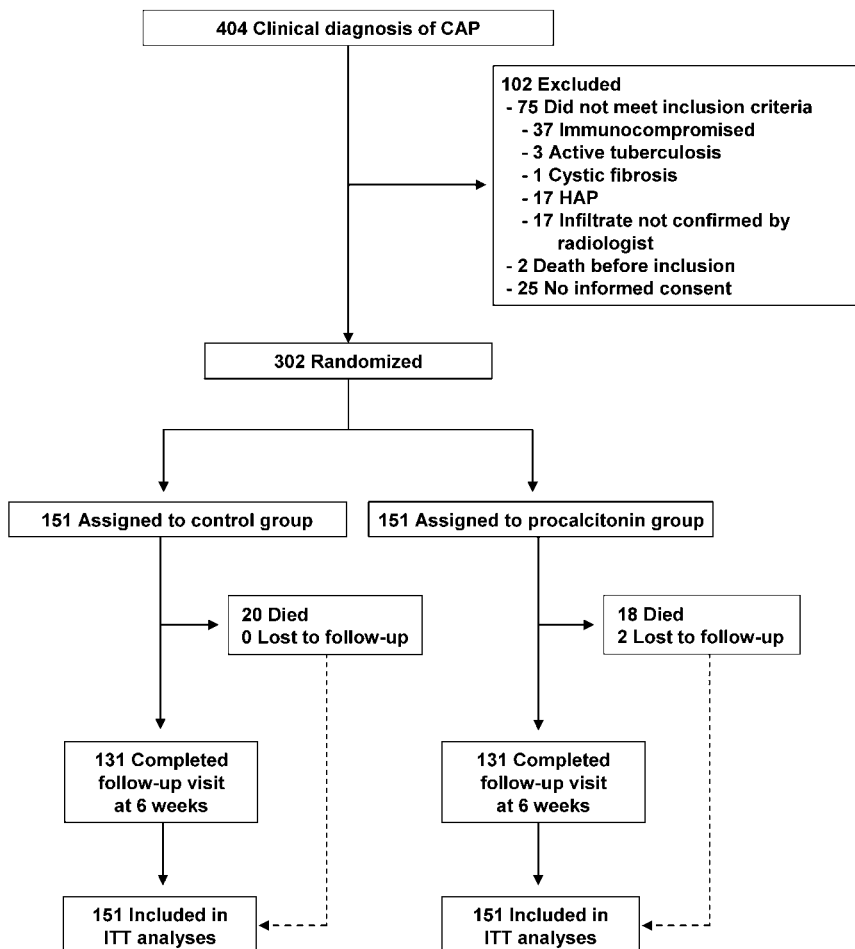


Figure 1. Trial profile. CAP = community-acquired pneumonia; HAP = health care-associated pneumonia; ITT = intention to treat.

advised to classify the patients into four groups, according to the probability of bacterial infection. This classification and the cutoffs used were derived by calculating multilevel likelihood ratios and validated in a previous study (13). A procalcitonin level of less than 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 was encouraged. A procalcitonin level greater than 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 from whom antibiotics were withheld. Procalcitonin levels were reassessed after 4, 6, and 8 d. Antibiotics were discontinued on the basis of the procalcitonin cutoffs defined above. In patients with very high procalcitonin values on admission (e.g., greater than 10 µg/L), discontinuation of antibiotics was encouraged if levels decreased to levels less than 10% of the initial value (e.g., 1 µg/L, instead of less than 0.25 µg/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). 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 wk, respectively. At the follow-up visit after 6 wk, 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 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 radiologic signs of CAP, and patients lost to follow-up.

Statistical Analysis

Discrete variables are expressed as counts (percentage) and continuous variables as means ± 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 d per patient assuming a two-tailed test, a 1% level of significance, and a SD of 6 d 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 α value of 0.05. Comparability of the control group and the procalcitonin group was analyzed by χ^2 test and nonparametric 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 for high-priced second-line antibiotics for future treatment) were not considered. The economic analysis was conducted in Swiss francs and then converted to U.S. dollars, using the average actual currency conversion rate during the trial period.

RESULTS

Baseline Characteristics of 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 exceeding 38°C was present in 60% of patients with CAP overall and in 55% in those with positive blood cultures. The temperature was not higher in those patients with CAP with positive cultures (38.4°C [37.7–38.9°C]) as compared with patients with negative blood cultures (38.4°C [37.7–39.2°C]; 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

TABLE 1. BASELINE CHARACTERISTICS OF 302 PATIENTS RANDOMIZED TO CONTROL GROUP OR PROCALCITONIN GROUP*

Characteristic	Procalcitonin Group (n = 151)	Control Group (n = 151)
Age, yr	70 ± 17	70 ± 17
Male sex, no. (%)	94 (62)	93 (62)
Smoking status		
Current smoker, no. (%)	34 (23)	39 (26)
Pack-years, current and ex-smokers	42 ± 27	38 ± 20
Antibiotic pretreatment, no. (%)	27 (18)	34 (23)
Coexisting illnesses, no. (%)		
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)
History, no. (%)		
Cough	134 (89)	136 (90)
Sputum	108 (72)	113 (75)
Dyspnea	118 (78)	111 (74)
Examination		
Rales, no. (%)	137 (91)	134 (89)
Body temperature, °C	38.4 ± 1.1	38.4 ± 1.1
Oxygen saturation, %	92 ± 5	91 ± 6
Respiratory rate, breaths/min	24 ± 7	23 ± 7
Heart rate, beats/min	96 ± 20	97 ± 19
Systolic blood pressure, mm Hg	130 ± 26	130 ± 24
Laboratory findings		
Procalcitonin (µg/L), median (IQR)	0.57 (0.2–2.5)	0.44 (0.2–1.9)
C-reactive protein (mg/L), median (IQR)	111 (57–204)	152 (72–212)
Leukocyte count (× 10 ⁹ /L)	13.7 ± 6.7	13.4 ± 6.6
Quality-of-Life score, points [†]	40 ± 13	39 ± 13
Visual Analog Scale, % [‡]	43 ± 20	39 ± 21
Imaging, no. (%)		
Pleural effusion	17 (11)	20 (13)
Multilobar pneumonia	24 (16)	29 (19)
PSI, points	99.7 ± 36.1	99.2 ± 34.5
PSI class, no. (%)		
I, II, and III	54 (36)	66 (44)
IV	68 (45)	62 (41)
V	29 (19)	23 (15)

Definition of abbreviations: IQR = interquartile range; PSI = Pneumonia Severity Index.

* Plus-minus values represent means ± SD. p Values of all comparisons between the control group and the procalcitonin group were not significant as assessed by χ^2 test or by nonparametric Mann-Whitney U test, as appropriate. Because of rounding, percentages may not sum to 100. The conversion factor for procalcitonin is as follows: µg/L × 0.161 = nmol/L.

[†] Higher Quality-of-Life scores indicate worse quality of life.

[‡] The Visual Analog Scale ranged from 0 (feeling extremely ill) to 100 (feeling completely healthy).

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 comorbidities. After diagnosis of CAP, 3% of all patients were discharged on the same day. On the day of admission, serum procalcitonin levels were less than $0.1 \mu\text{g/L}$ 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 in the control group and 32 in the procalcitonin group; $p = 0.56$), 0.25 to $0.49 \mu\text{g/L}$ in 55 patients (27 in the control group and 28 in the procalcitonin group; $p = 0.88$), and at least $0.5 \mu\text{g/L}$ in 159 patients (79 in the control group and 80 in the procalcitonin group; $p = 0.91$). Compiling both groups, 86 of 302 patients (28%) had procalcitonin levels less than $0.25 \mu\text{g/L}$ 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 five (10%) of the patients without antibiotic therapy based on an initial procalcitonin level less than $0.25 \mu\text{g/L}$, antibiotics were started when procalcitonin levels increased to more than $0.25 \mu\text{g/L}$ at the follow-up after 6 h. In only 2% of these patients did procalcitonin at the follow-up measurement after 6 h increase to greater than $0.5 \mu\text{g/L}$. All patients in whom antibiotics were withheld on admission based on low procalcitonin levels had ultimately a favorable outcome. The median (interquartile range) procalcitonin level in patients pretreated with antibiotics was $0.5 \mu\text{g/L}$ (0.2 – $1.6 \mu\text{g/L}$), which was not significantly different from that of patients without antibiotic pretreatment ($0.5 \mu\text{g/L}$ [0.2 – $2.4 \mu\text{g/L}$]).

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 with 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 2A). 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, 2.5 to 4.2; Figure 2B). Consequently, the total rate of antibiotic exposure decreased in patients with procalcitonin guidance (relative risk, 0.52; 95% confidence interval, 0.48–0.55; $p < 0.001$).

As compared with the control group, antibiotic duration was reduced by 55% in the procalcitonin group (median, 12 vs. 5 d; $p < 0.001$; Figure 3). Procalcitonin levels increased with increasing severity of CAP, as defined by the PSI score ($p < 0.001$). Patients with mild CAP, as defined by a PSI score of I–III, had significantly lower procalcitonin levels (median, $0.3 \mu\text{g/L}$; interquartile range, 0.1 – $1.1 \mu\text{g/L}$) as compared with patients with

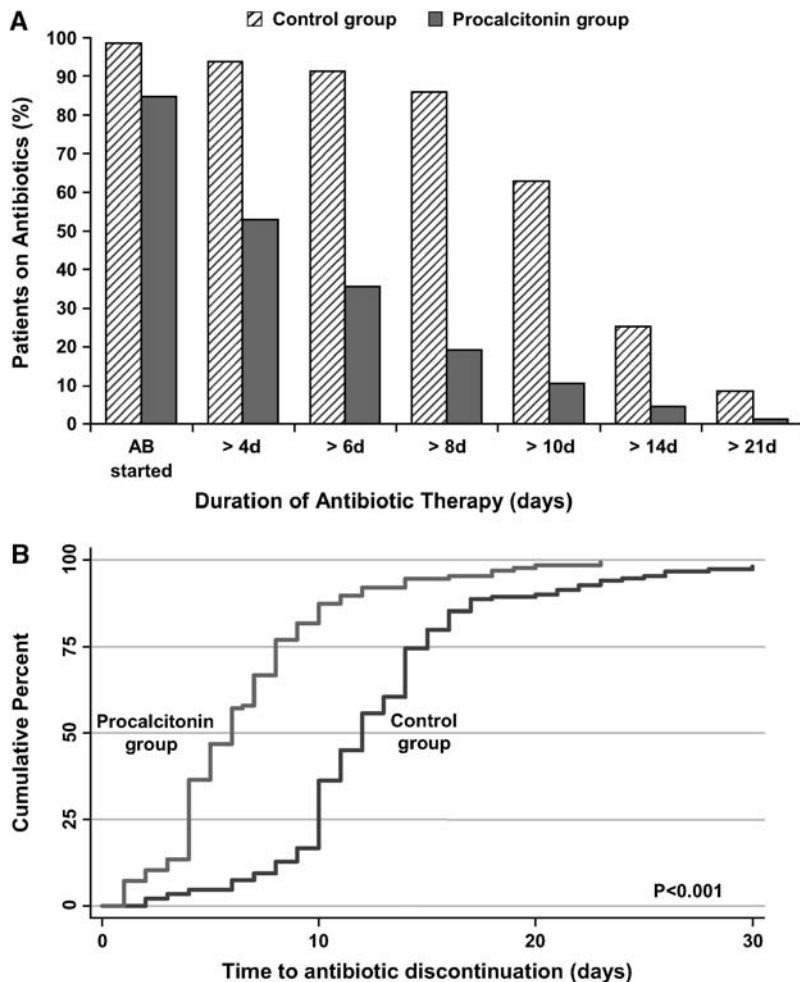


Figure 2. (A) Percentage of patients receiving antibiotic therapy in the control group and the procalcitonin group on admission and during the course of the disease. AB = antibiotics. (B) Cumulative frequency distribution curve for the time to discontinuation in patients for whom antibiotic therapy was prescribed. Patients in the procalcitonin group were compared with those in the control group.

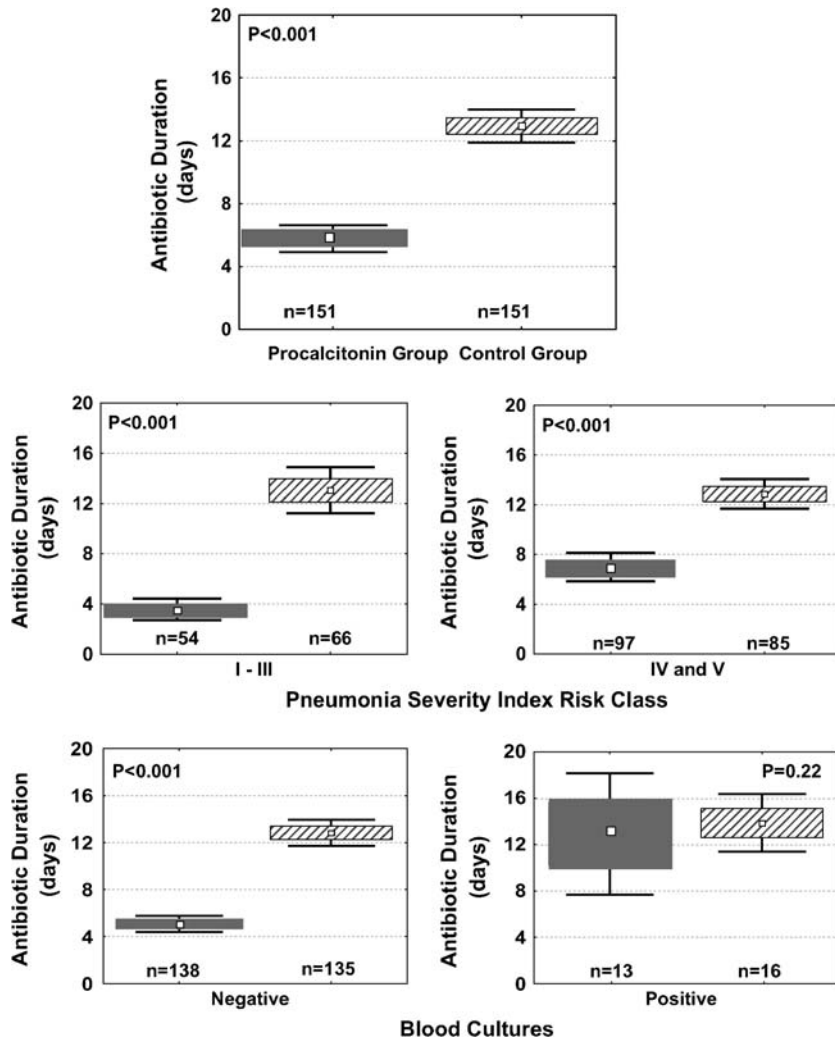


Figure 3. Antibiotic duration. The duration of antibiotic courses in the procalcitonin group and in the control group is given overall (*top*), in patients classified according to Pneumonia Severity Index risk class (*middle*), and blood culture result (*bottom*). Squares denote mean values, boxes the SEM, and whiskers $1.96 \times$ SEM. Results of the procalcitonin group are shown in the solid boxes, and results of the control group are in the hatched boxes.

CAP and a PSI score of IV or V (median, $0.7 \mu\text{g/L}$; interquartile range, $0.3\text{--}3.3 \mu\text{g/L}$; $p < 0.001$). Only in the procalcitonin group—not in the control group—did patients with a high PSI score (classes IV and V) have a significantly longer duration of antibiotic treatment compared with patients with a low PSI score (class I to III; Figure 3). Equally, only in the procalcitonin group was the mean antibiotic duration in patients with positive blood cultures significantly longer compared with patients with negative blood cultures (Figure 3). Duration of antibiotic therapy was similar in patients with bacteremia in the control and procalcitonin groups (Table 2). Antibiotic duration was influenced by a positive culture from respiratory specimens in the control group (17.7 ± 10.7 and 12.3 ± 5.6 d; $p = 0.03$), in contrast to the procalcitonin group (6.2 ± 5.8 and 4.8 ± 3.6 d; $p = 0.52$).

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 (control group, 55 [37%]; procalcitonin group, 44 [35%]), ceftriaxone (control group, 37 [25%]; procalcitonin group, 20 [16%]), and other agents (control group, 49 [33%]; procalcitonin group, 42 [33%]), with a similar distribution in both groups.

Antibiotic treatment including macrolides did not affect the change in 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 less than 0.1 ng/ml and in 19 patients (13%) with a procalcitonin level of 0.1 to $0.25 \mu\text{g/L}$ (6, severe chronic obstructive pulmonary disease; 2, end-stage pulmonary fibrosis; 11, other severe comorbidities). Antibiotics were not withdrawn after 4, 6, or 8 d 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 with \$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 24 h, 139 on Day 4, 128 on Day 6, and 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 (Days 4, 6, and 8; data not shown) and at follow-up after a mean of 6.9 ± 1.9 wk. Of the patients who completed the follow-up visit after 4 to 6 wk, 91% had a follow-up measurement on Day 4, 84% a follow-up measurement on Day 6, and 61%

TABLE 2. OUTCOME AND ANTIBIOTIC USE AT FOLLOW-UP AFTER 6 wk IN PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA ACCORDING TO TREATMENT ALGORITHM*

	Procalcitonin Group (n = 151)	Control Group (n = 151)	p Value
Procalcitonin, $\mu\text{g/L}$ 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
Primary outcome (antibiotic use)			
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, d	5.8 \pm 5.3	12.9 \pm 6.5	< 0.001
If prescribed, d [†]	6.8 \pm 5.1	13.1 \pm 6.4	< 0.001
If bacteremic, d	13.0 \pm 8.9	13.9 \pm 4.9	0.29
Per 1,000 d of follow-up, mean (95% CI)	136 (126–146)	323 (309–338)	< 0.001
Antibiotic costs total, U.S. dollars	29,428	59,535	< 0.001
Per patient, median (IQR)	100 (33–186)	190 (133–337)	< 0.001
Secondary outcomes			
Hospitalization, no. (%)	146 (97)	146 (97)	1.0
Hospitalization, d	12.0 \pm 9.1	13.0 \pm 9.0	0.35
Complications, no. (%)			
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 radiologic 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
Laboratory outcomes			
C-reactive protein (mg/L), median (IQR)	5 (2–11)	4 (2–12)	0.86
Day 6	26 (13–78)	47 (17–96)	0.1
Leukocyte count, $\times 10^9/\text{L}^\ddagger$	10.4 \pm 3.8	10.2 \pm 4.7	0.73
Day 6	10.2 \pm 3.7	10.6 \pm 5.6	0.44
Body temperature, $^\circ\text{C}$	36.8 \pm 0.4	36.7 \pm 0.5	0.93
Day 6	37.2 \pm 0.6	37.3 \pm 0.6	0.36
Oxygen saturation, %	96 \pm 3	95 \pm 3	0.22
Respiratory rate, breaths/min	17 \pm 2	18 \pm 3	0.24
Heart rate, beats/min	77 \pm 12	80 \pm 13	0.09
Day 6	76 \pm 13	79 \pm 13	0.41
Systolic blood pressure, mm Hg	129 \pm 14	129 \pm 14	0.42
Day 6	132 \pm 19	131 \pm 20	0.84
Quality-of-Life score, points [§]	10 \pm 10	11 \pm 10	0.14
Visual Analog Scale, %	79 \pm 18	74 \pm 20	0.29
Follow-up, no. (%)	149 (99)	151 (100)	0.16
Outcome at follow-up, 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

Definition of abbreviations: CI = confidence interval; ICU = intensive care unit; IQR = interquartile range.

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

[†] "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 wk.

[§] Higher Quality-of-Life scores indicate worse quality of life.

^{||} The Visual Analog Scale ranged from 0 (feeling extremely ill) to 100 (feeling completely healthy).

[¶] Including deaths and those lost to follow-up.

had a follow-up measurement on Day 8. There was a gradual decline in procalcitonin levels (median [interquartile range]) from admission (0.5 [0.2–2.2] $\mu\text{g/L}$), to Day 4 (0.3 [0.1–0.9] $\mu\text{g/L}$), Day 6 (0.2 [0.1–0.4] $\mu\text{g/L}$), and Day 8 (0.1 [0.09–0.3] $\mu\text{g/L}$), which was similar in both groups.

The final course of CAP (i.e., failure or success) as determined 4–6 wk 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 with patients who survived (median [interquartile range]: 0.7 [0.4–3.0] and 0.45 [0.2–2.0] $\mu\text{g/L}$, 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 Analog Scale score (31.1 \pm 18.8 and 41.8 \pm 20.4, respectively; $p < 0.001$). C-reactive protein (CRP) levels and leukocyte counts were similar in patients who died and in patients who survived (153 [93–204] vs. 126 [63–211] mg/dl, respectively; $p = 0.57$). On Day 4, both procalcitonin

TABLE 3. SENSITIVITY ANALYSES: EFFECT OF CHANGES IN TOTAL COSTS OF ANTIBIOTIC THERAPY AND PROCALCITONIN*

	Procalcitonin Group (n = 151)	Control Group (n = 151)	p Value
As in this trial [†]			
Costs for antibiotic therapy	100 (33–186)	190 (133–337)	< 0.001
Costs for procalcitonin measurement [†]	200 (150–200)	0	NA
Sum of costs for antibiotics and procalcitonin	290 (212–378)	190 (133–337)	< 0.001
Sum assuming higher antibiotic costs			
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
Sum assuming lower procalcitonin costs			
\$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
Sum assuming less procalcitonin measurements per patient			
Three measurements	250 (183–338)	190 (133–337)	0.001
Two measurements	200 (133–288)	190 (133–337)	0.60
One measurement	150 (83–238)	190 (133–337)	< 0.001

Definition of abbreviation: NA = not applicable.

* In U.S. dollars per patient, and assuming comparable costs for consummation of other hospital resources in the procalcitonin group and the control group based on the similar duration of hospital stay and rate of complications as listed in Table 2 (including intensive care unit 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 measurements per patient during the course of CAP and the price of procalcitonin (\$50 per measurement) and antibiotic therapy currently reimbursed by health insurances in Switzerland, respectively.

and CRP levels were higher in nonsurvivors as compared with 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 (eight in the control group and five in the procalcitonin group), cardiac failure (six and five, respectively), septic shock (two and three, respectively), tumor (three and three, respectively), multiorgan failure (none and two, respectively), and intracerebral hemorrhage (one and none, respectively). Eighteen of the 20 deceased patients in the control group had procalcitonin levels greater than 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 exceeding 0.25 $\mu\text{g/L}$ and 1 based on a procalcitonin value of 0.20 $\mu\text{g/L}$. Initial procalcitonin levels in patients with pleural effusion were (median [interquartile range]) as follows: patients with pleural effusion, 1.0 (0.2–5.3) $\mu\text{g/L}$; patients with empyema, 0.9 (0.2–3.4) $\mu\text{g/L}$ ($p = 0.4$). 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 d. 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 CRP and other laboratory markers (17, 32). Circulating procalcitonin levels correlate with the clinical course of a sys-

temic 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 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 cutoff of any surrogate marker. Therefore, we propagated and validated the use of cutoff 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 a 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 with 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 with routinely used clinical and other laboratory parameters. For example, only in the procalcitonin group was duration of antibiotic courses adapted to the severity of CAP. The presence of fever is an important clinical sign indicating infection. However, defervescence 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 more than 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 10 d.

In bacterial CAP, delayed initiation of antibiotic therapy can be associated with increased mortality (6). Therefore, in the emergency management of suspected CAP antibiotic therapy is rapidly initiated in all patients. The presence of nonbacterial diseases is usually suspected only after failure of antibiotic therapy, with the ensuing risks related to untreated, potentially life-threatening nonbacterial 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 from 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 greater than 0.25 µg/L to greater than 0.5 µg/L supports the clinician in his diagnosis of CAP.

Previous attempts to shorten antibiotic therapy in CAP used defined treatment regimens (e.g., 5 vs. 10 d) and excluded patients with severe pneumonia and a PSI score greater than 130 (43, 44). Azithromycin was also used for shorter antibiotic courses in CAP (45, 46). However, therapy for 3 to 5 d 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 spillover 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 toward null.

Second, in our cohort of predominantly elderly patients with CAP 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 in anything other than duration of antibiotic therapy, to minimize potential bias. This assured similar surveillance for complications during the early course of the infection in both study groups.

Third, because of the sample size, our study had limited power to prove 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).

Fourth, the mean duration of antibiotic therapy of 13 d in the control group appears rather long, as more recent guidelines

recommend a duration of antibiotic therapy in CAP of 7 to 10 d (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 d is the usual length of treatment, especially in severely sick patients who require admission to the hospital (12). In patients with PSI scores in classes I–III, procalcitonin guidance shortened the duration of antibiotic therapy safely to a mean of 4 d, well below the most recent guideline recommendation.

Fifth, our results refer mainly to hospitalized patients; whether procalcitonin guidance can reduce antibiotic use in the outpatient setting is currently being investigated (49).

One might argue that antibiotic duration in CAP could also be reduced using stewardship with CRP. To the best of our knowledge, no such study has been done. CRP is an acute-phase reactant that has 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, 17, 50). Thus, the routine use of standard laboratory tests such as 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 from a public health perspective. It could become cost-effective either by reducing the number of measurements; by lowering the cost 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 (51). Thus, if applied on a larger scale, 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 (49). Reduced costs, fewer side effects, improved patient compliance, and, most important, reduced selective pressure for the emergence of resistance favor shorter courses of antibiotic therapy (9, 52, 53).

In conclusion, procalcitonin guidance leads to 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 multicenter intervention trials are encouraged. Thereby, procalcitonin must 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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References

- Mortensen EM, Coley CM, Singer DE, Marrie TJ, Obrosky DS, Kapoor WN, Fine MJ. Causes of death for patients with community-acquired pneumonia: results from the Pneumonia Patient Outcomes Research Team cohort study. *Arch Intern Med* 2002;162:1059–1064.
- Niedermaier MS, Mandell LA, Anzueto A, Bass JB, Broughton WA, Campbell GD, Dean N, File T, Fine MJ, Gross PA, et al. Guidelines for the management of adults with community-acquired pneumonia: diagnosis, assessment of severity, antimicrobial therapy, and prevention. *Am J Respir Crit Care Med* 2001;163:1730–1754.
- Fine MJ, Smith MA, Carson CA, Mutha SS, Sankey SS, Weissfeld LA, Kapoor WN. Prognosis and outcomes of patients with community-acquired pneumonia: a meta-analysis. *JAMA* 1996;275:134–141.
- Kaplan V, Angus DC, Griffin MF, Clermont G, Scott Watson R, Linde-Zwirble WT. Hospitalized community-acquired pneumonia in the elderly: age- and sex-related patterns of care and outcome in the United States. *Am J Respir Crit Care Med* 2002;165:766–772.
- Janssens JP, Krause KH. Pneumonia in the very old. *Lancet Infect Dis* 2004;4:112–124.
- Meehan TP, Fine MJ, Krumholz HM, Scinto JD, Galusha DH, Mockalis JT, Weber GF, Petrillo MK, Houck PM, Fine JM. Quality of care, process, and outcomes in elderly patients with pneumonia. *JAMA* 1997;278:2080–2084.
- File TM Jr, Mandell LA. What is optimal antimicrobial therapy for bacteremic pneumococcal pneumonia? *Clin Infect Dis* 2003;36:396–398.
- Mandell LA, Bartlett JG, Dowell SF, File TM Jr, Musher DM, Whitney C. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. *Clin Infect Dis* 2003;37:1405–1433.
- File TM Jr. Clinical efficacy of newer agents in short-duration therapy for community-acquired pneumonia. *Clin Infect Dis* 2004;39:S159–S164.
- Menendez R, Torres A, Zalacain R, Aspa J, Martin-Villasclaras JJ, Borderias L, Benitez-Moya JM, Ruiz-Manzano J, de Castro FR, Blanquer J, et al. Guidelines for the treatment of community-acquired pneumonia: predictors of adherence and outcome. *Am J Respir Crit Care Med* 2005;172:757–762.
- Aujesky D, Fine MJ. Does guideline adherence for empiric antibiotic therapy reduce mortality in community-acquired pneumonia? *Am J Respir Crit Care Med* 2005;172:655–656.
- Mandell LA, File TM Jr. Short-course treatment of community-acquired pneumonia. *Clin Infect Dis* 2003;37:761–763.
- Christ-Crain M, Jaccard-Stolz D, Bingisser R, Gencay MM, Huber PR, Tamm M, Muller B. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. *Lancet* 2004;363:600–607.
- Wipf JE, Lipsky BA, Hirschmann JV, Boyko EJ, Takasugi J, Peugeot RL, Davis CL. Diagnosing pneumonia by physical examination: relevant or relic? *Arch Intern Med* 1999;159:1082–1087.
- Muller B. Procalcitonin and ventilator-associated pneumonia: yet another breath of fresh air. *Am J Respir Crit Care Med* 2005;171:2–3.
- Christ-Crain M, Muller B. Procalcitonin in bacterial infections: hype, hope, more or less? *Swiss Med Wkly* 2005;135:451–460.
- Muller B, Becker KL, Schachinger H, Rickenbacher PR, Huber PR, Zimmerli W, Ritz R. Calcitonin precursors are reliable markers of sepsis in a medical intensive care unit. *Crit Care Med* 2000;28:977–983.
- Becker KL, Nylén ES, White JC, Muller B, Snider RH Jr. Procalcitonin and the calcitonin gene family of peptides in inflammation, infection, and sepsis: a journey from calcitonin back to its precursors [Clinical Review 167]. *J Clin Endocrinol Metab* 2004;89:1512–1525.
- Linscheid P, Seboek D, Schaer DJ, Zulewski H, Keller U, Muller B. Expression and secretion of procalcitonin and calcitonin gene-related peptide by adherent monocytes and by macrophage-activated adipocytes. *Crit Care Med* 2004;32:1715–1721.
- Muller B, White JC, Nylén E, Snider RH, Becker KL, Habener JF. Ubiquitous expression of the calcitonin-1 gene in multiple tissues in response to sepsis. *J Clin Endocrinol Metab* 2001;86:396–404.
- Linscheid P, Seboek D, Nylén ES, Langer I, Schlatter M, Becker KL, Keller U, Muller B. *In vitro* and *in vivo* calcitonin I gene expression in parenchymal cells: a novel product of human adipose tissue. *Endocrinology* 2003;144:5578–5584.
- Nylén ES, Whang KT, Snider RH Jr, Steinwald PM, White JC, Becker KL. Mortality is increased by procalcitonin and decreased by an antiserum reactive to procalcitonin in experimental sepsis. *Crit Care Med* 1998;26:1001–1006.
- Wagner KE, Martinez JM, Vath SD, Snider RH, Nylén ES, Becker KL, Muller B, White JC. Early immunoneutralization of calcitonin precursors attenuates the adverse physiologic response to sepsis in pigs. *Crit Care Med* 2002;30:2313–2321.
- Harbarth S, Holeckova K, Froidevaux C, Pittet D, Ricou B, Grau GE, Vadas L, Pugin J. Diagnostic value of procalcitonin, interleukin-6, and interleukin-8 in critically ill patients admitted with suspected sepsis. *Am J Respir Crit Care Med* 2001;164:396–402.
- Christ-Crain M, Stolz D, Bingisser R, Huber P, Leuppi J, Müller C, Tamm M, Müller B. Procalcitonin guidance significantly reduces antibiotic duration in community-acquired pneumonia. Presented at the 45th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Washington, DC, December 16–19, 2005.
- Christ-Crain M, Stolz D, Bingisser R, Huber P, Leuppi J, Miedinger D, Müller C, Tamm M, Müller B. Procalcitonin guidance shortens antibiotic treatment in community-acquired pneumonia with similar outcome: the ProCAP study [abstract]. *Proc Am Thorac Soc* 2005;2:A798.
- Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, Gotzsche PC, Lang T. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med* 2001;134:663–694.
- Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, Coley CM, Marrie TJ, Kapoor WN. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med* 1997;336:243–250.
- Nylén ES, Muller B, Becker KL, Snyder RH. The future diagnostic role of procalcitonin levels: the need for improved sensitivity. *Clin Infect Dis* 2003;36:823–824.
- Halm EA, Teirstein AS. Clinical practice: management of community-acquired pneumonia. *N Engl J Med* 2002;347:2039–2045.
- Harbarth S, Garbino J, Pugin J, Romand JA, Lew D, Pittet D. Inappropriate initial antimicrobial therapy and its effect on survival in a clinical trial of immunomodulating therapy for severe sepsis. *Am J Med* 2003;115:529–535.
- Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. *Clin Infect Dis* 2004;39:206–217.
- Luyt CE, Guerin V, Combes A, Trouillet JL, Aayed SB, Bernard M, Gibert C, Chastre J. Procalcitonin kinetics as a prognostic marker of ventilator-associated pneumonia. *Am J Respir Crit Care Med* 2005;171:48–53.
- Muller B, Christ-Crain M, Nylén ES, Snider R, Becker KL. Limits to the use of the procalcitonin level as a diagnostic marker. *Clin Infect Dis* 2004;39:1867–1868.
- Hug B, Rossi M. A year's review of bacterial pneumonia at the central hospital of Lucerne, Switzerland. *Swiss Med Wkly* 2001;131:687–692.
- Carratala J, Fernandez-Sabe N, Ortega L, Castellsague X, Roson B, Dorca J, Fernandez-Aguera A, Verdager R, Martinez J, Manresa F, et al. Outpatient care compared with hospitalization for community-acquired pneumonia: a randomized trial in low-risk patients. *Ann Intern Med* 2005;142:165–172.
- File TM Jr, Lode H, Kurz H, Kozak R, Xie H, Berkowitz E. Double-blind, randomized study of the efficacy and safety of oral pharmacokinetically enhanced amoxicillin-clavulanate (2,000/125 milligrams) versus those of amoxicillin-clavulanate (875/125 milligrams), both given twice daily for 7 days, in treatment of bacterial community-acquired pneumonia in adults. *Antimicrob Agents Chemother* 2004;48:3323–3331.
- Musher DM, Alexandraki I, Graviss EA, Yanbeij N, Eid A, Inderias LA, Phan HM, Solomon E. Bacteremic and nonbacteremic pneumococcal pneumonia: a prospective study. *Medicine (Baltimore)* 2000;79:210–221.

39. Tan MJ, Tan JS, Hamor RH, File TM Jr, Breiman RF. The radiologic manifestations of Legionnaire's disease: the Ohio Community-based Pneumonia Incidence Study Group. *Chest* 2000;117:398–403.
40. Arancibia F, Bauer TT, Ewig S, Mensa J, Gonzalez J, Niederman MS, Torres A. Community-acquired pneumonia due to gram-negative bacteria and *Pseudomonas aeruginosa*: incidence, risk, and prognosis. *Arch Intern Med* 2002;162:1849–1858.
41. Genne D, Kaiser L, Kinge TN, Lew D. Community-acquired pneumonia: causes of treatment failure in patients enrolled in clinical trials. *Clin Microbiol Infect* 2003;9:949–954.
42. O'Donnell WJ, Kradin RL, Evins AE, Wittram C. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 39–2004. A 52-year-old woman with recurrent episodes of atypical pneumonia. *N Engl J Med* 2004;351:2741–2749.
43. Dunbar LM, Wunderink RG, Habib MP, Smith LG, Tennenberg AM, Khashab MM, Wiesinger BA, Xiang JX, Zadeikis N, Kahn JB. High-dose, short-course levofloxacin for community-acquired pneumonia: a new treatment paradigm. *Clin Infect Dis* 2003;37:752–760.
44. Schrag SJ, Pena C, Fernandez J, Sanchez J, Gomez V, Perez E, Feris JM, Besser RE. Effect of short-course, high-dose amoxicillin therapy on resistant pneumococcal carriage: a randomized trial. *JAMA* 2001; 286:49–56.
45. O'Doherty B, Muller O. Randomized, multicentre study of the efficacy and tolerance of azithromycin versus clarithromycin in the treatment of adults with mild to moderate community-acquired pneumonia: Azithromycin Study Group. *Eur J Clin Microbiol Infect Dis* 1998;17: 828–833.
46. Hoepelman IM, Mollers MJ, van Schie MH, Greefhorst AP, Schlosser NJ, Sinninghe Damste EJ, van de Moosdijk CN, Dalinghaus WH, Eland ME, Mol SJ, et al. A short (3-day) course of azithromycin tablets versus a 10-day course of amoxicillin–clavulanic acid (co-amoxiclav) in the treatment of adults with lower respiratory tract infections and effects on long-term outcome. *Int J Antimicrob Agents* 1997;9:141–146.
47. Dellamonica P. Preventing the risk of emergence of bacterial resistance associated with antibiotic therapy: what role for pharmacokinetic and pharmacodynamic data? *J Antimicrob Chemother* 2002;50:614–615.
48. Menendez R, Torres A, Rodriguez de Castro F, Zalacain R, Aspa J, Martin Villasclaras JJ, Borderias L, Benitez Moya JM, Ruiz-Manzano J, Blanquer J, et al. Reaching stability in community-acquired pneumonia: the effects of the severity of disease, treatment, and the characteristics of patients. *Clin Infect Dis* 2004;39:1783–1790.
49. Briel M, Christ-Crain M, Young J, Schuetz P, Huber P, Periat P, Bucher HC, Muller B. Procalcitonin-guided antibiotic use versus a standard approach for acute respiratory tract infections in primary care: study protocol for a randomised controlled trial and baseline characteristics of participating general practitioners [ISRCTN73182671]. *BMC Fam Pract* 2005;6:34.
50. Muller B, Peri G, Doni A, Perruchoud AP, Landmann R, Pasqualini F, Mantovani A. High circulating levels of the IL-1 type II decoy receptor in critically ill patients with sepsis: association of high decoy receptor levels with glucocorticoid administration. *J Leukoc Biol* 2002;72:643–649.
51. McCaig LF, Hughes JM. Trends in antimicrobial drug prescribing among office-based physicians in the United States. *JAMA* 1995;273:214–219.
52. Goossens H, Ferech M, Vander Stichele R, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet* 2005;365:579–587.
53. Dancer SJ. How antibiotics can make us sick: the less obvious adverse effects of antimicrobial chemotherapy. *Lancet Infect Dis* 2004;4:611–619.