Use of Procalcitonin to Shorten Antibiotic Treatment Duration in Septic Patients

A Randomized Trial

Vandack Nobre[1], Stephan Harbarth[2], Jean-Daniel Graf[3], Peter Rohner[4], and Jérôme Pugin[1]

[1]Intensive Care, [2]Infection Control Program, [3]Central Chemistry Laboratory, and [4]Microbiology Laboratory, University Hospitals of Geneva, and Faculty of Medicine, University of Geneva, Geneva, Switzerland

***Rationale*: The duration of antibiotic therapy in critically ill patients with sepsis can result in antibiotic overuse, increasing the risk of developing bacterial resistance.**

***Objectives*: To test the hypothesis that an algorithm based on serial measurements of procalcitonin (PCT) allows reduction in the duration of antibiotic therapy compared with empirical rules, and does not result in more adverse outcomes in patients with severe sepsis and septic shock.**

***Methods*: In patients randomly assigned to the intervention group, antibiotics were stopped when PCT levels had decreased 90% or more from the initial value (if clinicians agreed) but not before Day 3 (if baseline PCT levels were <1 μg/L) or Day 5 (if baseline PCT levels were ≥ 1 μg/L). In control patients, clinicians decided on the duration of antibiotic therapy based on empirical rules.**

***Measurements and* Main *Results*: Patients assigned to the PCT group had 3.5-day shorter median duration of antibiotic therapy for the first episode of infection than control subjects (intention-to-treat, n = 79, $P = 0.15$). In patients in whom a decision could be taken based on serial PCT measurements, PCT guidance resulted in a 4-day reduction in the duration of antibiotic therapy (per protocol, n = 68, $P = 0.003$) and a smaller overall antibiotic exposure ($P = 0.0002$). A similar mortality and recurrence of the primary infection were observed in PCT and control groups. A 2-day shorter intensive care unit stay was also observed in patients assigned to the PCT group ($P = 0.03$).**

***Conclusions*: Our results suggest that a protocol based on serial PCT measurement allows reducing antibiotic treatment duration and exposure in patients with severe sepsis and septic shock without apparent harm.**

Clinical trial registered with www.clinicaltrials.gov (NCT 00250666).

Keywords: procalcitonin; sepsis; intensive care; antibiotics; controlled trial

The duration of antibiotic therapy in critically ill patients with sepsis is based on empirical rules (1). It can result in antibiotic overuse, increasing the risk of developing bacterial resistance (2) and treatment-related costs (3).

Recent attempts to decrease the duration of the antibiotic therapy have been successful in critically ill patients (4). Patients with ventilator-associated pneumonia, for example, are equally well treated when they receive an 8-day treatment as compared with a 15-day course of antibiotics (5). This is, however, again based on empirical rules, and guidance of the duration of the antibiotic treatment customized for each patient and based on simple biomarkers could contribute an additional benefit.

Procalcitonin (PCT) is a rather specific marker for severe bacterial infection in patients presenting with suspected sepsis (6–8). PCT has been used to guide the initiation of antibiotic treatment in patients presenting in the emergency department with respiratory infection (9). This marker is also a useful tool to shorten the duration of antibiotic therapy in patients hospitalized with community-acquired pneumonia (10). In previous studies, we and others have shown that the dynamics of plasma PCT levels were markedly different between patients who died of sepsis compared with those who survived (7, 11). Despite a large body of literature in favor of this biomarker, there is still ongoing controversy about the clinical usefulness of PCT measurement in the critical care setting (12–14).

The aim of the present study was to test whether a simple algorithm based on the daily evolution of plasma PCT levels would help clinicians to shorten the duration of antibiotic therapy in critically ill patients with suspected or documented severe sepsis and septic shock. We hypothesized that a PCT-guided antibiotic discontinuation strategy may enable reducing antibiotic treatment duration without harming patients' safety. Preliminary results from this study were presented during the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Illinois, September 2007 (15).

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

The duration of antibiotic therapy in critically ill patients with sepsis is based on empirical rules, which may lead to antibiotic overuse and selection pressure.

What This Study Adds to the Field

The application of a decision algorithm based on plasma procalcitonin levels can significantly shorten the duration of antibiotic therapy and intensive care unit stay, without apparent harm to patients with severe sepsis and septic shock.

METHODS

Study Design

We conducted a randomized, controlled, open interventional trial involving patients with severe sepsis and septic shock hospitalized in our intensive care unit (ICU). In the PCT group, patients received antibiotics according to PCT guidance. In the control group, patients

(*Received in original form August 22, 2007; accepted in final form December 18, 2007*)

This study was presented in part at the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Illinois, September 2007.

Correspondence and requests for reprints should be addressed to Prof. Jérôme Pugin, M.D., Intensive Care, University Hospital of Geneva, 24, Micheli-du-Crest, 1211 Geneva 14, Switzerland. E-mail: jerome.pugin@medecine.unige.ch

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 177. pp 498–505, 2008
Originally Published in Press as DOI: 10.1164/rccm.200708-1238OC on December 20, 2007
Internet address: www.atsjournals.org

were treated according to standard practice. The study was approved by the ethics committee of University Hospitals of Geneva. Written, informed consent was obtained from all participants or a next of kin.

Study Setting and Subjects

This study was conducted at the University Hospitals of Geneva, Switzerland, a 1,200-bed tertiary care hospital. All patients with suspected severe sepsis or septic shock admitted to the ICU (32-bed, mixed medical and surgical adult patients with 3,200 admissions per year) from February 2006 to April 2007 were assessed for eligibility (Figure 1). Patients developing severe sepsis or septic shock during their ICU stay were also considered for enrollment. Patients were randomly assigned to either the PCT group or the control group if they met diagnostic criteria for severe sepsis or septic shock (16).

The reasons for exclusion were as follows: (*1*) microbiologically documented infections caused by *Pseudomonas aeruginosa*, *Acinetobacter baumanni*, *Listeria* spp., *Legionella pneumophila*, *Pneumocystis jiroveci*, or *Mycobacterium tuberculosis*, for which a prolonged duration of antibiotic therapy is standard-of-care (17); (*2*) severe infections due to viruses or parasites (e.g., hemorrhagic fever, malaria); (*3*) infectious conditions requiring prolonged antibiotic therapy (e.g., bacterial endocarditis, brain abscess, deep abscesses); (*4*) antibiotic therapy started 48 hours or more before enrollment; (*5*) chronic, localized infections (e.g., chronic osteomyelitis); (*6*) severely immunocompromised patients, such as patients infected with human immunodeficiency virus and with a CD4 count of less than 200 cells/mm^3, neutropenic patients (<500 neutrophils/mm^3), or patients on immunosuppressive therapy after solid organ transplantation; (*7*) withholding of life support; or (*8*) absence of antimicrobial treatment despite clinical suspicion of sepsis.

Variables recorded at baseline and daily during follow-up included demographic data, diagnosis, comorbidities, vital signs, respiratory parameters, routine blood tests, and results from microbiological cultures. The source of sepsis, when known, was also recorded. The severity of the patient's condition on admission was measured according to the Simplified Acute Physiology Score (SAPS) 3 (18). The presence of organ dysfunction was evaluated at baseline and daily during the entire ICU stay using the Sepsis-related Organ Failure Assessment (SOFA) score (19).

Cultures of urine, blood, bronchoalveolar lavage fluid, and tracheal aspirates were performed on admission and during ICU stay as clinically indicated. Blood gases and imaging exams were also performed as clinically indicated, similarly in both groups.

Interventions

The randomization was performed using a computer-based random number generation. Allocation was issued using opaque, sealed, numbered envelopes. All patients included in the study had circulating PCT levels measured at baseline and daily until the seventh day of follow-up (unless death or discharge occurred earlier), or until antibiotics were stopped in patients randomized to the PCT group. Thereafter, the PCT was measured at 5-day intervals even in those patients transferred to the ward. All patients received initial antibiotic therapy based on local guidelines and susceptibility patterns, according to the decision of the treating physician, who was unaware of the patient's initial PCT levels.

The study investigators did not interfere with the duration of antibiotic therapy in patients assigned to the control group. Broad-spectrum parenteral antibiotics were prescribed in patients with suspected severe sepsis or septic shock depending on the suspected source of infection and microbiological cultures, when available. The antibiotic spectrum was narrowed, when possible, based on cultures obtained after patient's admission. A combination of macrolides plus ceftriaxone or amoxicillin/clavulanic acid was initially administered in patients presenting with severe sepsis or septic shock due to community-acquired pneumonia.

In patients assigned to the PCT group presenting a favorable clinical course, investigators used predefined "stopping rules" based on circulating PCT levels to encourage caregivers to discontinue antibiotics (Figure E1 of the online supplement). Patients with baseline PCT level greater or equal to 1 μg/L were reevaluated at Day 5. Investigators

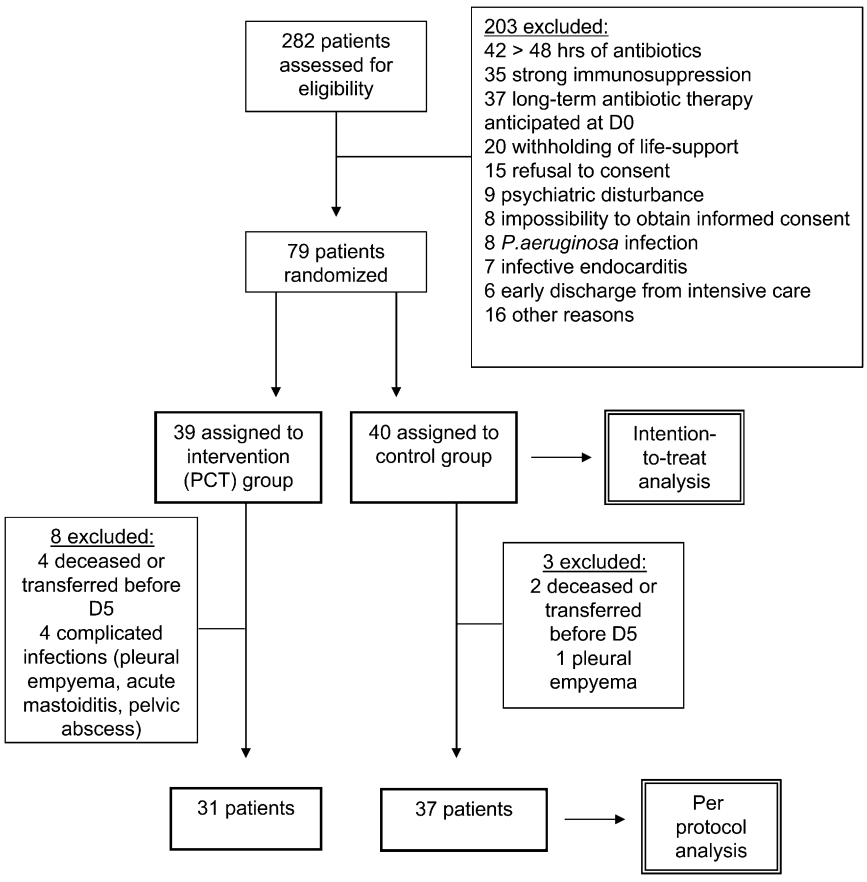

Figure 1. Trial profile. D0 = Day 0; D5 = Day 5; PCT = procalcitonin.

encouraged treating physicians to discontinue antibiotics when (*1*) PCT dropped more than 90% from the baseline peak level or (*2*) an absolute value below 0.25 μg/L was reached. Patients with PCT levels below 1 μg/L at baseline were reevaluated at Day 3, and treating physicians were encouraged to discontinue antibiotics when the PCT level was below 0.1 μg/L, and careful clinical evaluation ruled out severe infection. Of note, the final decision concerning the antibiotic therapy duration was always left to the discretion of the physician in charge. Cases in whom the antibiotic treatment was continued despite the encouragement of the investigators to stop it were classified as "algorithm overruling." Finally, patients with positive blood cultures were assured to receive at least 5 full days of parenteral antibiotic therapy.

PCT Measurement

Peripheral blood samples were collected in the morning, using vacuum tubes (BD Vacutainer SST II Plus plastic tubes; Becton Dickinson Diagnostic Systems, Allschwil, Switzerland). Circulating plasma PCT levels were measured with a time-resolved amplified cryptate emission technology assay (Kryptor PCT; Brahms AG, Hennigsdorf, Germany), with an assay sensitivity of 0.06 μg/L, approximately fourfold above mean normal levels (20). Measurements were performed 7 days a week. The time to obtain plasma PCT levels is about 1 hour, including centrifugation of blood and plasma PCT measurement. Results were provided to the clinical team within 3 hours after blood drawing for patients randomized in the PCT group, but kept in the laboratory and not communicated to the treating physicians of control patients.

Outcome

The primary endpoint was systemic antibiotic exposure (21), measured using three variables:

1. The "duration of antibiotic treatment" after inclusion, expressed in days, and corresponding to the antibiotic therapy given for the first episode of infection for which the patient was included in the study.
2. The incidence density of "antibiotic exposure days," defined as a period of continuous administration of a single antibiotic agent with no interruption, for more than 24 hours, per 1,000 inpatient days. This variable includes all antibiotics administered for more than 24 hours during the study's follow-up (28 d). The incidence rate ratio (IRR) of antibiotic exposure was calculated by the ratio of total antibiotic exposure days between control group and PCT group patients.
3. The "days alive without antibiotics," defined as a period of at least 24 hours without antibiotic administration for a given patient, and comprising the entire follow-up period (28 d, unless death or discharge occurred earlier).

Secondary endpoints were 28-day mortality, in-hospital mortality, length of stay in the ICU and hospital, clinical cure (defined as clinical signs and symptoms present at baseline that had resolved by the final clinical assessment), reoccurrence of the initial infection, and nosocomial superinfection. Death was classified as sepsis related or sepsis unrelated. Nosocomial superinfections were defined according to standard criteria and were generated from data of an ongoing surveillance system (22, 23).

Statistical Analysis

Discrete variables are expressed as percentage and continuous variables as mean ± SD for variables normally distributed and as median with range for nonnormally distributed variables. Patients were observed for at least 28 days from enrollment, or until death or loss to follow-up if either occurred in the interim. Primary endpoints were first analyzed on the basis of an intention-to-treat analysis, including all randomized patients. We then performed a "per protocol analysis" including patients with at least 5 days of follow-up under antibiotic therapy (or 3 d if baseline PCT value < 1 μg/L), because this was the population targeted in this study (i.e., patients in whom a decision to stop antibiotics could be taken on the basis of the PCT levels) (Figure 1). Patients with a diagnosis of complicated infections requiring extended antibiotic therapy (e.g., empyema, deep abscesses, endocarditis) established within 5 days after enrollment in case of initial PCT levels above or equal to 1 μg/L or within 3 days if the baseline PCT value was below 1 μg/L, as well as patients who died or were transferred to other centers before a decision could be taken, were kept in the intention-to-treat analysis, but excluded from the per-protocol analysis.

The trial was designed to enroll at least 66 patients, to obtain a power of 90% to detect a 33% (4 d) difference in the duration of antibiotic therapy for the initial infection between the two groups based on an estimated baseline duration of 12 days. We assumed an SD of 5 days in both groups and an α error of 0.05. Comparability of the standard group and the PCT group was analyzed by the χ^2 test (Yates' test or Fisher's exact test), two-sample *t* test, and Mann-Whitney *U* test, as appropriate.

A cumulative frequency distribution curve for the time to discontinuation of antibiotic treatment was compared between the two study groups using the log-rank test. The rate of antibiotic treatment discontinuation was estimated using Cox proportional hazards regression analysis, after adjustment for severity of illness at baseline. Results are presented as crude (unadjusted) and multivariate (adjusted) hazard ratios (HRs) and their 95% confidence intervals (CIs). Collected data were entered into a relational database (Access 2000; Microsoft Corp., Redmond, WA) and then converted into STATA files (STATA 9.1; Stata Corp., College Station, TX) for analysis. Significance was reported at a P value of 0.05 or less.

RESULTS

Study Patients

Seventy-nine of the 282 patients screened for eligibility were randomized; 39 in the PCT group and 40 in the control group (Figure 1). Baseline characteristics of all included patients are shown in Table E1. The two groups had similar demographic, clinical (including severity of illness at the time of admission), and laboratory characteristics (Table E1). A similar proportion of patients with community-acquired sepsis was included in both groups (71% in the PCT group vs. 65% control group, $P = 0.35$). Sepsis of pulmonary origin predominated in both groups, occurring in 67% of patients in the control group and 64% of patients in the PCT group ($P = 0.93$). Forty-two percent of the control group patients had septic shock as compared with 43.6% of those in the PCT group ($P = 0.89$). The 28-day mortality was 20% in the control group and 20.5% in the PCT group ($P = 0.82$). Twenty-five percent of the deaths in the control group (2/8 patients) were potentially related to sepsis, compared with 37.5% in the PCT group (3/8 patients, $P = 0.96$).

Median PCT levels on admission were similar in patients from the two groups (5.9 μg/L; range, 0.1–497 μg/L, in the control group, vs. 8.4 μg/L; range, 0.1–93.2 μg/L, in the PCT group; $P = 0.75$; Figure 2). Seven (17.5%) control patients and eight (20.5%) PCT patients had PCT levels on admission that were below 1 μg/L ($P = 0.9$).

Microbiology

The rate of microbiologically confirmed sepsis did not differ significantly between the PCT and the control group (47.5 vs. 53.8%, respectively; $P = 0.73$). Blood cultures were positive in 27.5% of patients in the control group and 35.9% in the PCT group ($P = 0.57$). Forty-nine causative microorganisms (24 in the PCT group and 25 in the control group) were isolated in different clinical specimens. The most frequent pathogens were *Escherichia coli* (28%, control group, vs. 29.1%, PCT group), *Streptococcus pneumoniae* (12%, control group, vs. 41.6%, PCT group), *Klebsiella* spp. (8%, control group, vs. 8.3%, PCT group), other enterobacteriaceae (12%, control group, vs. 4.1%, PCT group), and *Staphylococcus aureus* (12%, control group, vs. 4.1%, PCT group). No significant difference was observed in baseline

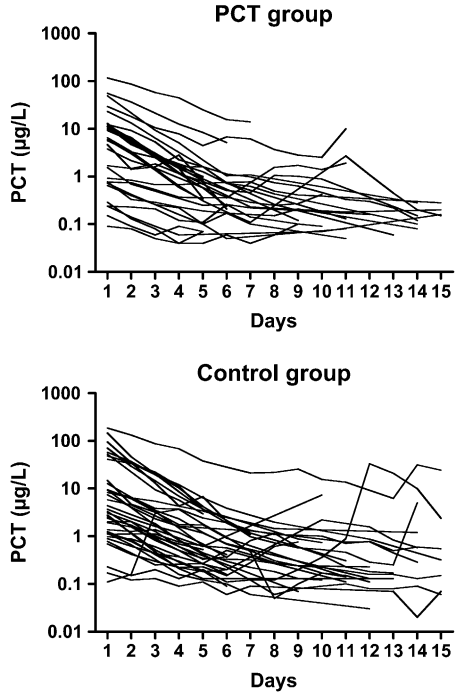

Figure 2. Plasma procalcitonin (PCT) levels over time in patients from the PCT group (n = 31) (*A*) and in control subjects (n = 37) (*B*), per-protocol analysis.

PCT levels and in the time course of PCT levels in patients with gram-positive versus gram-negative infections (data not shown).

Primary Endpoints

Overall, antibiotic exposure was lower in patients in whom antibiotics were interrupted according to the algorithm based on PCT levels. In the intention-to-treat analysis, the median of antibiotic duration for treatment of the first episode of infection was 3.5 days shorter in the PCT group (6 d; range, 2–33 d) than in the control group (9.5 d; range, 3–34 d), although this difference did not achieve statistical significance ($P = 0.15$, Table 2). Total antibiotic exposure days were lower in patients from the PCT group compared with controls (504 vs. 655 d, respectively; IRR, 1.1; 95% CI, 0.9–1.3; $P = 0.07$). More days alive without antibiotics were observed in patients from the PCT group than in those from the control group (mean ± SD: 15.3 ± 8.9 vs. 13.3 ± 8.2 d, respectively; $P = 0.28$).

Because of dropouts (early deaths and newly discovered complicated infections), 68 patients (control group, n = 37, and PCT group, n = 31) reached a time when a decision to stop antibiotics could be taken (PCT group) or potentially be taken (control group) based on the relative decrease of daily measured PCT levels (per-protocol analysis, Figure 1). Similarly to the intention-to-treat analysis, the two groups were balanced according to baseline characteristics (Table 1). "Algorithm overruling" in the PCT group (i.e., treating physician refused to stop the antibiotics, although the stopping rules allowed this) occurred in 6 of 31 (19%) patients of the PCT group. Patients strictly treated according to the PCT-guided protocol (deleting patients who had the algorithm overruled) had a significantly shorter median duration of antibiotic therapy for the first episode of infection than those in whom the protocol was not applied (6 d; range, 4–16 d, vs. 12.5 d; range, 8–16 d; $P = 0.0002$). In no case assigned to the PCT group did the treating physicians stop antibiotics before the time when patients had reached the criteria for discontinuation based on the algorithm.

Overall, the median antibiotic duration for the first episode of infection was significantly reduced in patients randomized to the PCT group compared with controls (6 d; range, 4–16 d, vs. 10 d; range, 3–33 d; $P = 0.003$). The probability to have antibiotics stopped earlier was almost twofold higher in the PCT group than in the control group (HR, 1.9; 95% CI, 1.2–3.1; $P = 0.009$; Figure 3). This difference persisted after adjusting for disease severity (SAPS 3) and type of sepsis (adjusted HR, 1.9; 95% CI, 1.2–3.2; $P = 0.009$). Patients assigned to PCT-guided antibiotic therapy had significantly fewer total antibiotic exposure days compared with control subjects (IRR, 1.3; 95% CI, 1.1–1.5; $P = 0.0002$; Table 3). Finally, the mean number of days alive without antibiotics was significantly higher in patients from the PCT group compared with those in the control group (17.4 ± 7.6 vs. 13.6 ± 7.6 d, respectively; $P = 0.04$). Similar significant results were observed when considering only the subset of patients with a PCT level at admission above or equal to 1 µg/L (Table E2). A recurrence of the primary infection after discontinuation of the antibiotic therapy occurred in one patient in each group ($P = 0.7$).

For the 22 patients with a positive blood culture (11 patients in each group), the median duration of antibiotic therapy was significantly shorter in patients assigned to the PCT group as compared with those assigned to the control group (7 d; range, 6–13 d, vs. 13 d; range, 6–33 d; $P = 0.01$; Table E3). Despite the relatively short duration of treatment in bacteremic patients assigned to the PCT group, no case of recurrence of infection was observed in these patients (Table E3).

Secondary Endpoints

In patients in whom a decision could be made based on PCT levels (per-protocol analysis), the antibiotic therapy resulted in a clinical cure in 83.8% of control patients and in 90.3% of patients from the PCT group ($P = 0.48$, Table 3). The 28-day mortality was 16.2% in both groups ($P = 0.74$, Table 3). Three deaths in the PCT group versus one death in the control group were considered to be related to sepsis. Two of the three patients who died in the PCT group were still receiving antibiotics at the time of death, due to a "refractory infection" as estimated by the treating physicians. The third patient died 7 days after the discontinuation of the initial antibiotic therapy (community-acquired pneumonia considered to be cured) from septic shock due to a secondary bowel perforation. The in-hospital mortality was also similar between the two groups (19.4% in the PCT group vs. 18.9% in the control group; $P = 0.79$; Table 3). Eleven of 37 (29.7%) patients in the control group and 7 of 31 (22.5%) patients in the PCT group presented with one or more episodes of nosocomial infection during the follow-up period ($P = 0.20$).

Patients randomized to the PCT group had a significantly shorter median ICU length of stay than control subjects (3 d; range, 1–18 d, vs. 5 d; range, 1–30 d, respectively; $P = 0.03$; Figure 4 and Table 3), and a tendency to stay for a shorter period in the hospital (14 d; range, 5–64 d, vs. 21 d; range, 5–89 d; $P = 0.16$; Figure 4 and Table 3).

DISCUSSION

We observed a significant reduction in antibiotic use, without apparent harm in patients with severe sepsis and septic shock for whom a decision could be made based an algorithm of serial PCT measurements (per-protocol analysis). Interestingly, patients assigned to the PCT group had a significantly shorter ICU length of stay. The duration of antimicrobial treatment is usually based on empirical rules. This is also the case for septic

TABLE 1. BASELINE CHARACTERISTICS OF THE PATIENTS (PER-PROTOCOL ANALYSIS)

Characteristic	Control Group (*n* = 37)	Procalcitonin Group (*n* = 31)	*P* Value
Age, yr, mean ± SD	66.9 ± 13.8	64.0 ± 12.3	0.36
Female sex, n (%)	12 (32.4)	10 (32.3)	0.80
Baseline organ failure, n (%)			
Acidosis	20 (54.1)	14 (45.2)	0.62
ARDS D0	6 (16.2)	7 (22.6)	0.72
Coma D0	4 (10.8)	5 (16.1)	0.38
Dialysis D0	4 (10.8)	5 (16.1)	0.38
Heart failure D0	2 (5.4)	2 (6.5)	0.62
Respiratory failure D0	28 (75.7)	23 (74.2)	0.88
Shock D0	20 (54.1)	14 (45.2)	0.62
Renal failure D0	5 (13.5)	1 (3.2)	0.14
Comorbidities, n (%)			
Neoplasia	5 (13.5)	12.9	0.61
Immunosuppression	1 (2.7)	1 (3.2)	0.70
Cardiopathy	17 (45.5)	11 (35.5)	0.85
COPD	7 (18.9)	12 (38.7)	0.12
ID diabetes mellitus	2 (5.4)	0	0.29
Non-ID diabetes mellitus	6 (16.2)	12.9	0.48
Chronic renal failure	6 (16.2)	2 (6.5)	0.19
Peripheral vascular disease	1 (2.7)	1 (3.2)	0.70
Chronic hepatopathy	5 (13.5)	5 (16.1)	0.51
Baseline characteristics of sepsis			
Pulmonary sepsis, n (%)	25 (67.6)	22 (71.0)	0.96
Abdominal sepsis, n (%)	6 (16.2)	2 (6.5)	0.27
Urinary sepsis, n (%)	5 (13.5)	5 (16.1)	0.96
Other sepsis, n (%)	1 (2.7)	2 (6.5)	0.58
Septic shock, n (%)	16 (43.2)	48.4	0.85
SAPS 3, points (mean ± SD)	70.1 ± 13.1	68.5 ± 12.1	0.60
SOFA, points (mean ± SD)	6.6 ± 3.0	6.4 ± 3.3	0.74
Laboratory			
Positive blood culture, n (%)	11 (29.7)	11 (35.5)	0.80
Baseline procalcitonin μg/L, median (range)	5.4 (0.1–354)	7.3 (0.1–93)	0.76
Procalcitonin < 1 μg/L, n (%)	6 (16.2)	7 (22.5)	0.72
Adjuvant therapy for sepsis, n (%)			
Ventilatory support	30 (81.1)	26 (83.9)	0.50
Vasopressors and/or inotropes	23 (62.2)	16 (51.6)	0.52

Definition of abbreviations: ARDS = acute respiratory distress syndrome; COPD = chronic obstructive pulmonary disease; D0 = Day 0; ID = insulin-dependent; SAPS = Simplified Acute Physiology Score; SOFA = Sequential Organ Failure Assessment.

patients, in whom antibiotic overuse is frequent (24), resulting in development of bacterial resistance (2) and increasing costs (3). Significant progress has been made in the last years to reduce the duration of antibiotic therapy in infected patients (25). On the basis of an empirical protocol, Chastre and colleagues showed that both the 28-day mortality and the frequency of recurrent infections were similar between patients receiving 15 days of antibiotic therapy and those treated for only 8 days (5). Of note, patients with pneumonia caused by nonfermenting gram-negative bacilli had a higher rate of recurrence of pulmonary infections when treated for only 8 days (5).

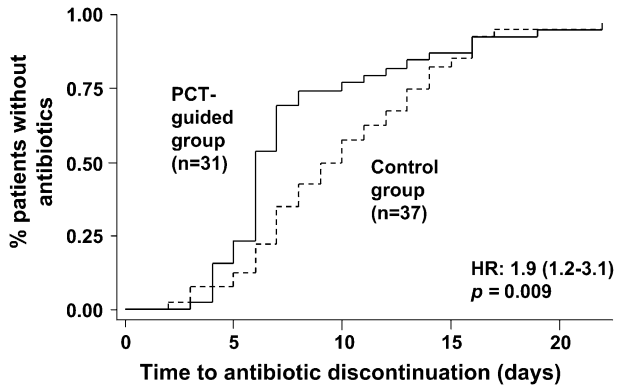

Figure 3. Kaplan-Meier plots showing the evolution with time of the percentage of patients who remained on antibiotics in the procalcitonin (PCT) and control group. HR = hazard ratio.

Much effort has been put into the search for sensitive and specific tools to guide antibiotic therapy in septic patients (26). Many clinicians agree that a noninvasive and readily available biochemical parameter would be highly desirable to attain this goal. PCT was demonstrated to be more accurate for the diagnosis of bacterial sepsis than any other routinely used inflammatory marker (7, 8, 27). Moreover, slowly decreasing, persistently elevated (7), or increasing PCT levels (11) are associated with poor outcomes in patients with severe infections. Three recent interventional trials have tested the role of PCT in guiding antibiotic therapy in patients admitted to the emergency department, either by limiting the use of these drugs in patients with low probability of bacterial infection or by shortening the duration of antimicrobial treatment. Overall, it was shown that PCT guidance allows reducing the use of antibiotics in patients presenting with symptoms of lower respiratory tract infection (9), in patients with acute exacerbation of chronic bronchitis (28), and in patients with community-acquired pneumonia (10). It should be emphasized that most of the published interventional studies on PCT predominantly enrolled mildly to moderately ill patients, except for the Procalcitonin Guidance of Antibiotic Therapy in Community-Acquired Pneumonia (ProCAP) study (10), which included a significant proportion of patients with severe community-acquired infections.

TABLE 2. OUTCOMES USING INTENTION-TO-TREAT ANALYSIS

Intention-to-Treat Analysis	Control Group (*n = 40*)	PCT Group (*n = 39*)	RR or Mean Difference (*95% CI*)	*P* Value
Primary outcomes				
Duration of antibiotic therapy, first episode of infection, median d (range)	9.5 (2–33)	6 (3–34)	Mean difference: 2.6 (−0.3 to 5.5)	0.15
Total antibiotic exposure days/1,000 d	644	541	1.1 (0.9 to 1.3)*	0.07
Days alive without antibiotics (mean ± SD)	13 ± 8.2	15.3 ± 8.9	Mean difference: 2.3 (−5.9 to 1.8)	0.28
Secondary outcomes				
Clinical cure, n (%)	32 (80)	31 (79.4)	1.0 (0.6 to 1.8)	0.82
28-d mortality, n (%)	8 (20)	8 (20.5)	0.9 (0.6 to 1.7)	0.82
In-hospital mortality, n (%)	9 (22.5)	9 (23.1)	0.9 (0.6 to 1.7)	0.83
Sepsis-related death, n (%)	2 (25)	3 (37.5)	0.7 (0.2 to 2.4)	0.96
Primary infection relapse rate, n (%)	1 (2.5)	1/39 (2.6)	1.0 (0.2 to 4.1)	0.74
ICU length of stay, median d (range)	7 (1–91)	4 (1–21)	Mean difference: 4.6 (1.0 to 8.2)	0.02
Hospital length of stay, median d (range)	23.5 (5–44)	17 (3–96)	Mean difference: 2.5 (−1.5 to 6.5)	0.85

Definition of abbreviations: CI = confidence interval; ICU = intensive care unit; PCT = procalcitonin; RR = relative risk.
* In these cases, the result expresses the index of relative risk.

Our study is the first randomized clinical trial in which a surrogate biochemical parameter was used to reduce the duration of antibiotic therapy in a population of critically ill patients admitted to the ICU for severe sepsis and septic shock. More than half of them required high-dose vasopressors, and 80% required mechanical ventilation. The effect on antibiotic use was most pronounced in patients in whom a decision could be made based on serial PCT measurements (per-protocol analysis). It is worthy to stress that in 19% of patients allocated to the PCT group, treating physicians refused to stop the antibiotics, although the stopping rules allowed this (Table E4). We can consider protocol overruling (i.e., prolongation of the antibiotic therapy by the treating physician beyond the stopping rule) as a "conservative bias." Interestingly, the median duration of antibiotic therapy in septic patients with positive blood culture was 7 days in the PCT group compared with 13 days in control patients (Table E3). In many centers, a minimum of 14 days of parenteral antibiotic therapy is the empirical rule for treatment of bacteremia in the context of sepsis. Although the numbers were small (11 patients), neither a recurrence of the primary infection nor increased mortality was noted in PCT patients who were treated for 1 week only.

Reducing the use of antibiotics in septic patients may result in several potential advantages. First, limiting the exposure to antibiotics is potentially the best strategy to avoid the selection of resistant bacteria and decrease the risk of cross-contamination between patients with these resistant microorganisms (29). Second, the use of prolonged antimicrobial therapy is associated with costs, particularly when broad-spectrum agents are used (3). An additional and even more impressive impact on the treatment-related costs may be expected from the possible reduction of hospital and ICU length of stay consequent to the shorter duration of intravenous antibiotic therapy. This effect was observed in our study, yet further studies have to confirm this finding. Although we do not have a definite explanation for this finding, it is conceivable that caregivers considered it safe to discharge their patients from the ICU (and subsequently from the hospital) because no adverse event was observed after earlier than anticipated antibiotic discontinuation. Finally, in contrast with empirical rules, the present study allows the clinician to customize the duration of antibiotic therapy in septic patients on the basis of an objective and reliable biomarker. It is likely that different septic patients may need different lengths of antibiotic therapy depending on the

TABLE 3. OUTCOMES USING PER-PROTOCOL ANALYSIS

Per-Protocol Analysis	Control Group (*n = 37*)	PCT Group (*n = 31*)	RR (*95% CI*)	*P* Value
Primary outcomes				
Duration of antibiotic therapy, first episode of infection, median d (range)	10 (3–33)	6 (4–16)	Mean difference: 3.2 (1.1 to 5.4)	0.003
Total antibiotic exposure days/1,000 d	655	504	1.3 (1.1 to 1.5)*	0.0002
Days alive without antibiotics, mean ± SD	13.6 ± 7.6	17.4 ± 7.6	Mean difference: 3.8 (0.1 to 7.5)	0.04
Secondary outcomes				
Clinical cure, n (%)	31 (83.8)	28 (90.3)	0.8 (0.5 to 1.3)	0.48
28-d mortality, n (%)	6 (16.2)	5 (16.1)	1.0 (0.5 to 1.8)	0.74
In-hospital mortality, n (%)	7 (18.9)	6 (19.4)	0.9 (0.6 to 1.7)	0.79
Sepsis-related death, n (%)	1/6 (16.6)	3/5 (60)	0.3 (0.1 to 2.0)	0.44
Primary infection relapse rate, n (%)	1 (2.7)	1 (3.2)	0.9 (0.9 to 3.7)	0.70
ICU length of stay, median d (range)	5 (1–30)	3 (1–18)	Mean difference: 4.3 (0.4 to 8.3)	0.03
Hospital length of stay, median d (range)	21 (5–89)	14 (5–64)	Mean difference: 2.2 (−1.9 to 6.3)	0.16

For definition of abbreviations, *see* Table 2.
* In these cases, the result expresses the index of relative risk.

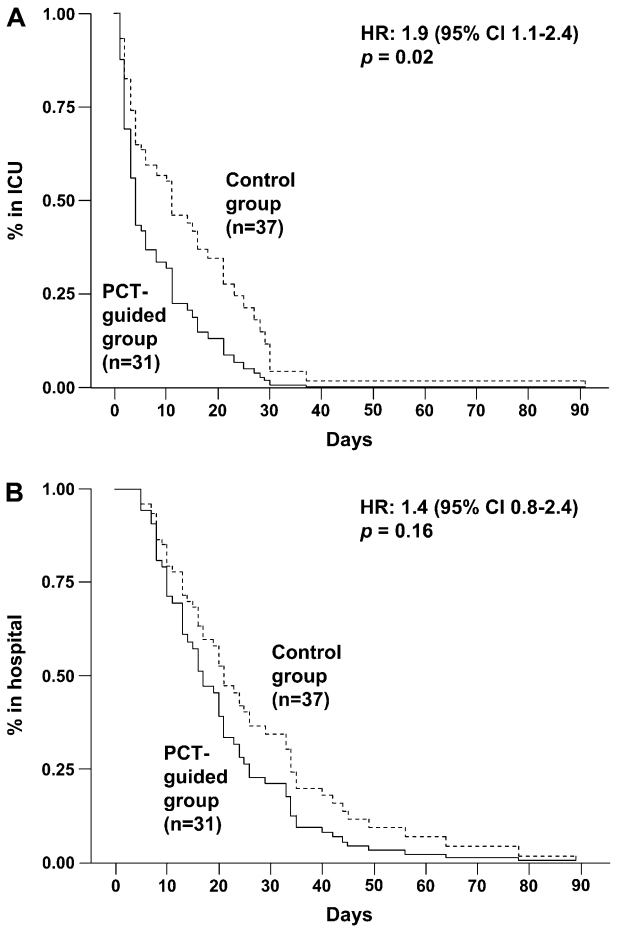

Figure 4. Kaplan-Meier plots showing the evolution with time of the percentage of patients remaining in the intensive care unit (ICU) (*A*) and in the hospital (*B*), in the procalcitonin (PCT) and the control group. HR = hazard ratio.

virulence of the causative microorganism and the clearance rate of the infectious process, factors potentially reflected in the rate of decrease of plasma PCT levels (Table E5).

Several limitations of the present study must be considered. First, this is a single-center study with a relatively small sample of patients, which could limit generalizing the results. Although we did not find signals of higher mortality or increased recurrence of the primary infection in the PCT group, we cannot exclude a potential harm of shortening antibiotic therapy based on PCT guidance given the relatively small number of patients studied. A noninferiority trial giving a definite answer on the safety of PCT-guided therapy, based on our results, would need to include several hundreds of septic patients per arm. Second, the number of dropouts observed in this trial was imbalanced between the two groups (8 patients in the PCT group vs. 3 patients in the control group, $P = 0.197$). However, the inclusion criteria for the per-protocol analysis were *a priori* defined, and all "dropout" decisions were made without identification of the patient's assignment group. It should be stressed that the patients included in the per-protocol analysis correspond to the target population for PCT guidance in real-life conditions. Third, the observed median duration of antibiotic therapy in the control group was somewhat shorter than expected in patients with severe sepsis and septic shock (10 d vs. 12 d anticipated). This may be due to a worldwide tendency to shorten empirical antibiotic duration or to a learning curve by treating physicians in our ICU who had detected that a short duration in the PCT group was not associated with significant harm. In any case, this represents a conservative bias reinforcing the usefulness of a PCT-guided approach. Fourth, the proportional frequency of bacterial species isolated was somewhat imbalanced between the two groups, with a higher incidence of *S. pneumoniae* in the PCT group. Whether this influenced outcomes is difficult to determine, because the optimal duration of antibiotic therapy for severe pneumococcal diseases is not known. Eighty percent of patients with pneumococcal infection in our study required mechanical ventilation, showing the severity of these cases. It remains possible, however, that patients with severe pneumococcal infection, but correctly treated (30), have a particularly rapid decrease in PCT levels, which may have positively impacted on the results of our study. Fifth, a small proportion of patients included in the study had low baseline PCT levels. These may correspond to false negatives or patients misdiagnosed at the time of admission, suffering from noninfectious systemic inflammatory response syndrome. Many of these patients, however, had microbiological cultures confirming bacterial infections (mostly ventilator-associated pneumonia). These cases may reflect low-grade bacterial infection, and such patients might benefit from an early reassessment and shorter antibiotic treatment duration, as proposed in our protocol.

Finally, the algorithm proposed in the present study cannot apply to all patients presenting in the ICU with severe sepsis and septic shock. For security, we excluded difficult-to-treat microorganisms, infections that are known to require prolonged antibiotic therapy, and severely immunocompromised and neutropenic patients.

Our data support the concept that PCT guidance allows reducing antibiotic exposure in critically ill patients with severe sepsis and septic shock, and that this strategy is not associated with worse outcomes. However, to evaluate if a PCT-based strategy is cost-efficient under real-life conditions, cost aspects should be carefully considered. In the ProCAP study, Christ-Crain and colleagues showed that despite a 6-day reduction in antibiotic use in patients enrolled in the PCT-guided group, the cost of the PCT measurement limited the daily use of this marker (10). Thus, lowering the price of PCT measurement may be crucial if the test is to be established as a cost-efficient measure for antibiotic stewardship in a public health perspective. In the present study, we performed daily measurement of PCT in the context of a clinical study protocol. However, the number of PCT measurements could be reduced in real life according to the "stopping rules" defined in our study. Only two to three PCT measurements (e.g., on Day 0 and Day 5, plus 1 subsequent day) may allow stopping antibiotics in a majority of patients. Three PCT dosages correspond to $177 at the current selling price in Switzerland. The PCT-related costs are therefore likely to be counterbalanced by the savings due to a 4-day shortening of parenteral antibiotic therapy. If indirect cost savings, such as shortening of ICU and hospital lengths of stay, are taken into account, then costs related to PCT measurement will largely be outweighed by those savings. Further studies are also needed to demonstrate the impact of shortening the duration of antibiotic therapy on important outcomes such as (*1*) the rate of nosocomial infections in critically ill patients and (*2*) the incidence of colonization and infection with multiresistant bacteria in the ICU.

Conclusions

An algorithm based on serial PCT measurements allows more judicious antibiotic use in patients with severe sepsis and septic

shock hospitalized in the ICU by reducing antibiotic exposure and lengths of hospital and ICU stay. No difference in 28-day mortality, clinical cure, and infection relapse rates was observed between patients treated according to PCT guidance and patients managed according to standard practice. A multicenter trial enrolling a large number of patients with severe sepsis and septic shock to test our PCT guidance protocol and its effect on ICU length of stay is desirable to validate our data.

Conflict of Interest Statement: V.N. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. S.H. and J.P. received a research grant from BRAHMS AG ($50,000). BRAHMS AG had no influence on study design, data analysis, or final preparation of this manuscript. S.H. received speaker honoraria ($1,500) from BRAHMS AG. J.-D.G. does not have a financial relationship with a commerical entity that has an interest in the subject of this manuscript. P.R. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.P. received speaking honoraria from BRAHMS AG (less than $1,000 in 2006 and 2007).

Acknowledgment: The authors thank the medical and nursing staff of the ICU at the University Hospitals of Geneva for their participation in the study, Jérôme Choffat for performing PCT measurements, and Louise Riberdy for helping with patient recruitment.

References

1. Calandra T, Cohen J. The International Sepsis Forum Consensus Conference on definitions of infection in the intensive care unit. *Crit Care Med* 2005;33:1538–1548.
2. Malhotra-Kumar S, Lammens C, Coenen S, Van Herck K, Goossens H. Effect of azithromycin and clarithromycin therapy on pharyngeal carriage of macrolide-resistant streptococci in healthy volunteers: a randomised, double-blind, placebo-controlled study. *Lancet* 2007;369: 482–490.
3. Evans HL, Lefrak SN, Lyman J, Smith RL, Chong TW, McElearney ST, Schulman AR, Hughes MG, Raymond DP, Pruett TL, *et al.* Cost of gram-negative resistance. *Crit Care Med* 2007;35:89–95.
4. Harbarth S, Nobre V, Pittet D. Does antibiotic selection impact patient outcome? *Clin Infect Dis* 2007;44:87–93.
5. Chastre J, Wolff M, Fagon JY, Chevret S, Thomas F, Wermert D, Clementi E, Gonzalez J, Jusserand D, Asfar P, *et al.* Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. *JAMA* 2003;290:2588–2598.
6. Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuon C. High serum procalcitonin concentrations in patients with sepsis and infection. *Lancet* 1993;341:515–518.
7. 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.
8. 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.
9. 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.
10. Christ-Crain M, Stolz D, Bingisser R, Muller C, Miedinger D, Huber PR, Zimmerli W, Harbarth S, Tamm M, Muller B. Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. *Am J Respir Crit Care Med* 2006;174:84–93.
11. Jensen JU, Heslet L, Jensen TH, Espersen K, Steffensen P, Tvede M. Procalcitonin increase in early identification of critically ill patients at high risk of mortality. *Crit Care Med* 2006;34:2596–2602.
12. Tang BM, Eslick GD, Craig JC, McLean AS. Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis. *Lancet Infect Dis* 2007;7:210–217.
13. Muller B, Christ-Crain M, Schuetz P. Meta-analysis of procalcitonin for sepsis detection. *Lancet Infect Dis* 2007;7:498–499.
14. Reinhart K, Brunkhorst FM. Meta-analysis of procalcitonin for sepsis detection. *Lancet Infect Dis* 2007;7:500–502.
15. Nobre V, Harbarth S, Graf J-D, Rohner P, Pugin J. Procalcitonin guidance allows shortening antibiotic treatment duration in patients with severe sepsis and septic shock: results of a randomized clinical trial [abstract L-613]. Presented at the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy meeting, Chicago, IL; September 17, 2007.
16. Bone RC, Sibbald WJ, Sprung CL. The ACCP-SCCM consensus conference on sepsis and organ failure. *Chest* 1992;101:1481–1483.
17. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, Dowell SF, File TM Jr, Musher DM, Niederman MS, *et al.* Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007;44:S27–S72.
18. Metnitz PG, Moreno RP, Almeida E, Jordan B, Bauer P, Campos RA, Iapichino G, Edbrooke D, Capuzzo M, Le Gall JR. SAPS 3: from evaluation of the patient to evaluation of the intensive care unit. Part 1: objectives, methods and cohort description. *Intensive Care Med* 2005;31:1336–1344.
19. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, Reinhart CK, Suter PM, Thijs LG, for the Working group on Sepsis-related Problems of the European Society of Intensive Care Medicine. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Med* 1996;22:707–710.
20. Nylen E, Muller B, Becker KL, Snider R. The future diagnostic role of procalcitonin levels: the need for improved sensitivity. *Clin Infect Dis* 2003;36:823–824. [Author reply, 826–827.]
21. Harbarth S, Viot M, Beeler I, Klastersky J, Szucs T. Variation in antimicrobial utilization for febrile neutropenia in cancer patients. The CEMIC study group (Club d'Etudes des Maladies Infectieuses en Cancer). *Infection* 2000;28:375–378.
22. Hugonnet S, Eggimann P, Sax H, Touveneau S, Chevrolet JC, Pittet D. Intensive care unit-acquired infections: is postdischarge surveillance useful? *Crit Care Med* 2002;30:2636–2638.
23. Eggimann P, Hugonnet S, Sax H, Harbarth S, Chevrolet JC, Pittet D. Long-term reduction of vascular access-associated bloodstream infection. *Ann Intern Med* 2005;142:875–876.
24. Harbarth S. Nosocomial transmission of antibiotic-resistant microorganisms. *Curr Opin Infect Dis* 2001;14:437–442.
25. el Moussaoui R, de Borgie CA, van den Broek P, Hustinx WN, Bresser P, van den Berk GE, Poley JW, van den Berg B, Krouwels FH, Bonten MJ, *et al.* Effectiveness of discontinuing antibiotic treatment after three days versus eight days in mild to moderate-severe community acquired pneumonia: randomised, double blind study. *BMJ* 2006;332:1355.
26. Reinhart K, Meisner M, Brunkhorst FM. Markers for sepsis diagnosis: what is useful? *Crit Care Clin* 2006;22:503–519.
27. Uzzan B, Cohen R, Nicolas P, Cucherat M, Perret GY. Procalcitonin as a diagnostic test for sepsis in critically ill adults and after surgery or trauma: a systematic review and meta-analysis. *Crit Care Med* 2006; 34:1996–2003.
28. Stolz D, Christ-Crain M, Bingisser R, Leuppi J, Miedinger D, Muller C, Huber P, Muller B, Tamm M. Antibiotic treatment of exacerbations of COPD: A randomized, controlled trial comparing procalcitonin-guidance with standard therapy. *Chest* 2007;131:9–19.
29. Harbarth S. [The effect of antimicrobial use on emergence and selection of resistance.] *Anasthesiol Intensivmed Notfallmed Schmerzther* 2007; 42:130–135. In German.
30. Lujan M, Gallego M, Fontanals D, Mariscal D, Rello J. Prospective observational study of bacteremic pneumococcal pneumonia: effect of discordant therapy on mortality. *Crit Care Med* 2004;32:625–631.