Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial

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Summary

Background Reduced duration of antibiotic treatment might contain the emergence of multidrug-resistant bacteria in intensive care units. We aimed to establish the effectiveness of an algorithm based on the biomarker procalcitonin to reduce antibiotic exposure in this setting.

Methods In this multicentre, prospective, parallel-group, open-label trial, we used an independent, computer-generated randomisation sequence to randomly assign patients in a 1:1 ratio to procalcitonin (n=311 patients) or control (n=319) groups; investigators were masked to assignment before, but not after, randomisation. For the procalcitonin group, antibiotics were started or stopped based on predefined cut-off ranges of procalcitonin concentrations; the control group received antibiotics according to present guidelines. Drug selection and the final decision to start or stop antibiotics were at the discretion of the physician. Patients were expected to stay in the intensive care unit for more than 3 days, had suspected bacterial infections, and were aged 18 years or older. Primary endpoints were mortality at days 28 and 60 (non-inferiority analysis), and number of days without antibiotics by day 28 (superiority analysis). Analyses were by intention to treat. The margin of non-inferiority was 10%. This trial is registered with ClinicalTrials.gov, number NCT00472667.

Findings Nine patients were excluded from the study; 307 patients in the procalcitonin group and 314 in the control group were included in analyses. Mortality of patients in the procalcitonin group seemed to be non-inferior to those in the control group at day 28 (21·2% [65/307] vs 20·4% [64/314]; absolute difference 0·8%, 90% CI −4·6 to 6·2) and day 60 (30·0% [92/307] vs 26·1% [82/314]; 3·8%, −2·1 to 9·7). Patients in the procalcitonin group had significantly more days without antibiotics than did those in the control group (14·3 days [SD 9·1] vs 11·6 days [SD 8·2]; absolute difference 2·7 days, 95% CI 1·4 to 4·1, p<0·0001).

Interpretation A procalcitonin-guided strategy to treat suspected bacterial infections in non-surgical patients in intensive care units could reduce antibiotic exposure and selective pressure with no apparent adverse outcomes.

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Introduction

Antimicrobial resistance has emerged as a major factor affecting patient outcomes and overall resources in intensive care units.[1] We are now heading towards extreme drug resistance, especially among gram-negative bacilli.[1–3] Insufficient measures to control infection and selective antibiotic pressure are two key factors associated with the emergence of bacterial resistance.[4] Compelling evidence that antibiotic use causes resistance has led to calls to stop inappropriate prescription of antibiotics.[4,5]

Antimicrobial consumption in the intensive care unit can be substantially reduced by starting of antibiotics only for patients with true bacterial infections, or shortening of treatment duration for those needing antibiotics, or both.[4–7] Guidance for duration of antibiotic treatment could be based on the results of studies comparing two different durations,[8–10] but such studies are still scarce for patients in intensive care units, and are applicable only for well defined infection sites.

Another approach is to identify easily obtainable biomarkers, in addition to usual clinical and bacteriological indicators, to guide physicians. The potential advantage of such a strategy would be to individualise antibiotic duration according to the patient's response to antimicrobial treatment.

Procalcitonin, a calcitonin precursor hormone, is judged to be a fairly specific marker for severe bacterial infection in patients with suspected sepsis.[11–13] Guidance about serum procalcitonin concentration has substantially reduced antibiotic use in patients presenting at the emergency department or admitted to hospital for lower-respiratory-tract infections.[14–17] Despite these encouraging results, the potential usefulness of procalcitonin as an instrument to guide antibiotic use in all intensive care units has not yet been shown. Results from two small studies, each in one centre, have suggested that a protocol based on serial serum procalcitonin measurements could achieve shortening of antibiotic

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treatment by 2–3·5 days for patients in the intensive care unit with sepsis or septic shock.[18,19]

We therefore undertook a randomised, multicentre effectiveness trial to assess the benefit of procalcitonin to help physicians start, continue, or stop antibiotics for patients in intensive care units with suspected bacterial infections. Our objective was to establish whether a strategy based on procalcitonin concentration would achieve reduced antibiotic consumption. Because shortening of antibiotic treatment might be harmful, our trial was designed to assure that this strategy did not affect outcome.

Methods

Study design and participants
The prospective, parallel-group, open-label PROcalcitonin to Reduce Antibiotic Treatments in Acutely ill patients (PRORATA) trial was undertaken in France between June, 2007, and May, 2008. We assessed critically ill patients with suspected bacterial infections in seven (five medical, two surgical) intensive care units in five university-affiliated hospitals, and one medicosurgical intensive care unit in a general hospital; in total these units comprised 140 beds.

All adults with suspected bacterial infections at admission to or during their stay in intensive care units were assessed for eligibility. Patients admitted with suspected infections were eligible if they were not receiving antibiotics before inclusion in the study or if they had received antibiotics for less than 24 h, provided that the interval between admission and inclusion was less than 12 h. Patients who developed sepsis during their stay in intensive care units were also considered for enrolment.

Exclusion criteria were: age under 18 years; known pregnancy; expected stay in the intensive care unit of less than 3 days; bone-marrow transplant or chemotherapy-induced neutropenia (<500 neutrophils per mL); infections for which long-term antibiotic treatment is strongly recommended (ie, infective endocarditis, osteoarticular infections, anterior mediastinitis after cardiac surgery, hepatic or cerebral abscesses, chronic prostatitis, or infection with *Mycobacterium tuberculosis*, *Pneumocystis jirovecii*, or *Toxoplasma gondii*); poor chance of survival, defined as a simplified acute physiology score (SAPS II) of more than 65 points at screening; and do-not-resuscitate orders.

The study protocol was approved for all centres by the ethics committee of the Saint-Louis University Hospital (Comité de Protection des Personnes), Paris, France, and written informed consent was obtained from the patients or their surrogates. An independent data and safety monitoring board reviewed the trial's progress and adverse events according to treatment assignment.

Randomisation and masking
After baseline screening, an independent, centralised, computer-generated randomisation sequence (CleanWeb, Télémedecine, Technologies, Boulogne, France) was used to randomly assign patients in a 1:1 ratio to the procalcitonin or control groups. Patients were stratified by centre with random block sizes of 2, 4, or 6; investigators were masked to assignment before, but not after, randomisation, as per our open-label design. This system was password protected and accessed by the principal investigator or study coordinator after the patient or surrogate gave consent and had met inclusion criteria. The patient's initials and date of birth were entered and then the patient's allocation was assigned. Although treatment assignments were not masked, all investigators were unaware of aggregate outcomes during the study, and primary endpoints were strictly defined and not patient-reported.

Procedures
For patients in the procalcitonin group, two interventions were used to manage antibiotics: the first used the procalcitonin concentration to decide whether antibiotic treatment should be started; the second used serial serum procalcitonin concentrations to decide to stop antibiotics. Investigators used predefined algorithms to guide physicians to start or discontinue antibiotics according to serum procalcitonin concentrations, using a modified version of a previously published algorithm.[14] According to the baseline procalcitonin concentration, starting of antibiotics was discouraged or encouraged (figure 1). When antimicrobials were initially withheld, physicians were advised to repeat clinical assessments and procalcitonin measurements 6–12 h later to detect a late peak in procalcitonin concentration and ensure that antibiotics were provided to all patients with true bacterial infections. For patients who subsequently received antibiotics, procalcitonin concentrations were assessed daily until that treatment was finished.

Investigators were encouraged to discontinue antibiotics when procalcitonin concentration was less than 80% of the peak concentration or an absolute concentration of less than 0·5 μg/L was reached. For these patients, procalcitonin guidance for starting and continuing of antibiotics was used for the first and all subsequent infectious episodes until day 28, except for those discharged earlier from the intensive care unit. Additionally, the final decision with respect to starting and continuing of antibiotics was at the discretion of the patients' physicians, irrespective of the procalcitonin concentration. For all patients, we noted algorithm adherence for starting and stopping of antibiotics, reasons for overruling the algorithm (ie, continued antibiotics for clinically persistent infection, or patient deemed to have no infection), and whether treatment had been stopped because of discharge from the unit.

For patients in the control group, before study onset all investigators received and approved a reminder including recommendations for duration of antimicrobial treatment for the most frequent infections (webappendix pp 1–3); these recommendations were derived from international and local guidelines. However, investigators were free to

decide the optimum duration of antibiotic treatment based on their own assessment of the infection's clinical course, especially because present recommendations do not always give fixed treatment durations for every type of infection.

For both groups, drug selection was at the discretion of the patients' physicians. Nevertheless, broad-spectrum antibiotics were recommended for initial empirical treatment (ie, before the susceptibility patterns of the responsible pathogens became known) of severe sepsis or septic shock, and for most severe infections. Notably, investigators were encouraged to start antibiotics as soon as possible in patients with severe infections, like septic shock, community-acquired pneumonia, ventilator-associated pneumonia, or bacterial meningitis.[20,21] Antibiotic de-escalation with narrower-spectrum antibiotics was strongly recommended, when possible, on the basis of culture results from specimens obtained at infection onset.

For the procalcitonin group, blood samples were obtained at inclusion, at each infectious episode until day 28, and every morning for patients receiving antibiotics. Procalcitonin concentration was assessed in every centre with time-resolved amplified cryptate-emission technology (Kryptor procalcitonin, Brahms, Hennigsdorf, Germany) and functional assay (detection concentration 0·06 μg/L). Total procalcitonin-assay imprecision was reported by Brahms to be 10% at 0·20 μg/L and less than 6% at more than 0·30 μg/L. The same reagents were used in all study laboratories throughout the study period; two quality-control materials were run daily with the lowest mean measurement of 0·25 μg/L (total imprecision range 5·8–8·8%) and the highest mean measurement of 10 μg/L (4·7–4·8%). Measurements were obtained 7 days per week and results were transmitted to the treating physician within 2 h after blood was drawn. This method was used to measure procalcitonin concentration for patients in the control group from four of the seven centres (data were not available for the other three centres), but results were not sent to the treating physicians and were used for our analysis only.

Data collection and definitions

At admission to the intensive care unit, data collected were: age, sex, pre-existing comorbidities, previous location before admission, admission category, reason for admission, SAPS II, the presence and type of organ dysfunction using the sequential organ-failure assessment (SOFA) score,[22] and use of mechanical ventilation. Additionally, at inclusion and during follow-up we recorded: SAPS II (at inclusion only), SOFA score and type of organ or system failure (at inclusion and on days 7, 14, 21, and 28), vital signs, daily need for mechanical ventilation, source of infection when known, results of microbiological cultures, and adequacy of the initial empirical antibiotics. Septic shock was defined according to previously published criteria.[23]

Adequate antimicrobial treatment for patients with microbiologically documented infection was defined as an initial antimicrobial regimen with in-vitro activity against
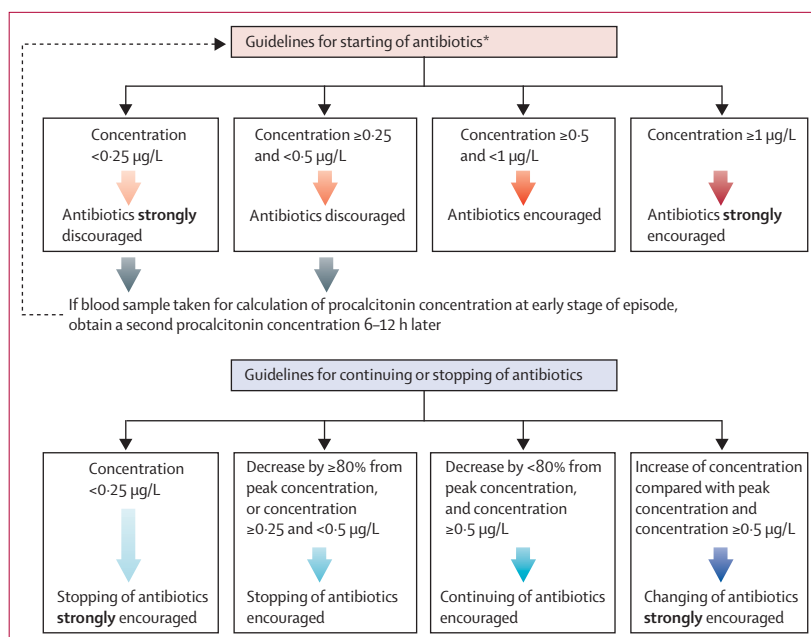

Figure 1: **Guidelines for starting, continuing, or stopping of antibiotics according to procalcitonin concentrations**
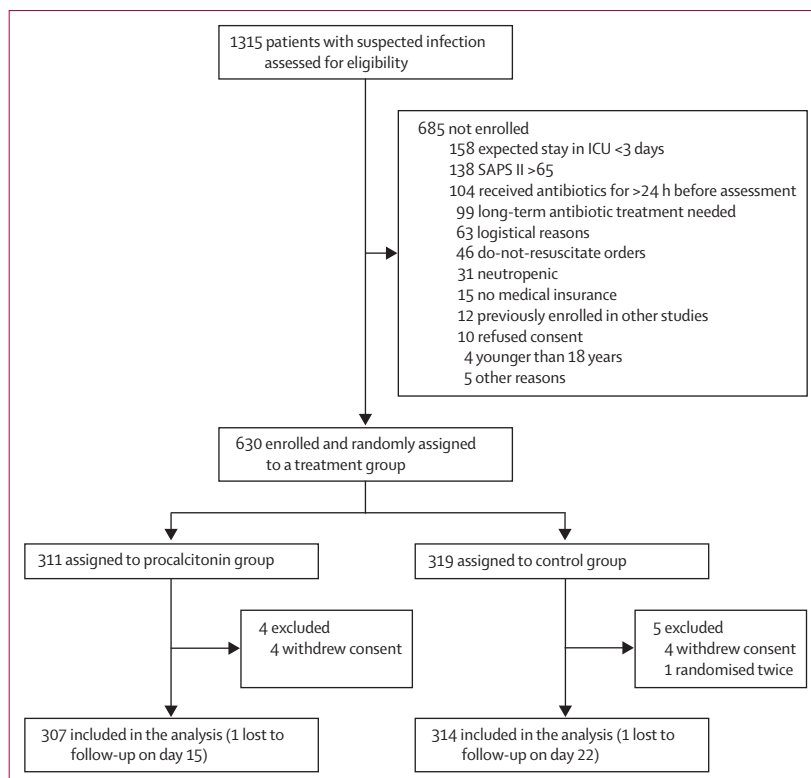*Excludes situations requiring immediate antibiotic treatment (eg, septic shock, purulent meningitis).

Figure 2: **Trial profile**
ICU=intensive care unit. SAPS II= simplified acute physiology score.

one or more pathogens that were judged to be responsible for the infection. Relapse was defined as the growth of one or more of the initial causative bacterial strains (ie, same genus, species) from a second sample taken from the same infection site at 48 h or more after stopping of antibiotics, combined with clinical signs or symptoms of infection. Superinfection was defined as the isolation from the same or another site of one or more pathogens different from that identified during the first infectious episode, together with clinical signs or symptoms of infection. Multidrug-resistant bacteria were defined as one of the following: ticarcillin-resistant *Pseudomonas aeruginosa, Acinetobacter baumannii,* or *Stenotrophomonas maltophilia*; extended-spectrum β-lactam-producing Enterobacteriaceae; high-concentration cephalosporinase-producing AmpC Enterobacteriaceae; and meticillin-resistant *Staphylococcus aureus.*

At the end of follow-up, every suspected infectious episode was classified by the investigator on the basis of clinical, laboratory, and imaging or microbiological findings, or both. The four classifications were: microbiologically documented infection (presence of a clinical or radiological infectious focus, or both, and pathogen identification); clinically documented infection (presence of a clinical or radiological infectious focus, or both, without causative pathogen identification); absence of infection (absence of a clinical or radiological infectious focus, or both, and antibiotics given for <2 days); and possible infection (all other situations). An adjudication committee—comprised of four specialists in infectious diseases and critical-care medicine who were masked to the randomisation assignment—reviewed and validated all infectious episode classifications by consensus.

Primary endpoints were death from any cause by days 28 and 60, and number of days without antibiotics at 28 days after inclusion. Secondary outcome measures were percentage of patients with relapse or superinfection (days 1–28); number of days without mechanical ventilation, defined as unassisted breathing (days 1–28); SOFA score (days 1, 7, 14, 21, and 28); length of stay in the intensive care unit and hospital; days of exposure to each antibiotic per 1000 inpatient days, defined as the number of days (>24 h) of continuous antibiotic treatment (days 1–28); duration of antibiotic treatment according to infection site; and percentage of emerging multidrug-resistant bacteria isolated from specimens taken for routine microbiological assessments (days 1–28).

Statistical analysis

The trial was designed to establish whether the procalcitonin-guided strategy was superior in terms of antibiotic use, as assessed by the number of days alive and without antibiotics, and its non-inferiority in terms of death.[24] Assuming a mean of 12 days (SD 7·5) without antibiotics for the control group,[6,8] 133 patients per study group would provide 90% power at a two-sided $\alpha=0.05$ to detect a 3-day increase in the number of days without antibiotics. To test for non-inferiority with a 10% α-risk, we needed 300 patients per study group to achieve 80% power to exclude a 10% between-group mortality difference, assuming 35% mortality in the control group.[6,8,25–27] To account for possible patients lost to follow-up, we planned to enrol 630 patients.

SAS software (version 9.1) was used for statistical analyses. Superiority and non-inferiority analyses were by intention to treat. For the primary endpoint of mortality, the two-sided 90% CI was calculated for the percentage-point absolute difference between mortality in the two study groups (non-inferiority analysis). Conversely, the between-group absolute difference in the primary endpoint of number of days without antibiotics was analysed with the Student's *t* test and calculation of 95% CI for that mean

	Procalcitonin group (n=307)	Control group (n=314)
At admission to ICU		
Age (years)	61·0 (15·2)	62·1 (15·0)
Men	207 (67%)	204 (65%)
Admission category		
Medical	275 (90%)	280 (89%)
Emergency surgery	20 (7%)	25 (8%)
Elective surgery	12 (4%)	9 (3%)
Origin		
Emergency department	144 (47%)	168 (54%)
Medical or surgical department	138 (45%)	119 (38%)
Other ICU	25 (8%)	27 (9%)
Severe comorbidities		
NYHA III/IV heart failure	16 (5%)	13 (4%)
Insulin-dependent diabetes mellitus	27 (9%)	22 (7%)
Cirrhosis	20 (7%)	13 (4%)
Oxygen therapy at home	23 (7%)	18 (6%)
Chronic renal failure requiring dialysis	17 (6%)	11 (4%)
Metastatic cancer	8 (3%)	5 (2%)
Immunocompromised*	47 (15%)	51 (16%)
SAPS II	47·1 (17·9)	46·9 (17·2)
SOFA score	8·0 (4·7)	7·7 (4·6)
Organ or system failure†		
Respiratory	153 (50%)	131 (42%)
Cardiovascular	140 (46%)	141 (45%)
Renal	60 (20%)	49 (16%)
CNS	117 (38%)	111 (35%)
Hepatic	19 (6%)	16 (5%)
Coagulation	24 (8%)	25 (8%)
Reason for admission to ICU		
Septic shock	53 (17%)	55 (18%)
Non-septic shock	46 (15%)	46 (15%)
Acute respiratory failure	115 (37%)	127 (40%)
Renal failure	9 (3%)	6 (2%)
Neurological failure	34 (11%)	36 (11%)
Multiorgan failure	20 (7%)	20 (6%)
Other‡	30 (10%)	24 (8%)
		(Continues on next page)

difference (superiority analysis). Although not specified in the protocol, a worst-case imputation method was used for missing data to conform with the intention-to-treat analysis. To further establish the prognostic effect of the procalcitonin algorithm for antibiotic treatment, logistic-regression analysis was applied to the endpoints of day-28 and day-60 mortality, adjusted for age, sex, pre-existing comorbidities, location before and reason for admission to the intensive care unit, SOFA score at admission, type of infection, blood culture results, septic shock, and mechanical ventilation at inclusion.

For the primary endpoints, subgroup analyses were prespecified for: type of infection (patients with community-acquired or hospital-acquired infection); patients with ventilator-associated pneumonia; immuno-compromised patients; and patients strictly managed according to the study algorithms. The treatment effect of the procalcitonin algorithm within each of these subgroups was investigated with the same methods as for the main analysis. Secondary outcome measures were compared between study groups with χ^2 or Student's t tests, or both, as appropriate. Percentages of patients on antibiotics in each study group were plotted against time (days 1–28) and compared with a linear generalised model for repeated measures.[28] Cumulative-event curves were estimated with the Kaplan-Meier method, and a hazard ratio estimate (90% CI) was calculated.

This trial is registered with ClinicalTrials.gov, number NCT00472667.

Role of the funding source
The study sponsors did not participate in the study design, data collection, data analysis, data interpretation, or writing of the report. LB, C-EL, FT, JC, and MW had full access to all the data and had final responsibility for the decision to submit for publication.

Results
1315 patients with suspected infections were screened for eligibility, of whom 630 were enrolled and randomly assigned to the procalcitonin group (n=311 patients) or the control group (n=319; figure 2). Four patients in the procalcitonin group and five in the control group were subsequently excluded from the analysis. Table 1 and webappendix pp 4–5 show the clinical characteristics of the remaining 621 patients at admission to the intensive care unit and inclusion into the study. For patients in the procalcitonin (n=307) and control (n=314) groups, respectively, infections at inclusion were classified as microbiologically documented in: 213 (69%) and 222 (71%), clinically documented in 36 (12%) and 52 (17%), possible in 11 (4%) and seven (2%), and absent in 47 (15%) and 33 (11%). Empirical antimicrobial treatment for patients with microbiologically documented infections was regarded as adequate for 193 (91%) patients in the procalcitonin group compared with 207 (93%) in the control group.

	Procalcitonin group (n=307)	Control group (n=314)
(Continued from previous page)		
At inclusion to study		
SAPS II	43·8 (16·1)	43·4 (15·4)
SOFA score	7·5 (4·4)	7·2 (4·4)
Organ or system failure†		
Respiratory	148 (48%)	137 (44%)
Cardiovascular	135 (44%)	127 (40%)
Renal	58 (19%)	48 (15%)
CNS	101 (33%)	100 (32%)
Hepatic	13 (4%)	13 (4%)
Coagulation	25 (8%)	21 (7%)
Mechanical ventilation	211 (69%)	208 (66%)
Type of infection		
Community-acquired infection	153 (50%)	173 (55%)
Hospital-acquired infection	154 (50%)	141 (45%)
Septic shock	138 (45%)	129 (41%)
Serum lactate (>2 mmol/L)§	91 (37%)	96 (38%)
Positive blood cultures	55 (18%)	53 (17%)
Procalcitonin (µg/L)¶	12·0 (30·9); 1·6 (0·5–6·6)	12·0 (32·6); 1·5 (0·4–6·8)
C-reactive protein (mg/L)‖	156·8 (109·2); 144·2 (63·0–229·0)	159·6 (114·2); 137·2 (61·0–244·0)
Infection site**		
Pulmonary	183 (71%)††	211 (74%)‡‡
Urinary tract	24 (9%)	18 (6%)
Skin and soft tissue	5 (2%)	6 (2%)
Intra-abdominal	14 (5%)	20 (7%)
CNS	7 (3%)	6 (2%)
Catheter-related infection	5 (2%)	3 (1%)
Primary bloodstream infection	9 (3%)	11 (4%)
Other¶¶	11 (4%)	9 (3%)

Data are mean (SD), number (%), or median (IQR). ICU=intensive care unit. NYHA=New York Heart Association stage of disease. SAPS II=simplified acute physiology score. SOFA=sequential organ-failure assessment. *Includes patients with acquired immunodeficiency syndrome, solid-organ transplantation, or haematological malignancy, and those receiving chemotherapy or radiotherapy, immunosuppressive agents, or long-term corticosteroid therapy. †Defined by SOFA score >2. ‡Trauma (n=5 patients in procalcitonin group; n=4 in control group), need for continuous monitoring (n=12; n=10), and cardiac arrest (n=13; n=10). §Data were obtained for 247 patients in the procalcitonin group, and 255 in the control group; data were missing for remaining patients. ¶Data were obtained for 307 patients in the procalcitonin group, and 192 in the control group; data were missing for remaining patients. ‖Data were obtained for 276 patients in the procalcitonin group, and 195 in the control group; data were missing for remaining patients. **Data were obtained for 258 patients in the procalcitonin group, and 284 in the control group; data were missing for remaining patients. ††79 community-acquired pneumonia episodes, 75 ventilator-associated pneumonia episodes, and 29 hospital-acquired pneumonia episodes in non-mechanically ventilated patients. ‡‡101 community-acquired pneumonia episodes, 66 ventilator-associated pneumonia episodes, and 44 hospital-acquired pneumonia episodes in non-mechanically ventilated patients. ¶¶Endocarditis (n=1 in procalcitonin group), mediastinitis (n=1 in control group), and unknown (n=10 in procalcitonin group; n=8 in control group); cases of endocarditis and mediastinitis were diagnosed after inclusion so these patients were not excluded from the analysis.

Table 1: Patient characteristics at baseline

Only two patients were lost to follow-up, one from each group. In the procalcitonin group, the patient died on day 25 but no information was available about antibiotic exposure for days 15–25. From worst-case imputation, this patient was judged to have received antibiotics until death. In the control group, the patient was lost to follow-up on day 22 but was judged to have survived until day 60, without receiving any antibiotics after day 22.

	Procalcitonin group (n=307)	Control group (n=314)	Between-group absolute difference	p value
Primary endpoints				
28-day mortality*	65 (21·2%)	64 (20·4%)	0·8% (–4·6 to 6·2)	NA
60-day mortality*	92 (30·0%)	82 (26·1%)	3·8% (–2·1 to 9·7)	NA
Number of days without antibiotics	14·3 (9·1)	11·6 (8·2)	2·7 (1·4 to 4·1)	<0·0001
Secondary endpoints (days 1–28)				
Relapse	20 (6·5%)	16 (5·1%)	1·4% (–2·3 to 5·1)	0·45
Superinfection	106 (34·5%)	97 (30·9%)	3·6% (–3·8 to 11·0)	0·29
Number of days without mechanical ventilation	16·2 (11·1)	16·9 (10·9)	–0·7 (–2·4 to 1·1)	0·47
SOFA score				
Day 1	7·5 (4·4)	7·2 (4·4)	0·3 (–0·4 to 1·0)	0·39
Day 7	4·1 (4·2)	4·0 (4·2)	0·1 (–0·6 to 0·8)	0·73
Day 14	2·8 (3·5)	2·8 (3·6)	0 (–0·6 to 0·7)	0·87
Day 21	2·1 (3·3)	1·9 (3·1)	0·2 (–0·4 to 0·8)	0·52
Day 28	1·5 (3·0)	0·9 (2·4)	0·6 (0·0 to 1·1)	0·0370
Length of stay in ICU from inclusion (days)	15·9 (16·1)	14·4 (14·1)	1·5 (–0·9 to 3·9)	0·23
Length of stay in hospital from inclusion (days)	26·1 (19·3)	26·4 (18·3)	–0·3 (–3·2 to 2·7)	0·87
Multidrug-resistant bacteria†	55 (17·9%)	52 (16·6%)	1·3% (–4·6 to 7·2)	0·67
Days of antibiotic exposure per 1000 inpatient days	653	812	–159 (–185 to –131)	<0·0001
Duration of first episode of antibiotic treatment (number [%]; days [SD])				
Overall population	307 (100%); 6·1 (6·0)	314 (100%); 9·9 (7·1)	–3·8 (–4·8 to –2·7)	<0·0001
Community-acquired pneumonia	79 (26%); 5·5 (4·0)	101 (32%); 10·5 (6·4)	–5·0 (–6·6 to –3·4)	<0·0001
Ventilator-associated pneumonia	75 (24%); 7·3 (5·3)	66 (21%); 9·4 (5·7)	–2·1 (–4·0 to –0·3)	0·0210
Intra-abdominal infection	14 (5%); 8·1 (7·7)	20 (6%); 10·8 (6·7)	–2·7 (–7·7 to 2·4)	0·29
Urinary tract infection	24 (8%); 7·4 (6·3)	18 (6%); 14·5 (9·3)	–7·1 (–11·9 to –2·2)	0·0053
Infection with positive blood culture	55 (18%); 9·8 (7·7)	53 (17%); 12·8 (8·1)	–3·0 (–6·0 to 0·1)	0·06

Data are number (%), difference (95% CI), or mean (SD), unless otherwise indicated. NA=not applicable. SOFA=sequential organ-failure assessment. ICU=intensive care unit. *Difference (90% CI).

***Table 2:* Main outcome variables**

Recommendations about duration of antimicrobial treatment for the procalcitonin group were not followed in 219 episodes. At inclusion, physicians immediately gave antibiotics to 65 patients because they judged that infection could not be ruled out, despite procalcitonin concentration of less than 0·5 μg/L. Conversely, they did not give antibiotics to four patients because they believed that procalcitonin concentrations of more than 0·5 μg/L were clearly explained by non-infectious events. During follow-up, physicians stopped antibiotics for 39 patients because they regarded the infection as clinically cured, despite persistently raised procalcitonin above 0·5 μg/L. Antibiotics were continued for 111 patients: 32 were discharged from the intensive care unit, so procalcitonin concentrations were no longer available and the algorithm to stop antibiotics could not be used; and 79 were clinically unstable despite procalcitonin concentrations below 0·5 μg/L.

For 14 of the 79 patients who were clinically unstable and continued antibiotics, physicians prolonged antibiotics for a mean of 8·8 days (SD 5) beyond the recommended duration, despite low procalcitonin concentrations, because they thought that stopping of the course any earlier would have been too early—ie, before the lower limit of the recommended antibiotic duration. Of these 14 patients, ten had not received appropriate initial treatment or were infected with multidrug-resistant strains (eg, *P aeruginosa*), or both. Of the 219 episodes in which the procalcitonin algorithm was not followed, the algorithm was overruled at inclusion and during follow-up for 57 patients, and therefore the algorithm was not adhered to in 162 patients, corresponding to 53% of the procalcitonin group.

Recommendations about duration of antimicrobial treatment for the control group were not heeded in 146 episodes because antibiotics were initially postponed (n=15) as physicians judged that infection was unlikely, antibiotics were stopped prematurely (n=46) as physicians judged that infection was cured, or antibiotics were unduly continued (n=85) as physicians judged that infection was not cured and still needed antibiotics. The control algorithm was overruled at inclusion and during follow-up for five patients, and therefore the algorithm was not adhered to in 141 patients, corresponding to 45% of the control group.

Table 2 shows the proportion of deaths and the between-group absolute difference of mortality by days 28 and 60 after inclusion. According to our definition of non-

inferiority, mortality in the procalcitonin group was non-inferior to that in the control group. The Kaplan-Meier estimates of day-60 survival probability did not differ between the two groups (figure 3). After adjustment, the odds ratio for death for patients in the procalcitonin group versus the control group was 0·89 (90% CI 0·62–1·28) for day 28, and 1·09 (0·79–1·51) for day 60. 27 patients in the procalcitonin group and 18 in the control group died during days 29–60 due to: multiorgan failure with persistent respiratory failure (11 vs nine); underlying disease (eight vs three); non-infectious complications (eg, cardiac arrest or stroke; five vs three); and treatment withdrawal at the families' request (three in each group). No deaths were recorded as related to relapse of infection.

During the 28 days after inclusion, patients in the procalcitonin group had a 23% relative reduction in days of antibiotic exposure compared with the control group (table 2). Patients in the procalcitonin group received antibiotics for a total of 10·3 days (SD 7·7) and those in the control group for 13·3 days (7·6) (p<0·0001). The between-group absolute difference in the percentages of patients receiving antibiotics was only 5·6% (95% CI 1·4–9·8) on day 1, but rose to 22·2% (19·1–25·9) on day 5, 37·6% (30·5–45·1) on day 7, 10·5% (2·5–18·7) on day 15, and 6·2% (1·6–14·3) on day 20 (p<0·0001; figure 4).

28 patients in the procalcitonin group did not receive antibiotics at inclusion in accordance with the algorithm (procalcitonin <0·5 μg/L). For only eight of these patients, antibiotics were given within 5 days, and all but one (who died on day 18 from underlying disease) survived until day 60. Of 15 patients in the control group who did not receive antibiotics at inclusion, eight received antibiotics within 5 days and four had died by day 60. For 17 patients (6 with community-aquired pneumonia, 11 with ventilator-associated pneumonia), the procalcitonin-guided strategy led to longer duration of antibiotic prescribing than did the recommendations for the control group. For patients randomised to the procalcitonin group, procalcitonin concentration when antibiotics were stopped was a median of 0·8 μg/L (IQR 0·3–3·2). No centre-effect was reported for the two main endpoints of death and antibiotic exposure.

For most secondary outcome measures (percentages of patients with relapse or superinfection; number of days without mechanical ventilation; SOFA score apart from at day 28; length of stay in the intensive care unit and hospital; and percentage of emerging multidrug-resistant bacteria) no significant difference was recorded between study groups (table 2). After day 28, 119 (39%) of patients in the procalcitonin group and 122 (39%) in the control group were still in hospital, but only 53 (17%) and 43 (14%) were still in the intensive care unit.

Duration of antibiotic exposure for the first infectious episode was significantly shorter for patients assigned to receive procalcitonin-guided treatment than for those in the control group for the overall population, and those with community-acquired pneumonia, ventilator-
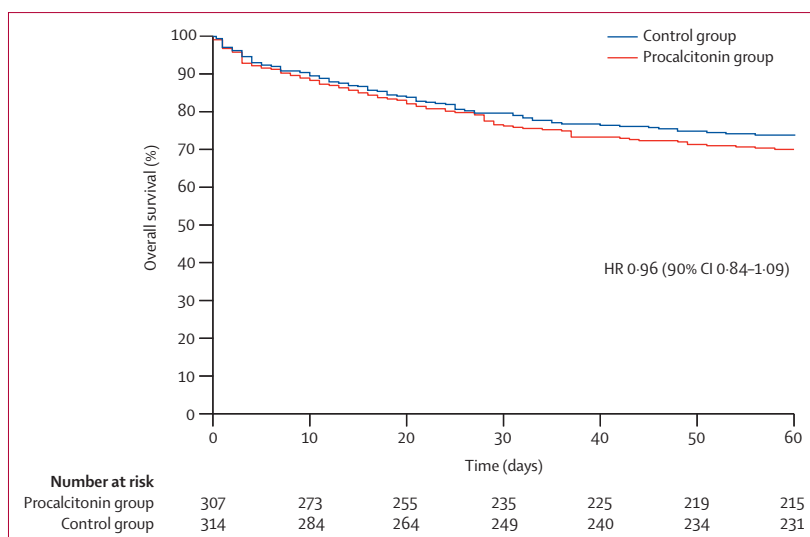

Figure 3: **Kaplan-Meier estimates of the probability of survival**
HR=hazard ratio. No significant difference (log-rank test) was recorded between patients assigned to the procalcitonin group and control group.

associated pneumonia, urinary tract infections, and positive blood cultures (table 2). Patients in the procalcitonin group also had fewer days of antibiotic exposure per 1000 inpatient days (table 2).

Antibiotic exposure was significantly lower for patients in the procalcitonin group than in the control group in all predefined subgroups: community-acquired infection (3·3 days), hospital-acquired infection (2·3 days), ventilator-associated pneumonia (3·1 days), immuno-compromised patients (3·6 days), and patients strictly managed according to the study algorithms (3·2 days; figure 5A). By contrast, patient mortality by day 28 in the procalcitonin group seemed to be non-inferior to the control group, but for some subgroups, there was insufficient evidence for non-inferiority (figure 5B). Although not prespecified in the protocol, we did several other exploratory subgroup analyses on the basis of age, sex, microbiologically documented infections, presence or absence of one or more positive blood cultures, septic shock, mechanical ventilation, and SOFA score at inclusion. These analyses confirmed the results of the main analysis. A significant treatment-by-sex interaction for antibiotic exposure was recorded (figure 5B): for patients in the procalcitonin group, women were less exposed to antibiotics than men were.

Discussion
The results of our study show that for patients with suspected infections, either at admission to the intensive care unit or during their stay in the unit, procalcitonin-guided antibiotic treatment substantially lowers antibiotic exposure and is non-inferior to standard care with respect to outcomes. For patients in the procalcitonin group, the absolute difference of 2·7 days between the mean numbers of days without antibiotics by day 28
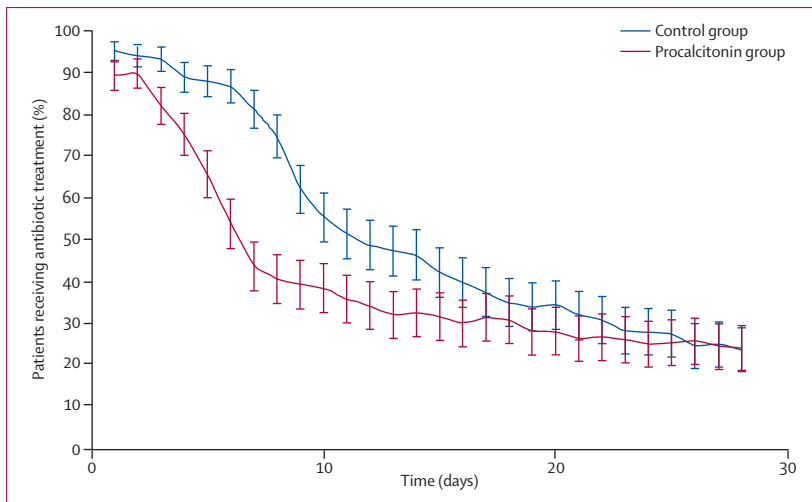
***Figure 4:* Patients receiving antibiotics for days 1–28**
Significantly fewer patients assigned to the procalcitonin group received antibiotics than did those assigned to the control group (p<0·0001, generalised linear model test for repeated measures).

corresponds to a 23% relative reduction in antibiotic exposure.

Procalcitonin, one of the calcitonin precursors, is a useful biomarker for the diagnosis of bacterial sepsis.[11,12] To the best of our knowledge, eight randomised controlled trials assessing the use of procalcitonin to reduce antibiotic exposure have been published (table 3). Five trials done in either emergency departments on patients with lower-respiratory-tract infections,[14,29] community-acquired pneumonia[16] or acute exacerbation of chronic bronchitis,[17] or in primary care on patients with acute respiratory tract infections[15] reported that a predefined algorithm to guide antibiotic prescription substantially decreased antibiotic use compared with standard care. The only previous trials of patients in intensive care units[18,19,30] included small numbers of patients, and were underpowered for safety, which in this setting is of the utmost importance. We studied patients with a wide range of infections and who were critically ill—all patients had high SAPS II and SOFA scores, 40% had septic shock, and two-thirds needed mechanical ventilation—which underscores the effective contribution of a procalcitonin-guided strategy to lowering of antibiotic consumption in this setting. Moreover, this result was obtained while the control group's duration of antimicrobial treatment was well within the range recommended in published reports.[5,8,31,32]

Chastre and colleagues[8] showed that most patients with ventilator-associated pneumonia could be safely treated for 8 days. However, their study excluded immunosuppressed patients and those who had received inappropriate initial antibiotics; moreover, those with *P aeruginosa* lung infections had a slightly increased relapse rate. For our study, we recommended that physicians treat patients with ventilator-associated pneumonia from *P aeruginosa*, those who were

immunosuppressed, or those who did not initially receive appropriate treatment for 15 days. These recommendations are in accordance with the 2005 guidelines from the American Thoracic Society and Infectious Diseases Society of America,[32] and recommendations made by the British Society for Antimicrobial Chemotherapy[33] and the Canadian Critical Care Trials Group.[34] Furthermore, although several studies showed that giving antibiotics for as little as 5 days can be sufficient for some patients with community-acquired pneumonia, standard care is 7–10 days and very short durations are not recommended for some pathogens (eg, *Legionella pneumophila*).[31]

Results of research have not yet established the ideal threshold to start or withdraw antibiotics for patients who are critically ill, and the percentage decline of procalcitonin from the peak concentration. Although investigators for previous studies on patients with lower-respiratory-tract infections chose a threshold of 0·25 µg/L,[14–17,29] the bacterial infection threshold for critically ill patients was 0·5–1 µg/L.[11,18,35,36] We chose 0·5 µg/L as a compromise between a low threshold, which could have led to unnecessary prescription of antibiotics, and a high threshold, which could have had detrimental consequences for the patient. As expected, antibiotic-sparing was obtained mainly during the first 10 days by shortening of the duration of antibiotic treatment, whereas reduced antibiotic exposure was only marginal on day 1 (figure 4). Because crude procalcitonin concentrations in the intensive care unit could have poor diagnostic benefit,[12,13,37] intensivists are understandably reluctant to rely exclusively on biological markers when severe infection is suspected. Thus, procalcitonin might be more useful for stopping antibiotics than for use as a marker to exclude infection.

Despite lower antibiotic exposure in the procalcitonin group than in the control group, we were unable to show a between-group difference for the rates of emerging multidrug-resistant bacteria. Nonetheless, we stress that infection is the tip of the iceberg compared with digestive colonisation.[38] Rectal, nasal, and axillary swab screening was not routinely done and might more accurately show antibiotic selective pressure. Moreover, a 3-day reduction of antibiotic use for only a small subset of admitted patients might not be sufficient to record a decreased resistance-emergence rate, especially for some intensive care units with high cross-transmission rates.

By contrast with findings from patients in intensive care units,[18,19] we did not note any difference in the length of stay in the unit between the groups, despite reduced duration of antibiotic treatment in the procalcitonin group. But length of stay can depend on many factors that are not directly linked to duration of antibiotic treatment. Furthermore, the perceived need by physicians to continue to monitor patients in the intensive care unit who received very short-term antibiotics might also explain the similar lengths of stay
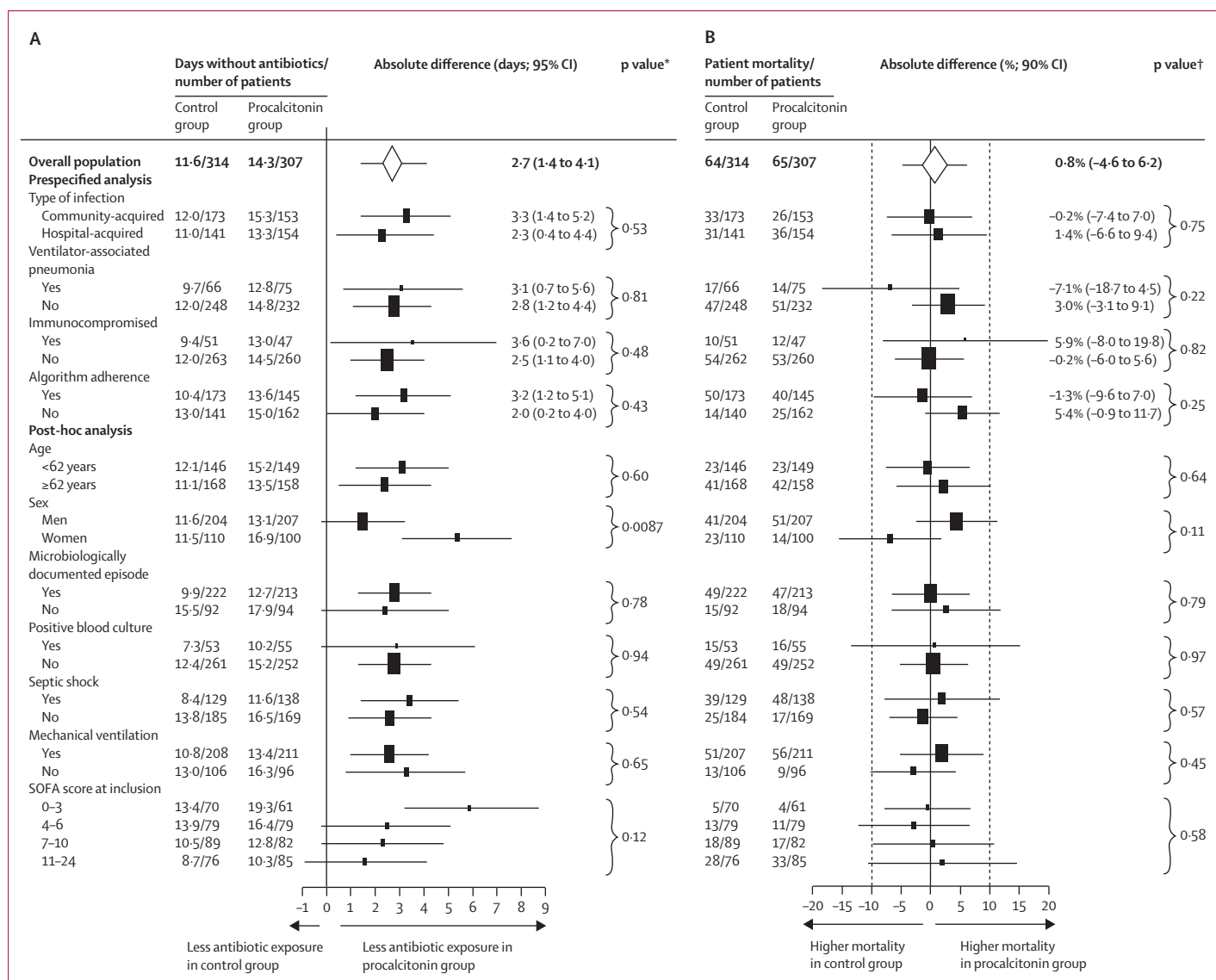
A

	Days without antibiotics/ number of patients		Absolute difference (days; 95% CI)	p value*
	Control group	Procalcitonin group		
Overall population Prespecified analysis	11·6/314	14·3/307	2·7 (1·4 to 4·1)	
Type of infection				
Community-acquired	12·0/173	15·3/153	3·3 (1·4 to 5·2)	0·53
Hospital-acquired	11·0/141	13·3/154	2·3 (0·4 to 4·4)	
Ventilator-associated pneumonia				
Yes	9·7/66	12·8/75	3·1 (0·7 to 5·6)	0·81
No	12·0/248	14·8/232	2·8 (1·2 to 4·4)	
Immunocompromised				
Yes	9·4/51	13·0/47	3·6 (0·2 to 7·0)	0·48
No	12·0/263	14·5/260	2·5 (1·1 to 4·0)	
Algorithm adherence				
Yes	10·4/173	13·6/145	3·2 (1·2 to 5·1)	0·43
No	13·0/141	15·0/162	2·0 (0·2 to 4·0)	
Post-hoc analysis				
Age				
<62 years	12·1/146	15·2/149		0·60
≥62 years	11·1/168	13·5/158		
Sex				
Men	11·6/204	13·1/207		0·0087
Women	11·5/110	16·9/100		
Microbiologically documented episode				
Yes	9·9/222	12·7/213		0·78
No	15·5/92	17·9/94		
Positive blood culture				
Yes	7·3/53	10·2/55		0·94
No	12·4/261	15·2/252		
Septic shock				
Yes	8·4/129	11·6/138		0·54
No	13·8/185	16·5/169		
Mechanical ventilation				
Yes	10·8/208	13·4/211		0·65
No	13·0/106	16·3/96		
SOFA score at inclusion				
0–3	13·4/70	19·3/61		0·12
4–6	13·9/79	16·4/79		
7–10	10·5/89	12·8/82		
11–24	8·7/76	10·3/85		

x-axis: −1 0 1 2 3 4 5 6 7 8 9

Less antibiotic exposure in control group ← → Less antibiotic exposure in procalcitonin group

B

	Patient mortality/ number of patients		Absolute difference (%; 90% CI)	p value†
	Control group	Procalcitonin group		
Overall population	64/314	65/307	0·8% (–4·6 to 6·2)	
Community-acquired	33/173	26/153	–0·2% (–7·4 to 7·0)	0·75
Hospital-acquired	31/141	36/154	1·4% (–6·6 to 9·4)	
Yes	17/66	14/75	–7·1% (–18·7 to 4·5)	0·22
No	47/248	51/232	3·0% (–3·1 to 9·1)	
Yes	10/51	12/47	5·9% (–8·0 to 19·8)	0·82
No	54/262	53/260	–0·2% (–6·0 to 5·6)	
Yes	50/173	40/145	–1·3% (–9·6 to 7·0)	0·25
No	14/140	25/162	5·4% (–0·9 to 11·7)	
<62 years	23/146	23/149		0·64
≥62 years	41/168	42/158		
Men	41/204	51/207		0·11
Women	23/110	14/100		
Yes	49/222	47/213		0·79
No	15/92	18/94		
Yes	15/53	16/55		0·97
No	49/261	49/252		
Yes	39/129	48/138		0·57
No	25/184	17/169		
Yes	51/207	56/211		0·45
No	13/106	9/96		
0–3	5/70	4/61		0·58
4–6	13/79	11/79		
7–10	18/89	17/82		
11–24	28/76	33/85		

x-axis: −20 −15 −10 −5 0 5 10 15 20

Higher mortality in control group ← → Higher mortality in procalcitonin group

Figure 5: **Days without antibiotics (A) and patient mortality by day 28 (B), according to prespecified and post-hoc baseline characteristics**
Dotted vertical lines in B show clinical non-inferiority margins that were calculated a priori. SOFA=sequential organ-failure assessment. *p values show the interaction between the subgroup and days without antibiotics. †p values show the interaction between the subgroup and patient mortality.

between the procalcitonin and control groups. Intriguingly, we reported a significant treatment-by-sex interaction for duration of antibiotic exposure. However, since no imbalances of disease severity or any other factors were reported between men and women in the two treatment groups, we think that the most plausible explanation is a chance finding.

Several limitations of our study should be mentioned. First, although our trial was multicentre and randomised, the design was open and only eight intensive care units participated. Second, surgical patients represented only 10% of the study population. Therefore, our findings cannot be extrapolated to surgical patients, in whom procalcitonin might be heightened even in the absence of infection,[37] or to other subsets of patients, especially those who might need long-term antibiotic treatment, are neutropenic, or are infected with high-risk pathogens (eg, *P aeruginosa*), since they were excluded or represented only a small fraction of our study population.

Third, 53% of patients randomised to the procalcitonin group were not given algorithm-guided treatment, either because the algorithm was overruled (physicians refused to start or stop antibiotics, even though the algorithm recommended it), or because they were discharged from the intensive care unit, precluding serial serum procalcitonin measurements. However, we were still able to show significantly reduced antibiotic use during the 28-day period after inclusion. Notably, after exclusion of all patients in both study groups for whom treatment algorithms were overruled, patients in

	Type of infection; setting	Patients		Effect on antibiotic exposure of procalcitonin strategy *vs* control	Mortality	
		Procalcitonin	Control		Procalcitonin	Control
Christ-Crain et al (2004)[14]	Lower-respiratory tract infection; emergency department	124	119	0·49 (95% CI 0·44–0·55)*	3·2%	3·4%
Christ-Crain et al (2006)[16]	Community-acquired pneumonia; emergency department	151	151	0·52 (95% CI 0·48–0·55)†	11·9%	13·2%
Stolz et al (2007)[17]	COPD exacerbation; emergency department	102	106	0·76 (95% CI 0·64–0·92)†	4·9%	8·5%
Briel et al (2008)[15]	Respiratory-tract infection; primary care	232	226	72% (95% CI 66–78)‡	0%	0·5%
Schuetz et al (2009)[29]	Lower-respiratory-tract infection; emergency department	671	688	5·7 *vs* 8·7§	5·1%	4·8%
Nobre et al (2008)[18]	Severe sepsis or septic shock; ICU	31¶	37¶	17·4 (SD 7·6) *vs* 13·6 (7·6)‖	16·1%	16·2%
Hochreiter et al (2009)[19]	Infection with systemic inflammatory-response syndrome; surgical ICU	57	53	5·9 (SD 1·1) *vs* 7·9 (0·5)**	26·3%	26·4%
Stolz et al (2009)[30]	Ventilator-associated pneumonia; ICU	51	50	10 (IQR 6–16) *vs* 15 (10–23)††	20%	28%‡‡

COPD=chronic obstructive pulmonary disease. ICU=intensive care unit. *Adjusted relative risk of antibiotic exposure. †Relative risk of antibiotic exposure. ‡Percentage reduction of antibiotic prescriptions. §Mean days of antibiotic treatment; relative change in mean days –34·8% (–40·3 to –28·7). ¶Number of patients included in the per-protocol analysis. ‖Mean number of days without antibiotics for days 1–28; p=0·04 for between-group comparison. **Mean days of antibiotic treatment; p<0·001 for between-group comparison. ††Median days of antibiotic treatment; p=0·038 for between-group comparison. ‡‡p=0·32 for between-group comparison.

Table 3: Studies that have used procalcitonin to reduce patient exposure to antibiotics

the procalcitonin group still had significantly more days without antibiotics than did controls (absolute difference 3·2 days, 95% CI 1·2 to 5·1), without a significant difference in 28-day mortality (absolute difference –1·3%, 95% CI –9·6 to 7·0).

Fourth, a slightly higher number of patients in the procalcitonin group than in the control group died between days 29 and 60, potentially questioning the safety of a procalcitonin-guided strategy in the intensive care unit. However, no patient in either group who died during days 29–60 had an infection relapse, and most deaths resulted from complications directly related to the severity of underlying disease. Importantly, after taking into account the potential confounders, the odds ratio for death by day 60 was not significantly different between the study groups, and none of the secondary outcome measures differed significantly between study groups, including the type and number of organ dysfunctions, number of days without mechanical ventilation, length of stay in the intensive care unit and hospital, and rate of relapse.

Fifth, our trial's sample size was calculated to have sufficient power to exclude a 10% between-group mortality difference, which can be debated. To support this margin, we searched published reports to establish the effect-size of an antimicrobial drug versus no active treatment against severe infections, including ventilator-associated and community-acquired pneumonia. Substantial treatment effects of antimicrobial treatment were shown in all studies identified,[26,39–41] with increased mortality ranging from 10% to more than 40% when no effective antimicrobial treatment was prescribed. These findings justified a non-inferiority safety margin of 10% in accordance with preservation of 50% or more of the comparator drug's or intervention's efficacy relative to placebo or no treatment.[42] This margin is also in accordance with the Infectious Diseases Society of America recommendation for non-inferiority trials assessing

antibiotic treatment for severe community-acquired pneumonia, defined as a pneumonia severity index of IV–V.[27] Our study was designed assuming 35% mortality for control patients, whereas we recorded a crude mortality of 26·2% by day 60. This reduced mortality in the control group slightly increases the power of our study and, therefore, the probability of concluding non-inferiority.

Sixth, our definitions of relapse and superinfection were based on microbiological criteria and therefore needed microbiological results, some of which might have been less easily obtained once the patients were discharged from the intensive care unit; consequently, the occurrence of late relapse or superinfection could have been underestimated. Last, no formal cost-effectiveness evaluation was done. In France, procalcitonin analysis costs €10–15, an expenditure which should be compared with that of unnecessary antibiotics, especially when broad-spectrum or newly licensed agents are used.[4,43] In 2008, Vandijck and colleagues[43] reported that the acquisition cost of antibiotics used to treat nosocomial bloodstream infections in adult patients in the intensive care unit was €114 daily.

The diverse clinical characteristics and reasons for admissions to the intensive care unit for patients enrolled in this study suggest that our conclusions could be applicable to most non-surgical patients in the intensive care unit, including those who are immunocompromised. A procalcitonin-guided strategy could reduce antibiotic selective pressure with potential benefits in the era of multiresistance.

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