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


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 –0·6 to 1·3), 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.

Funding Assistance Publique-Hôpitaux de Paris, France, and Brahms, Germany.

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.2,3 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.5,6

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.7–11 Guidance for duration of antibiotic treatment could be based on the results of studies comparing two different durations,12–18 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.19–21 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.22–24 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
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 medicsurgical 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 neutropaenia (<500 neutrophils per mL); infections for which long-term antibiotic treatment is strongly recommended (ie, infective endocarditis, ostearticular 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, Télémédecine, 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.20 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 narrow-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-essay 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 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-essay 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

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
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. Assuming a mean of 12 days (SD 7·5) without antibiotics for the control group, 133 patients per study group would provide 90% power at a two-sided α=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. 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.

<table>
<thead>
<tr>
<th>At admission to ICU</th>
<th>Procalcitonin group (n=307)</th>
<th>Control group (n=314)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61·0 (15·2)</td>
<td>62·1 (15·0)</td>
</tr>
<tr>
<td>Men</td>
<td>207 (67%)</td>
<td>204 (65%)</td>
</tr>
<tr>
<td>Admission category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical</td>
<td>275 (90%)</td>
<td>280 (89%)</td>
</tr>
<tr>
<td>Emergency surgery</td>
<td>20 (7%)</td>
<td>25 (8%)</td>
</tr>
<tr>
<td>Elective surgery</td>
<td>12 (4%)</td>
<td>9 (3%)</td>
</tr>
<tr>
<td>Reason for admission to ICU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septic shock</td>
<td>53 (17%)</td>
<td>55 (18%)</td>
</tr>
<tr>
<td>Non-septic shock</td>
<td>46 (15%)</td>
<td>46 (15%)</td>
</tr>
<tr>
<td>Acute respiratory failure</td>
<td>115 (37%)</td>
<td>127 (40%)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>9 (3%)</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>Neurological failure</td>
<td>34 (11%)</td>
<td>36 (11%)</td>
</tr>
<tr>
<td>Multiorgan failure</td>
<td>20 (7%)</td>
<td>20 (6%)</td>
</tr>
<tr>
<td>Other†</td>
<td>30 (10%)</td>
<td>24 (8%)</td>
</tr>
</tbody>
</table>

(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; immunocompromised 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 χ² 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. 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 group (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.

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.

<table>
<thead>
<tr>
<th>Procalcitonin group (n=307)</th>
<th>Control group (n=314)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infection site</strong></td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>183 (71%)‡‡</td>
</tr>
<tr>
<td>Other¶¶</td>
<td>11 (4%)</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>24 (9%)</td>
</tr>
<tr>
<td>Skin and soft tissue</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Intra-abdominal</td>
<td>14 (5%)</td>
</tr>
<tr>
<td>CNS</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>Catheter-related infection</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Primary bloodstream infection</td>
<td>9 (3%)</td>
</tr>
<tr>
<td><strong>Positive blood cultures</strong></td>
<td></td>
</tr>
<tr>
<td>55 (18%)</td>
<td>53 (17%)</td>
</tr>
<tr>
<td><strong>Serum lactate (&gt;2 mmol/L)</strong></td>
<td></td>
</tr>
<tr>
<td>91 (37%)</td>
<td>96 (38%)</td>
</tr>
<tr>
<td><strong>C-reactive protein (mg/L)</strong>¶</td>
<td></td>
</tr>
<tr>
<td>12·0 (30·9); 1·6 (0·5–6·6)</td>
<td>12·0 (32·6); 1·5 (0·4–6·8)</td>
</tr>
<tr>
<td><strong>SOFA score</strong></td>
<td></td>
</tr>
<tr>
<td>144·2 (63·0–229·0)</td>
<td>137·2 (61·0–244·0)</td>
</tr>
<tr>
<td><strong>Day-28 mortality</strong></td>
<td></td>
</tr>
<tr>
<td>Procalcitonin group</td>
<td>55 (18%)</td>
</tr>
<tr>
<td>Control group</td>
<td>55 (17%)</td>
</tr>
<tr>
<td><strong>SAPS II</strong></td>
<td></td>
</tr>
<tr>
<td>43·8 (16·1)</td>
<td>43·4 (15·4)</td>
</tr>
<tr>
<td><strong>SOFA score</strong></td>
<td></td>
</tr>
<tr>
<td>7·5 (4·4)</td>
<td>7·2 (4·4)</td>
</tr>
<tr>
<td><strong>Type of infection</strong></td>
<td></td>
</tr>
<tr>
<td>Community-acquired infection</td>
<td>153 (50%)</td>
</tr>
<tr>
<td>Hospital-acquired infection</td>
<td>154 (50%)</td>
</tr>
<tr>
<td>Septic shock</td>
<td>138 (45%)</td>
</tr>
<tr>
<td>Severe hypotension—*defined by SOFA score &gt;2.††</td>
<td>135 (44%)</td>
</tr>
<tr>
<td>Positive blood cultures</td>
<td></td>
</tr>
<tr>
<td>55 (18%)</td>
<td>53 (17%)</td>
</tr>
<tr>
<td><strong>Procalcitonin (μg/L)</strong>¶</td>
<td></td>
</tr>
<tr>
<td>12·0 (30·9); 1·6 (0·5–6·6)</td>
<td>12·0 (32·6); 1·5 (0·4–6·8)</td>
</tr>
<tr>
<td><strong>C-reactive protein (mg/L)</strong>¶</td>
<td></td>
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<td>12·0 (30·9); 1·6 (0·5–6·6)</td>
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</tr>
<tr>
<td><strong>SOFA score</strong></td>
<td></td>
</tr>
<tr>
<td>7·5 (4·4)</td>
<td>7·2 (4·4)</td>
</tr>
</tbody>
</table>

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 274 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. ¶¶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
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 the course any earlier would have been too early—i.e, 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 as physicians judged that infection was unlikely, antibiotics were stopped prematurely as physicians judged that infection was cured, or antibiotics were unduly continued 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-

<table>
<thead>
<tr>
<th>Table 2: Main outcome variables</th>
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<tbody>
<tr>
<td><strong>Primary endpoints</strong></td>
</tr>
<tr>
<td>Procalcitonin group (n=307)</td>
</tr>
<tr>
<td>28-day mortality*</td>
</tr>
<tr>
<td>60-day mortality*</td>
</tr>
<tr>
<td>Number of days without antibiotics</td>
</tr>
</tbody>
</table>

**Secondary endpoints (days 1–28)**

- Relapse: 20 (6·5%) in the procalcitonin group and 16 (5·1%) in the control group, with a difference of 1·4% (–2·3 to 5·1) and a p value of 0·45.
- Superinfection: 106 (34·5%) in the procalcitonin group and 97 (30·9%) in the control group, with a difference of 3·6% (–3·8 to 11·0) and a p value of 0·29.
- Number of days without mechanical ventilation: 16·2 (11·1) days in the procalcitonin group and 16·9 (10·9) days in the control group, with a difference of –0·7 (–2·4 to 1·1) and a p value of 0·47.

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

*Diff erence (90% CI).
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
(e.g., 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-acquired 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-
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 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 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.
The only previous trials of patients in intensive care units18,19 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.1,9,11,12

Chastre and colleagues8 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 Chemotherapy11 and the Canadian Critical Care Trials Group.14 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_).11

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,16–17 the bacterial infection threshold for critically ill patients was 0·5–1 μg/L. 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,11,13,17 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.10 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,16,17 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
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, 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

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**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.
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, 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. 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. The study was designed assuming 35% mortality for control patients, whereas we recorded a crude mortality of 26–29% 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.

In 2008, Vandijck and colleagues 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.

### Contributors
As principal investigators of the PRORATA trial, LB, C-EL, MW, JC, and FT had full access to all the study data, and take responsibility for their integrity and the accuracy of their analysis. LB, MW, JC, and FT participated in the study design. LB, MW, and FT obtained funding for the study. LB, MW, JC, and FT supervised the study, and LB, C-EL, CC, AA, CS, FS, SL, BV, and JC collected the data. BP and FT analysed the data. FT provided statistical expertise. LB, MW, JC, FT, and C-EL drafted the report, and the report was revised for important intellectual content.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of infection; setting</th>
<th>Patients</th>
<th>Effect on antibiotic exposure of procalcitonin strategy vs control</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Procalcitonin</td>
<td>Control</td>
<td>Procalcitonin</td>
</tr>
<tr>
<td>Stolz et al (2009)</td>
<td>COPD exacerbation; emergency department</td>
<td>102</td>
<td>106</td>
<td>0.76 (95% CI 0.64–0.92)†</td>
</tr>
<tr>
<td>Nobre et al (2008)</td>
<td>Severe sepsis or septic shock; ICU</td>
<td>31¶</td>
<td>37¶</td>
<td>17·4 (SD 7·6)</td>
</tr>
<tr>
<td>Hochreiter et al (2009)</td>
<td>Infection with systemic inflammatory-response syndrome; surgical ICU</td>
<td>57</td>
<td>53</td>
<td>5·9 (95% CI 4·1–7·5)‡</td>
</tr>
<tr>
<td>Stolz et al (2009)</td>
<td>Ventilator-associated pneumonia; ICU</td>
<td>51</td>
<td>50</td>
<td>10 (IQR 6–16) vs 15 (10–23)††</td>
</tr>
</tbody>
</table>

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 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.
by CC, AA, CS, FS, SL, BV, BR, CB-B, MD, and MB, LB, C-EL, CC, AA, CS, FS, SL, BV, JC, and FT provided administrative, technical, or material support.

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Conflicts of interest
C-EL has received lecture fees from Brahms, and Merck Sharp & Dohme-Chibret. BR has served as a consultant for AstraZeneca, Merck Sharp & Dohme-Chibret, and Lilly. JC has received consulting and lecture fees from Pfizer, Brahms, Wyeth, Johnson & Johnson, Nektar-Bayer, and Arpida. MW has received consulting and lectures fees from Merck Sharp & Dohme-Chibret, Jansen-Cilag, Gilead, and AstraZeneca. All other authors declare that they have no conflicts of interest.

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References


