Procalcitonin to Reduce Long-Term Infection-associated Adverse Events in Sepsis
A Randomized Trial

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Abstract

Rationale: Although early antimicrobial discontinuation guided by procalcitonin (PCT) has shown decreased antibiotic consumption in lower respiratory tract infections, the outcomes in long-term sepsis sequelae remain unclear.

Objectives: To investigate if PCT guidance may reduce the incidence of long-term infection-associated adverse events in sepsis.

Methods: In this multicenter trial, 266 patients with sepsis (by Sepsis-3 definitions) with lower respiratory tract infections, acute pyelonephritis, or primary bloodstream infection were randomized (1:1) to receive either PCT-guided discontinuation of antimicrobials or standard of care. The discontinuation criterion was >80% reduction in PCT levels or any PCT <0.5 µg/L at Day 5 or later. The primary outcome was the rate of infection-associated adverse events at Day 180, a composite of the incidence of any new infection by Clostridioides difficile or multidrug-resistant organisms, or any death attributed to baseline C. difficile or multidrug-resistant organism infection. Secondary outcomes included 28-day mortality, length of antibiotic therapy, and cost of hospitalization.

Measurements and Main Results: The rate of infection-associated adverse events was 7.2% (95% confidence interval [CI], 3.8–13.1%; 9/125) versus 15.3% (95% CI, 10.1–22.4%; 20/131) (hazard ratio, 0.45; 95% CI, 0.20–0.98; P = 0.045); 28-day mortality 15.2% (95% CI, 10–22.5%; 19/125) versus 28.2% (95% CI, 21.2–36.5%; 37/131) (hazard ratio, 0.51; 95% CI, 0.29–0.89; P = 0.02); and median length of antibiotic therapy 5 (range, 5–7) versus 10 (range, 7–15) days (P < 0.001) in the PCT and standard-of-care arms, respectively. The cost of hospitalization was also reduced in the PCT arm.

Conclusions: In sepsis, PCT guidance was effective in reducing infection-associated adverse events, 28-day mortality, and cost of hospitalization.

Clinical trial registered with www.clinicaltrials.gov (NCT03333304).

Keywords: procalcitonin; sepsis; multidrug-resistant; mortality

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This article has a related editorial.

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The PCT-guided discontinuation of antibiotic therapy was demonstrated to reduce antibiotic exposure and the risk for adverse outcomes in patients with lower respiratory tract infections (LRTIs) compared with the standard of care (SOC) in several randomized trials (5–10). Additionally, data from meta-analyses of randomized clinical trials have confirmed the survival benefit of PCT-guided discontinuation of antibiotics (11–13). However, the mechanisms underlying this survival benefit are yet to be clarified.

Long-term use of antibiotics causes substantial damage to the gut flora, increasing the risk of infections caused by C. difficile and MDROs in critically ill patients, which are associated with poor clinical outcomes (14, 15). We conducted the PROGRESS (Procalcitonin-guided Antimicrobial Therapy to Reduce Long-Term Sequelae of Infections) trial to investigate whether the PCT-guided early discontinuation of antibiotic therapy would reduce the incidence of adverse events associated with these long-term infection sequelae in patients with sepsis that are driven by the prolonged use of antibiotics. These include death by MDROs and acquisition of infections by C. difficile and MDROs.

Some of the results have been previously reported in the form of an abstract (https://www.escmid.org/escmid_publications/ecmid_abstract_book/).

Methods

Participants

Enrolled patients were adults hospitalized with LRTIs (community, hospital-acquired, or ventilator-associated), acute pyelonephritis, or primary bloodstream infection and meeting the Sepsis-3 definitions (16) (see online supplement). PROGRESS was conducted in seven departments of Internal Medicine (National Ethics Committee approval 62/17; National Organization for Medicines approval IS-62/17). Exclusion criteria were need of prolonged treatment, viral or parasite infections, tuberculosis, cystic fibrosis, neutropenia, infection by HIV with low CD4 count, and pregnancy or lactation. Written informed consent was provided by the patient or legal representative before enrollment.

Procedures

The first 24 hours from the start of antibiotics, patients were 1:1 randomized into the PCT-guidance arm or the SOC arm by a generated list per site kept in a sealed envelope until randomization. Patients and investigators were aware of treatment assignment.

Attending physicians prescribed antimicrobials according to European and national guidelines (17). Blood samples were collected at baseline and on Day 5 for procalcitonin measurements using the VIDAS assay (lower detection limit 0.05 μg/L; bioMérieux). Antibiotics were discontinued if PCT was reduced by at least 80% or if it was <0.5 μg/L. When the rule did not apply, blood sampling was repeated daily and antibiotics were discontinued when the rule was met. Exceptions were allowed for medically unstable patients defined as febrile and/or requiring vasopressors. For patients in the SOC arm, the investigators were unaware of PCT kinetics and the duration of antimicrobial treatment was decided according to international guidelines (18).

Stool samples of 0.5 g were collected at baseline and on follow-up Days 7, 28, and 180 to detect C. difficile and MDRO colonization (see online supplement).

Outcomes

The rate of infection-associated adverse events until Day 180 was the primary outcome. This was an endpoint composed of any of the following: new case of C. difficile infection; new case of MDRO infection; and death associated with either MDROs or C. difficile baseline infection (see online supplement).

The time until the incidence of the first infection episode by MDROs or C. difficile during follow-up was recorded. Secondary endpoints were the time until the first new infection, the length of antibiotic therapy (LOT), 28-day and 180-day mortality, and cost of hospitalization.

Data were captured by investigators blinded to the allocation group. Discharged patients were followed up monthly by phone calls; if their health status had changed, outpatient clinical assessment was performed. Study was monitored for serious and nonserious adverse events (see online supplement).

Statistical Analysis

The sample size was calculated assuming the primary outcome would decrease from 30% in the SOC to 15% in the PCT arm. To achieve so with 80% power at the 5% level of
significance, 133 patients were calculated in each arm. Predefined analysis was done among the intention-to-treat population using the Fisher’s exact test and confirmatory forward stepwise Cox analysis (IBM SPSS Statistics v. 25.0). Sensitivity analyses were conducted for the effect of early death, protocol compliance, and extreme LOT. Any two-sided P value <0.05 was statistically significant. Adjustment for multiple comparisons was not performed because the endpoints were predefined (19).

Results

From November 2017 through January 2019, 266 patients were enrolled and randomized; 10 patients withdrew consent before Day 5 and requested removal of all data, leaving a final intention-to-treat analysis cohort of 256 patients. No patient was reported as lost to follow-up (Figure 1). Baseline characteristics were similar between the two arms (Tables 1 and E1 in the online supplement). The serum levels of C-reactive protein and PCT were not significantly different on Day 5 when intervention was started (Table E2). In total, 109 patients in the PCT arm met the predefined criteria for antimicrobial discontinuation: 89 patients on Day 5 and another 20 patients in the next days. However, antimicrobials were discontinued in 96 patients (76.8%) because 13 (10.4%) were considered medically unstable.

Bacterial pathogens were isolated at baseline among 105 patients: 56 in the SOC arm and 49 in the PCT arm; 98.2% and 98.0%, respectively, were treated with an antibiotic active against the pathogens. These percentages signify the antimicrobial activity of the administered antibiotics and not their appropriateness from the antimicrobial policy point of view.

In the intention-to-treat population, the primary outcome of infection-associated adverse events at Day 180 developed in 9 of 125 patients (7.2%; 95% confidence interval [CI], 3.8–13.1%) in the PCT-guidance group compared with 20 of 131 patients (15.3%; 95% CI, 10.1–22.4%) in the SOC group (hazard ratio, 0.45; 95% CI, 0.20–0.98; P = 0.045) (Figure 2A and
In the SOC arm, the patients’ risk to reach the primary outcome was higher among those colonized by C. difficile or MDROs compared with noncolonized patients. This was shown by the results of the fecal colonization tests of both Days 7 and 28 (odds ratio, 12.6; 95% CI, 3.7–42.8; P < 0.001 for Day 7; and 10.8; 95% CI, 3.6–32.5; P = 0.003 for Day 28). However, in the PCT-guidance arm, the risk to reach the primary outcome was not different by the presence or absence of colonization on Days 7 and 28 (odds ratio, 1.3; 95% CI, 0.1–11.6; P = 0.59; and 3.4; 95% CI, 0.7–16.4; P = 0.14, respectively) (Figure 2B).

Major benefit from PCT guidance was observed in three main secondary endpoints: 28-day mortality, LOT, and cost of hospitalization (Table 2). More precisely, 28-day mortality was lower in the PCT-guidance arm compared with the SOC arm (15.2% [19/125 patients] vs. 28.2% [37/131 patients]; hazard ratio, 0.51; 95% CI, 0.29–0.89; P = 0.02). PCT guidance was also an independent protective factor from death after 28 days (hazard ratio, 0.51; 95% CI, 0.29–0.89; P = 0.02) (Figure 3 and Table 2).

The decision to randomize patients was made by the attending physicians and/or primary investigators according to the PCT stopping rule and the patients’ medical condition, which was classified as being either extremely prolonged LOT or not. The allocation of treatment was randomized among patients who survived at least 5 days to reach the primary outcome among those colonized by C. difficile or MDROs as compared with noncolonized patients. This was shown by the results of the fecal colonization tests of both Days 7 and 28 (odds ratio, 12.6; 95% CI, 3.7–42.8; P < 0.001 for Day 7; and 10.8; 95% CI, 3.6–32.5; P = 0.003 for Day 28). However, in the SOC-guidance arm, the risk to reach the primary outcome was not different by the presence or absence of colonization on Days 7 and 28 (odds ratio, 1.3; 95% CI, 0.1–11.6; P = 0.59; and 3.4; 95% CI, 0.7–16.4; P = 0.14, respectively) (Figure 2B).

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A trend for decreased 180-day mortality was shown in the PCT-guidance arm (30.4%) compared with SOC (38.2%), but it did not reach statistical significance (hazard ratio, 0.71; 95% CI, 0.42–1.19; P = 0.24). Median LOT was 10 days in the SOC arm compared with 5 days in the PCT-guidance arm (P < 0.001); this reduction in the LOT was observed irrespective of the type of underlying infection (Figures E1 and E2). Furthermore, the median hospital stay was shorter in the PCT-guidance arm (Figure E3).

The median cost of hospitalization was estimated to be €1,183.49 per patient in the SOC arm and €956.99 in the PCT-guidance arm (P = 0.05) (Table 2). This difference was mainly due to the decrease in the consumption of drugs (Figure E4).

Exploratory analysis showed that treatment with at least two broad-spectrum antibiotics was associated with the highest colonization rate. Analyzed antibiotics were piperacillin/tazobactam, ceftolozane/tazobactam, carbapenems, tigecycline, and amikacin. Treatment with any two was associated with higher colonization by MDROs on Days 7 and 28 in the SOC arm but not in the PCT-guidance arm (Figure E5).

The incidence of antimicrobial-associated adverse events, particularly diarrhea and acute kidney injury, was lower in the PCT-guidance arm (Table 4 and Figure E6A). These adverse events developed earlier in the SOC arm (Figures E6B and E6C). Moreover, the incidence of serious adverse events did not differ and none of the serious adverse events were related to the study.

Discussion

In this multicenter randomized trial, we found that early discontinuation of antimicrobial therapy guided by a PCT measurement below <0.5 μg/L or a reduction of at least 80% from the baseline at Day 5 or later significantly reduced the rate of infection-associated adverse events. Following the PCT-guidance approach, the length of antibiotic therapy was reduced and there were survival benefits in terms of reduction in both in-hospital and 28-day mortality reflecting a direct impact on all baseline infections.

In the PROGRESS trial, we demonstrate for the first time that PCT-guided early discontinuation of antimicrobials in patients with sepsis prevents infection caused by MDROs and/or C. difficile. Two important findings of this trial could be attributed to observed clinical benefits. First, the rate of gut colonization by MDROs and C. difficile did not differ between the two groups on Days 7 and 28, and second, the risk to develop an infection-associated adverse event was significantly higher in colonized patients in

Table E5 and E6).
Table 2. Primary and Secondary Study Outcomes

| Parameters                                             | Standard of Care \( (n = 131) \) | PCT Guidance \( (n = 125) \) | Odds Ratio \( (95\% CI) \) | \( P \) Value |
|--------------------------------------------------------|-----------------------------------|-----------------------------|-----------------------------|--------------|
| Infection-associated adverse events until Day 180, n (%) | 20 (15.3)                         | 9 (7.2)                     | 0.43 (0.19–0.99)            | 0.045        |
| New infection by MDROs until Day 180, n (%)             | 8 (6.1)                           | 5 (4.0)                     | 0.64 (0.20–2.01)            | 0.57         |
| New infection by \( C. \text{ difficile} \) until Day 180, n (%) | 12 (9.2)                         | 6 (4.8)                     | 0.50 (0.18–1.38)            | 0.22         |
| Mortality associated with baseline infection by MDROs, n (%) | 5 (3.8)                          | 1 (0.8)                     | 0.20 (0.02–1.76)            | 0.21         |
| In-hospital mortality, n (%)                           | 33 (25.2)                         | 17 (13.6)                   | 0.47 (0.25–0.89)            | 0.03         |
| 28-d mortality, n (%)                                  | 37 (28.2)                         | 19 (15.2)                   | 0.46 (0.26–0.85)            | 0.02         |
| 180-d mortality, n (%)                                 | 50 (38.2)                         | 38 (30.4)                   | 0.71 (0.42–1.19)            | 0.24         |
| Antimicrobial treatment duration, median (Q1–Q3), d      | 10 (7–15)                         | 5 (5–7)                     | N/A                         | <0.001       |
| Cost of hospitalization, median (Q1–Q3), €              | 1,183.49 (718.98–2,011.57)        | 956.99 (725.02–1,355.90)    | N/A                         | 0.05         |
| Fecal colonization by Day 180, n (%)                   | 13 (9.9)                          | 14 (11.2)                   | 1.15 (0.52–2.54)            | 0.84         |
| \( C. \text{ difficile} \)                             | 13 (9.9)                          | 15 (13.3)                   | 1.22 (0.55–2.70)            | 0.69         |

Table 3. PCT Guidance as an Independent Protective Factor from Development of IAAEs by Day 180

| Parameters                                             | IAAE (−) \( (n = 227) \) | IAAE (+) \( (n = 29) \) | Univariate Analysis | Multivariate Analysis |
|--------------------------------------------------------|--------------------------|--------------------------|---------------------|----------------------|
| PCT guidance                                           | 116 (51.1)               | 9 (31.0)                 | 0.45 (0.20–0.98)    | 0.045                |
| Dementia                                               | 54 (23.8)                | 16 (55.2)                | 3.53 (1.70–7.34)    | 0.001                |
| Residency in healthcare facilities                     | 14 (6.2)                 | 6 (20.7)                 | 3.56 (1.45–8.74)    | 0.006                |
| Hospitalization in last 3 mo                           | 39 (17.2)                | 10 (34.5)                | 2.47 (1.15–5.31)    | 0.02                 |
| SOFA score >4                                          | 74 (32.6)                | 15 (51.7)                | 2.09 (1.01–4.34)    | 0.05                 |
| Community-acquired pneumonia                           | 105 (46.3)               | 7 (24.1)                 | 0.39 (0.17–0.90)    | 0.03                 |
| Primary or secondary bacteremia                        | 31 (13.7)                | 11 (37.9)                | 3.52 (1.66–7.45)    | 0.001                |
| Septic shock                                           | 13 (5.7)                 | 5 (17.2)                 | 3.17 (1.21–8.32)    | 0.02                 |
| Empiric treatment according to the ESCMID guidelines   | 86 (37.9)                | 17 (58.6)                | 2.25 (1.07–4.70)    | 0.001                |

Definition of abbreviations: \( C. \text{ difficile} \) = \text{Clostridioides difficile}; CI = confidence interval; MDROs = multidrug-resistant organisms; N/A = not applicable; PCT = procalcitonin; Q = quartile.

Bold indicates any \( P < 0.05 \).

the SOC arm but not in the PCT-guidance arm. These results indicate that despite initial colonization after exposure to antimicrobials, early discontinuation of antimicrobials in the PCT-guidance arm did not allow development of clinical infection. However, long-term antibiotic exposure to gut microbiota in the SOC arm could either affect the integrity of the mucosal barrier or modulate the composition of the gut microbiota and explain the increased incidence of infections by MDROs and \( C. \text{ difficile} \).

Our study reveals that the use of PCT-guided early discontinuation of antimicrobials led to reduction in 28-day mortality, early discharge from hospital, and lower hospitalization cost. The results of this study are consistent with those reported by de Jong and colleagues (9). Although PCT was not used to guide antibiotic therapy in these studies, the decreased need for ICU admission and stay in the PCT-guidance arm reflects the improved clinical outcomes. The findings of our study are in line with the results of the PROGRESS trial (13), which demonstrated a significant reduction in mortality associated with baseline infection by \( C. \text{ difficile} \) in the PCT-guidance arm compared to the SOC arm. However, the use of PCT-guided antibiotic treatment needs to be emphasized that the compliance to the stopping rule in the PROGRESS trial was the highest (76.8%) among all trials conducted so far studying the PCT-guided early stop of antibiotics. Participants of the SAPS trial were hospitalized in an ICU. This did not happen in our trial, where patients, although septic, received treatment in the wards under advanced supportive care. This is happening because of the shortage of ICU beds in our country. The results of the SAPS
The results of the PROGRESS trial are consistent with these observations showing a higher incidence of diarrhea, acute kidney injury, electrolyte disorders, elevated liver enzymes, and arrhythmia in the SOC arm versus the PCT-guidance arm. From these findings, we postulate that survival benefits offered by PCT guidance could be due to reduction in these antibiotic-associated events. Although the overall incidence of the adverse events was reduced, a similar decrease was not found for the incidence of at least one serious adverse event probably because not all adverse events met the definition of seriousness.

Our findings are in agreement with those of previous studies conducted in patients with LRTIs with or without sepsis that demonstrated that the use of PCT guidance may effectively shorten the duration of antibiotic treatment (5–10, 24–31). Based on this evidence, the U.S. Food and Drug Administration approved the use of PCT guidance for early discontinuation of antibiotics in LRTIs (32). The ProACT (Procalcitonin Antibiotic Consensus Trial) trial failed to replicate these results (33). In this trial, 834 patients were allocated to the SOC arm and 830 patients to the arm of early stop of antibiotics guided by PCT. It should, however, be emphasized that the median length of therapy in the SOC arm was only 4.4 days, raising considerations that this was already too short to allow for the PCT guidance to further shorten this.

Importantly, the cohort of the PROGRESS

Table 4. Adverse Events

| Event                                                                 | Standard of Care (n = 131) | PCT Guidance (n = 125) | Odds Ratio (95% CI) | P Value |
|----------------------------------------------------------------------|-----------------------------|------------------------|---------------------|---------|
| At least one serious adverse event by Day 180, n (%)                 | 71 (54.2)                   | 68 (54.4)              | 1.01 (0.62–1.65)    | >0.99   |
| More than two serious adverse events, n (%)                         | 8 (6.1)                     | 1 (0.8)                | 0.12 (0.02–0.99)    | 0.04    |
| Type of serious adverse event, n (%)                                | 37 (28.2)                   | 19 (15.2)              | 0.46 (0.26–0.85)    | 0.02    |
| Death by Day 180                                                    | 50 (38.2)                   | 38 (30.4)              | 0.71 (0.42–1.19)    | 0.24    |
| Rehospitalization by Day 28, n/total n of discharged patients       | 9/98 (9.2)                  | 9/108 (8.3)            | 1.02 (0.38–2.76)    | >0.99   |
| Rehospitalization by Day 180, n/total n of discharged patients      | 23/98 (23.5)                | 34/108 (31.5)          | 1.50 (0.81–2.78)    | 0.22    |
| Rehospitalization due to infection by Day 180, n/total n of discharged patients | 16/98 (16.3)                | 20/108 (18.5)          | 1.17 (0.57–2.40)    | 0.72    |
| Extended hospitalization, n (%)                                      | 17 (13.0)                   | 11 (8.8)               | 0.65 (0.29–1.44)    | 0.32    |
| Life-threatening event, n (%)                                        | 8 (6.1)                     | 4 (3.2)                | 0.51 (0.15–1.73)    | 0.38    |
| At least one adverse event, n (%)                                    | 83 (63.4)                   | 64 (51.2)              | 0.61 (0.37–0.99)    | 0.05    |
| More than two adverse events, n (%)                                  | 20 (15.3)                   | 6 (4.8)                | 0.28 (0.11–0.72)    | 0.007   |
| Type of adverse event, n (%)                                         | 48 (36.6)                   | 24 (19.2)              | 0.41 (0.23–0.73)    | 0.002   |
| Acute kidney injury                                                  | 23 (17.6)                   | 9 (7.2)                | 0.36 (0.16–0.82)    | 0.01    |
| Nonserious organ-threatening adverse event                            | 47 (35.9)                   | 20 (16.0)              | 0.36 (0.20–0.66)    | <0.001  |

Definition of abbreviations: CI = confidence interval; PCT = procalcitonin.
Bold indicates any P < 0.05.
*None of the serious adverse events were judged by the site principal investigator as study related.
trial was not limited to patients with LRTIs but also enrolled patients with acute pyelonephritis. This indicates that the use of PCT as a surrogate tool for early discontinuation of antimicrobials could be broadened to critically ill patients, particularly for those who are treated with broad-spectrum antibiotics and exert a strong selection pressure, as this was the case for the majority of patients enrolled in our trial. Moreover, the decrease in hospitalization cost is another benefit, which strongly argues in favor of implementing PCT guidance.

The main strengths of the PROGRESS trial are the inclusion of patients meeting the Sepsis-3 definitions, the study of infections other than LRTIs, and the study of infection-associated adverse events as an endpoint that has never been studied so far. The main limitations are the limited stool sampling and the generalizability of the results. More precisely, a large window of stool sampling between Days 28 and 180 was left, making the changes in microbiota difficult to interpret. The effect of this large window can barely be covered even with stool microbiome analysis. PROGRESS is an open-label trial that was conducted in a country with high antimicrobial consumption and high antimicrobial resistance. This should be interpreted in the light of emerging infections by MDROs and *C. difficile* as a worldwide calamity.

**Conclusions**

The use of PCT guidance for early discontinuation of antimicrobials in medically stable and afebrile patients with sepsis demonstrated significant clinical benefits. The PCT-guidance approach was associated with lower infection-associated adverse events, lower 28-day mortality, shorter LOT, early hospital discharge, and decreased costs of hospitalization. These benefits may have substantial impact on public health, particularly for countries with high antimicrobial consumption.

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