# Guideline-Based Clinical Assessment Versus Procalcitonin-Guided Antibiotic Use in Pneumonia: A Pragmatic Randomized Trial

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**Study objective:** Efforts to reduce unnecessary and unnecessarily long antibiotic treatment for community-acquired pneumonia have been attempted through use of procalcitonin and through guidelines based on serial clinical assessment. Our aim is to compare guideline-based clinical assessment– and procalcitonin algorithm–guided antibiotic use among patients with community-acquired pneumonia.

**Methods:** We performed a pragmatic, randomized, multicenter trial from November 2012 to April 2015 at 12 French hospitals. We included emergency department (ED) patients older than 18 years with community-acquired pneumonia. Patients were randomly assigned to either the procalcitonin-guided or clinical assessment group. In accordance with past studies, we hypothesized that serial clinical assessment would be superior to procalcitonin-guided care. The primary outcome was antibiotic duration, and secondary outcomes included rates of antibiotic duration less than or equal to 5 days, and clinical success and combined serious adverse outcomes at 30 days in the intention-to-treat population.

**Results:** Of 370 eligible patients, 285 (77%) were randomly assigned to either clinical assessment– (n=143) or procalcitonin-guided care (n=142). Median age was 67 years (range 18 to 93 years) and 40% of patients were deemed to have Pneumonia Severity Index class IV or V. Procalcitonin algorithm adherence was 76%. Antibiotic duration was not significantly different between clinical assessment– and procalcitonin-guided groups (median 9 versus 10 days, respectively). Clinical success rate was 92% in each group and serious adverse outcome rates were similar (15% versus 20%, respectively).

**Conclusion:** Guideline-based serial clinical assessment did not reduce antibiotic exposure compared with procalcitonin-guided care among ED patients with community-acquired pneumonia. The strategies were similar in terms of duration of antibiotic use and clinical outcomes. [Ann Emerg Med. 2019;74:580-591.]

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## INTRODUCTION

### Background

Efforts to reduce unnecessary and unnecessarily long antibiotic treatment for community-acquired pneumonia have been made through use of biomarkers, specifically procalcitonin,[1-3] and through guidelines relying on serial clinical assessment.[4,5] Procalcitonin level has been associated with bacterial as opposed to nonbacterial infection.[6] Trials in which patients with lower respiratory tract infection were randomized to antibiotic treatment based on an algorithm of initial and serial procalcitonin measurements or usual care have found significantly lower rates of antibiotic exposure with the procalcitonin strategy, with similar rates of adverse clinical outcomes, including for patients with community-acquired pneumonia.[1-3] Guidelines for clinical stability criteria have also been developed and used to minimize antibiotic duration for patients with community-acquired pneumonia.[7] A randomized trial comparing clinical guideline–directed care with usual care found that guideline-directed care significantly reduced antibiotic exposure, with similar rates of clinical success and no more adverse outcomes.[5]

Previous procalcitonin trials of antibiotic reduction in lower respiratory tract infection have been limited by active

**Editor's Capsule Summary**

*What is already known on this topic*

Procalcitonin levels increase in acute bacterial respiratory infections and may help guide antibiotic use, as may bedside guideline-based approaches.

*What question this study addressed*

How does a procalcitonin-guided antibiotic strategy compare with a consensus clinical guideline–based approach?

*What this study adds to our knowledge*

In 12 French hospitals treating 285 emergency department (ED) patients with presumed community-acquired pneumonia who were randomly assigned to one of the approaches, the group antibiotic duration, success, and adverse events did not reveal the difference hypothesized before the trial.

*How this is relevant to clinical practice*

Individuals creating ED community-acquired pneumonia care approaches can use either consensus clinically based or procalcitonin-driven strategies.

real-time direction only to clinicians caring for patients assigned to the procalcitonin strategy, comparison with usual care that was not informed by current clinical guidelines for antibiotic discontinuation by the Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS)[7] and in which newer short-course treatment regimens were unavailable,[8,9] and evaluation of mixed populations of patients with lower respiratory tract infection, including patients with diagnoses for which antibiotics have been demonstrated to be of no clinical benefit (eg, acute bronchitis). In the largest trial of patients with community-acquired pneumonia managed by a procalcitonin-based algorithm, median antibiotic duration was 8 days; however, it was 5 days in a trial in which patients with community-acquired pneumonia were managed by clinical assessment based on the IDSA/ATS guidelines.[3,5] Consequently, for patients with community-acquired pneumonia, the advantage of procalcitonin-guided care compared with clinical assessment–guided care to safely reduce antibiotic exposure is presently unclear.

### Importance

Reducing inappropriate antibiotic use is associated with avoidable costs and adverse events, as well as decreased promotion of bacterial resistance.[10,11] Reducing inappropriate use (ie, when antibiotics are prescribed for conditions for which no patient benefit is likely) is a priority of public health agencies.[12,13]

### Goals of This Investigation

To identify the optimal approach to reducing unnecessary antibiotic exposure, we compared outcomes among 285 emergency department (ED) patients with community-acquired pneumonia who were randomly assigned to antibiotic management by serial clinical assessment based on IDSA/ATS guidelines[7] or a previously studied procalcitonin algorithm.[1-3]

## MATERIALS AND METHODS

### Study Design and Setting

We conducted a pragmatic, multicenter, open-label, randomized, controlled, interventional trial from November 2012 to April 2015 at 12 French hospitals (Table E1, available online at http://www.annemergmed.com). The Nantes University Hospital ethical committee approved the study protocol and informed consent procedures. An independent data and safety monitoring board was established. All patients provided written informed consent before inclusion in the study.

### Selection of Participants

We enrolled adults who presented to the ED for whom the attending emergency physician made the presumptive diagnosis of community-acquired pneumonia. During most periods, consecutive patients were enrolled; however, during some times when EDs were particularly busy, some potentially eligible patients were missed. All enrolled patients were randomized between the 2 groups, with stratification based on site. The randomization was realized by blocks with a random block size. Provider participants were those already caring for the patient at enrollment. Therefore, the strategy followed by the provider was determined by the care group to which the patient was randomized.

Standard laboratory and radiographic testing was conducted at the discretion of the patient's treating clinician. We enrolled patients who had at least 2 of 3 respiratory infection criteria: an acute respiratory symptom (ie, cough, sputum production, dyspnea, tachypnea, or pleuritic pain); abnormal lung auscultatory sounds; and signs of infection (ie, oral temperature $\geq$38.0°C (100.4°F) or <36.0°C (96.8°F), sweats, chills, or leukocyte count >10,000/μL or <4,000/μL) and a new infiltrate on chest radiograph (sputum with WBCs was not required).[14]

We excluded patients with pregnancy, immunosuppression (ie, HIV infection and a CD4 count

<200 cells/mL, neutropenia, active cancer, organ transplant, and active treatment with immunosuppressive drugs), exacerbation of chronic obstructive pulmonary disease, or a life-threatening presentation expected to lead to possible imminent death (according to provider assessment), or who had received antibiotics for the current episode of illness. Because the protocol required repeated assessment at 6 to 24 hours, patients who were anticipated to be discharged from the ED within 6 hours of their registration were excluded.

## Methods of Measurement

On patient enrollment, we recorded demographics, clinical history, coexistent illnesses, examination findings, and laboratory and imaging results based on the radiologist's interpretation, and calculated the Pneumonia Severity Index class. Participants were then followed and we recorded procalcitonin levels, antibiotic use, hospitalization, guideline-based clinical stability criteria at day 5 (ie, pulse rate ≤100 beats/min, respiratory rate ≤24 breaths/min, systolic blood pressure ≥90 mm Hg, $Sao_2$ ≥90%, or $Po_2$ ≥60 mm Hg on room air),[7] clinical cure (defined as resolution of all pneumonia-related signs and symptoms or improvement of chest radiographic findings), and serious adverse outcomes (defined as death from any cause, ICU admission for any reason, and disease-specific complications [ie, lung abscess, empyema, or acute respiratory distress syndrome], or recurrent community-acquired pneumonia requiring antibiotic treatment with or without readmission). These outcomes were assessed by daily physical visits during hospital stay and by a structured telephone interview on day 30 (Appendix E1, available online at http://www.annemergmed.com).

Procalcitonin was measured with a rapid sensitive assay with a functional assay sensitivity of 0.06 μg/L (Kryptor PCT; Brahms, Hennigsdorf, Germany).[2] This laboratory test was performed on site in the laboratory of each participating hospital.

## Interventions

Study interventions are detailed in Figure 1. Using a double-blind computer-generated list, we assigned participants in a 1:1 ratio to the clinical assessment– or procalcitonin-guided care group. Physicians were allowed to manage patients according to their assigned group without real-time investigator monitoring of their care, and were not required to justify algorithm or clinical guideline deviations. Protocol adherence was retrospectively determined according to review of participant records.

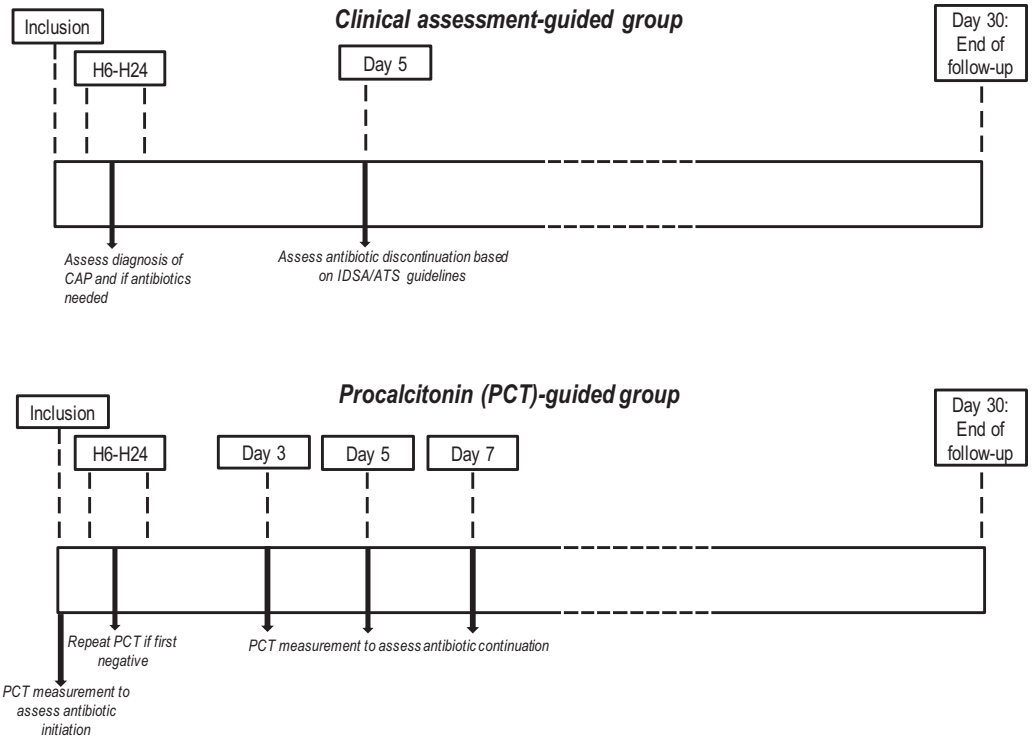


**Figure 1.** Study interventions. *H6-H24*, Hour 6 and hour 24 after randomization; *CAP*, community-acquired pneumonia; *PCT*, procalcitonin.

Before the study, the procalcitonin algorithm was known and procalcitonin measurement was available and used in each participating hospital for at least 3 years, and IDSA/ATS guidelines had been published, but neither was part of any hospital policy or care pathway. In the 3 months before the beginning of the trial, all physicians in the ED and hospital received approximately 2 hours of training about the background and use of guideline-directed clinical assessment and the procalcitonin algorithm. This training consisted of prestudy meetings set up by the principal investigator with local physicians. Training included examples and exercises of antibiotic prescription or discontinuation based on the 2 strategies to be compared. The procalcitonin algorithm was based on that used in previous studies[2,3] and was as follows: initiation of antibiotics was strongly not recommended if the procalcitonin level was less than 0.1 μg/L and was not recommended if the level was less than or equal to 0.25 μg/L; and initiation of antibiotics was strongly recommended if the procalcitonin level was greater than 0.5 μg/L and recommended if the level was greater than 0.25 μg/L. If antibiotics were not initiated in the ED after the first procalcitonin result, procalcitonin measurements were repeated after 6 to 24 hours, and initiation of antibiotics was evaluated with the same cutoff ranges. Prespecified allowed exceptions to the procalcitonin algorithm included immediate need for ICU admission, respiratory or hemodynamic instability, and severe community-acquired pneumonia (Pneumonia Severity Index class IV or V).[2,3] However, the procalcitonin algorithm was a guideline that could be overruled by the treating physician according to his or her judgment. For participants in the procalcitonin group, serum procalcitonin levels were available to the emergency physician, with other laboratory results in usual computer records, and antibiotic treatment was guided by procalcitonin levels as described above. Initial procalcitonin level was also measured in participants in the clinical assessment group; however, the result was not made available to the treating physician. Results were routinely available within 1 hour.

Similar to the procalcitonin testing strategy, in an attempt to balance the 2 strategies and model typical care patterns of primary care and hospitalist physician reassessment, participants in the clinical assessment group were evaluated 6 to 24 hours after randomization—but in this case, clinically—for continuation or discontinuation of antibiotics started in the ED. The clinical assessment strategy was as follows: participants receiving a diagnosis of community-acquired pneumonia in the ED were prescribed antibiotic treatment by their treating emergency physician. Then, participants who received antibiotic treatment in the ED were reassessed 6 to 24 hours after randomization by a different attending hospital physician to confirm or invalidate the diagnosis of community-acquired pneumonia and need to continue antibiotics. This intervention was based on review of clinical findings, chest radiograph, and laboratory tests (except procalcitonin) performed in the ED and on the participant's clinical evolution to that point. If the diagnosis of community-acquired pneumonia was not confirmed, then antibiotic discontinuation was recommended; if another infection requiring antibiotic treatment was diagnosed, then antibiotic continuation was recommended. The second intervention occurred on day 5, when hospitalized participants were evaluated by the treating hospital physician using clinical stability criteria based on IDSA/ATS guidelines to stop antibiotic treatment as follows: if the participant was afebrile for 48 to 72 hours and had no more than 1 community-acquired pneumonia–associated sign of clinical instability (ie, pulse rate >100 beats/min, respiratory rate >24 breaths/min, systolic blood pressure <90 mm Hg, $Sa_{O_2}$ <90%, or $P_{O_2}$ <60 mm Hg on room air), then discontinuation of antibiotics was strongly recommended. If the patient did not fulfill these criteria, then continuation of antibiotics was recommended for 2 more days, and then the patient was reevaluated.[7] In the clinical assessment group, among participants discharged from the ED initially or from the hospital subsequently before day 5, the day 5 intervention did not occur and antibiotic treatment for 5 days was recommended.

If antibiotics were not initiated after the first procalcitonin result, then procalcitonin measurements were repeated after 6 to 24 hours and subsequent antibiotic initiation was evaluated with the same criteria. Among hospitalized participants treated with antibiotics, procalcitonin measurements were repeated on days 3, 5, and 7, and antibiotic continuation or discontinuation was recommended or not recommended according to the same criteria. For participants who were discharged from the ED initially or from the hospital subsequently before day 5, in the procalcitonin group, procalcitonin measurement was halted, and duration of antibiotic therapy was guided by the last obtained procalcitonin value, as specified in the procalcitonin algorithm.[2,3] If the allowed exceptions to the procalcitonin algorithm occurred, then procalcitonin measurements were continued on the same schedule, with antibiotic continuation or discontinuation recommended according to the same criteria.

### Outcome Measures

The primary outcome was total days of antibiotic exposure within 30 days after ED admission in the intention-to-treat population. Secondary outcomes included total days of antibiotic exposure within 30 days after randomization in the modified intention-to-treat population, in which patients who received antibiotics for diagnoses other than community-acquired pneumonia or who were found to have Legionnaires' disease were excluded. We set up this modified intention-to-treat analysis because confirmation of the diagnosis of community-acquired pneumonia is occasionally difficult in the ED absent later knowledge of clinical course, laboratory results, and imaging results. Thus, if community-acquired pneumonia was misdiagnosed and the patient actually had another infection, then procalcitonin and clinical assessment strategy would not be applicable. Because the recommended treatment duration for Legionnaires' disease is 10 to 14 days, procalcitonin would not be used.[15] Other secondary outcomes were evaluated in the intention-to-treat population and included proportion of participants treated with antibiotics for less than or equal to 5 days, adherence to the procalcitonin algorithm and clinical reassessment protocol, rates of clinical cure, serious adverse outcomes, hospitalization, and hospital length of stay at day 30. Clinical success at day 30 was defined as the return to the precommunity-acquired pneumonia state (ie, all pneumonia-related symptoms had disappeared) according to the participant's telephone interview.

### Primary Data Analysis

We tested for a reduction in antibiotic duration of greater than or equal to 2 days for clinical assessment– compared with procalcitonin-guided care. With an SD[1] of 5.5 and type I error of 0.05, a sample size of 260 participants provided a 90% power to detect superiority of clinical assessment– compared with procalcitonin-guided antibiotic duration. We tested superiority of clinical assessment– to procalcitonin-guided care because of past studies suggesting that the former led to greater reduction in antibiotic duration compared with usual care. Because we also planned a secondary analysis in the modified intention-to-treat population, we anticipated that approximately 10% of the randomized patients would receive antibiotic treatment for diagnoses other than community-acquired pneumonia or would have Legionnaires' disease, and determined that 286 participants should be included. The statistical analysis plan is provided in Appendix E2, available online at http://www.annemergmed.com.

Results are given as medians and interquartile ranges (IQRs) for continuous variables and as frequencies and percentages for categoric variables. Mann-Whitney tests were used for continuous variables. We provide a *P* value for the primary outcome analysis and 95% confidence intervals (CIs) of the difference for other outcome comparisons. The proportion of patients with antibiotic treatment within the 30-day follow-up period was described with Kaplan-Meier curves and compared with the log-rank test. For patients with a missing value for duration of antibiotic treatment, this outcome was imputed with the mean length of the antibiotic treatment at 30 days for the assigned care group. All statistical tests were 2 sided. Analyses were performed with Stata (version 15; StataCorp, College Station, TX).

## RESULTS

### Characteristics of Study Subjects

During the study period, 370 consecutive patients with community-acquired pneumonia were screened as described in Figure 2. Two hundred eighty-five patients provided consent and were randomized (intention-to-treat population) to the clinical assessment–guided group (n=143) or the procalcitonin-guided group (n=142). The modified intention-to-treat population included 131 participants in each group. Baseline characteristics of participants in the 2 groups were similar (Table 1). Median age was 67 years (range 18 to 93 years) and 59% were men. Sixty-five percent of patients had temperature greater than 38.0°C and 40% were in Pneumonia Severity Index class IV or V for high-risk community-acquired pneumonia. Major comorbidities were present in 57% of clinical assessment and 53% of procalcitonin participants. Initial median procalcitonin level was 0.83 μg/L (IQR 0.14 to 3.18 μg/L; range 0.03 to 45.82 μg/L) in the clinical assessment group and 0.71 μg/L (IQR 0.17 to 3.06 μg/L; range 0.04 to 37.69 μg/L) in the procalcitonin group. Of 142 participants in the procalcitonin group, initial procalcitonin values were less than 0.1 μg/L in 19 (13%), 0.1 to less than or equal to 0.25 μg/L in 30 (21%), 0.25 to less than or equal to 0.5 μg/L in 14 (10%), and greater than 0.5 μg/L in 79 (56%). Antibiotics administered in the ED included amoxicillin (clinical assessment group 32 [22%], procalcitonin group 26 [18%]), amoxicillin-clavulanate (clinical assessment group 62 [43%], procalcitonin group 57 [40%]), a fluoroquinolone (clinical assessment group 7 [5%], procalcitonin group 5 [3%]), ceftriaxone (clinical assessment group 42 [29%], procalcitonin group 38 [27%]), and others (clinical assessment group 18 [13%], procalcitonin group 26

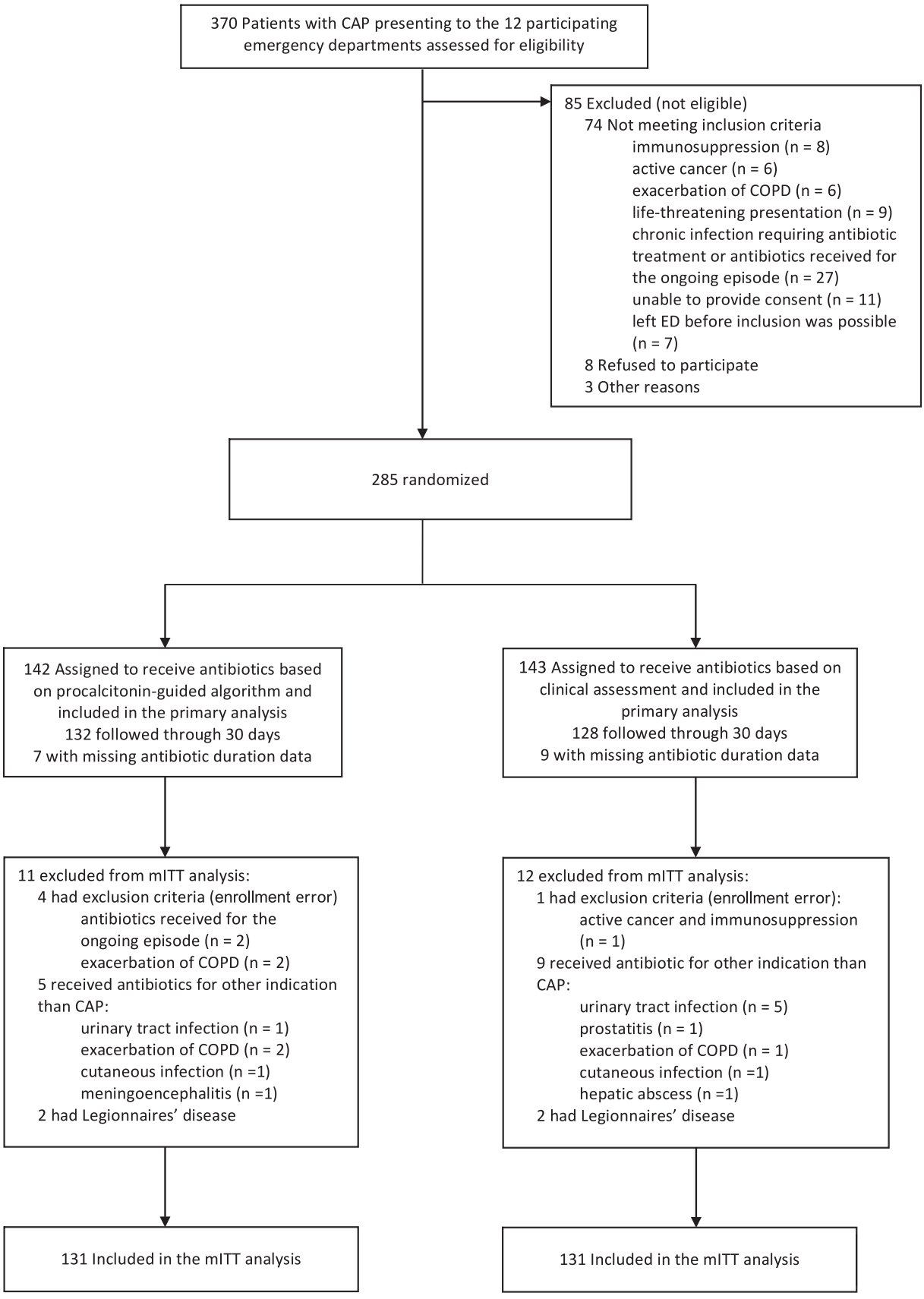


**Figure 2.** Study flow diagram. *COPD*, Chronic obstructive pulmonary disease; *mITT*, modified intention to treat.

**Table 1.** Baseline characteristics of patients with community-acquired pneumonia randomized to clinical assessment– or procalcitonin-guided care in the intention-to-treat population.

| Characteristics | CA-Guided Group (n=143) | PCT-Guided Group (n=142) |
|---|---|---|
| Demographics | | |
| Age, median (IQR), y | 67 (47–81) | 67 (46–83) |
| Female sex, No. (%) | 54 (38) | 62 (44) |
| Past and current smoking, No. (%) | 45 (31) | 51 (36) |
| Current smoker | 29 (20) | 31 (22) |
| Coexisting illnesses, No. (%) | | |
| Coronary heart disease | 16 (11) | 19 (13) |
| Cerebrovascular disease | 4 (3) | 4 (3) |
| Renal dysfunction | 2 (1) | 7 (5) |
| COPD | 16 (11) | 11 (8) |
| Neoplastic disease | 8 (6) | 7 (5) |
| Diabetes | 35 (24) | 27 (19) |
| Clinical history, No. (%) | | |
| Cough | 112 (78) | 113 (80) |
| Sputum production | 62 (43) | 67 (47) |
| Dyspnea | 109 (76) | 103 (73) |
| Examination | | |
| Rales, No. (%) | 105 (73) | 114 (80) |
| Body temperature, median (IQR), °C | 38.4 (37.6–39.0) | 38.3 (37.5–39.0) |
| Confusion, No. (%) | 0 | 5 (4) |
| Respiratory rate, median (IQR), breaths/min | 22 (18–28) | 22 (20–28) |
| Pulse rate, median (IQR), beats/min | 96 (83–109) | 98 (84–111) |
| Systolic blood pressure, median (IQR), mm Hg | 131 (110–143) | 132 (117–145) |
| Laboratory findings, median (IQR) | | |
| Initial PCT level, μg/L | 0.83 (0.14–3.18) | 0.71 (0.17–3.06) |
| Leukocyte count, cells/μL | 12.6 (9.7–17.5) | 12.7 (9.3–18.7) |
| PSI points overall, median (IQR) | | |
| PSI class, No. (%) | | |
| I/II | 56 (39) | 54 (38) |
| III | 33 (23) | 27 (19) |
| IV | 47 (33) | 49 (35) |
| V | 7 (5) | 12 (8) |
| Hospitalized within 24 h, No. (%) | 114 (88) | 126 (80) |

*CA*, Clinical assessment; *PSI*, pneumonia Severity Index.

[18%]). The proportion of participants who subsequently were found to have an infection other than community-acquired pneumonia was 6% in the clinical assessment group and 4% in the procalcitonin group.

## Main Results

In the intention-to-treat population, antibiotic duration was not significantly different between the clinical assessment– and procalcitonin-guided groups (median 9 days [IQR range 6 to 13 days; range 0 to 30 days] versus 10 days [IQR 7 to 14 days; range 1 to 29 days], respectively; $P$=.21). Significantly more participants received antibiotic treatment for less than or equal to 5 days in the clinical assessment group compared with the procalcitonin group (32 [22%] versus 19 [13%], respectively; difference 9%; 95% CI 2% to 18%). In the modified intention-to-treat population, antibiotic duration was not significantly different between the clinical assessment group and the procalcitonin group (median 9 days [IQR 6 to 11 days; range 0 to 30 days] versus 10 days [IQR 7 to 15 days; range 1 to 29 days], respectively; $P$=.59). One site enrolled

34.4% of participants compared with 14.8% for the site with the next-highest enrollment; the former site's results were within the range of those for sites with the highest and lowest median antibiotic duration. With a mixed linear model including site as a random variable, no site effect was found for either the intention-to-treat or modified intention-to-treat analyses (Table E1, available online at http://www.annemergmed.com). We did not find a secular trend for antibiotic duration during the different periods of the trial (Figure E1, available online at http://www.annemergmed.com). Kaplan-Meier curves demonstrate the proportion of participants in each group receiving antibiotics during 30 days (Figure 3 and Figure E2, available online at http://www.annemergmed.com). Clinical cure rates at 30 days were 92% in both groups.

Antibiotics were initiated in the ED in 125 participants (88%) in the procalcitonin group after the first procalcitonin measurement. Antibiotics were administered to 7 patients (37%) with a procalcitonin level less than 0.1 μg/L despite the algorithm that indicated that antibiotics were not recommend, and to 4 patients with a procalcitonin level less than 0.1 μg/L who had a prespecified criterion allowing antibiotic administration. Antibiotics were administered to 15 patients (50%) with a procalcitonin level of 0.1 μg/L to less than or equal to 0.25 μg/L despite the algorithm that indicated that antibiotics were strongly not recommended, and to 7 patients with a procalcitonin level of 0.1 μg/L to less than or equal to 0.25 μg/L who had a prespecified criterion allowing antibiotic administration. Four participants with an initial procalcitonin level less than or equal to 0.25 μg/L first received antibiotics when procalcitonin levels increased to greater than 0.25 μg/L on follow-up after 6 hours. Antibiotics were given to 11 of 12 participants (92%) with an initial procalcitonin level of 0.25 μg/L to less than or equal to 0.5 μg/L and to 75 of 75 (100%) with a level greater than 0.5 μg/L. In the ED, the procalcitonin algorithm was followed for 84% of the participants. For participants with an initial procalcitonin level less than or equal to 0.25 μg/L, antibiotic duration was 10.4 days compared with 12.2 days for those with an initial procalcitonin level greater than 0.25 μg/L (difference 1.8 days; 95% CI –0.7 to 4.3 days). Antibiotic duration by procalcitonin tier is provided in Figure E3, available online at http://www.annemergmed.com.

Overall, in the procalcitonin group, the algorithm was followed for 76% of the participants, varying from 56% to 100% between the sites (Table E1, available online at http://www.annemergmed.com). The reasons for procalcitonin algorithm deviation were antibiotic initiation or continuation despite a procalcitonin value less than or equal to 0.25 μg/L in 22 of 142 patients (15%) on day 0 (among them, 17 participants had 2 negative procalcitonin-measurement results [ie, at hour 0 and hours 6 to 24], and 6 had only 1 negative procalcitonin-measurement result during the first 24 hours), in 24 of 98 (25%) on day 3, in 26 of 62 (42%) on day 5, and in 10 of 36 (28%) on day 7. One participant, a woman severely underweight (body mass index 15 kg/m$^2$), for whom antibiotics were withheld according to low procalcitonin levels from the first 2 measurements and who was considered to have viral pneumonia, ultimately presented with a lung abscess that required rehospitalization and antibiotic treatment.

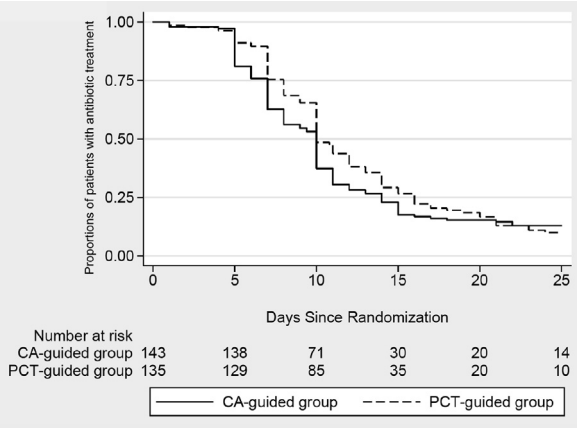


**Figure 3.** Kaplan-Meier curves comparing cumulative antibiotic treatment, including stopped and started treatment through 30 days, among patients with community-acquired pneumonia randomized to clinical assessment– or procalcitonin-guided care in the intention-to-treat population.

In the clinical assessment group, antibiotics were started in all participants initially and were discontinued in 16 (12%) after the first clinical reassessment 6 to 24 hours after randomization. Of 65 patients (45%) who were evaluated for clinical stability criteria on day 5, 45 (69%) reached clinical stability; 59 (91%) had a pulse rate less than or equal to 100 beats/min, 43 (89%) a respiratory rate less than or equal to 24 breaths/min, 62 (95%) a systolic blood pressure greater than or equal to 90 mm Hg, and 56 (86%) an $Sa_{O_2}$ greater than or equal to 90% on room air. Antibiotics were then discontinued on day 5 for 21 of these participants (47%), varying from 25% to 100% between sites (Table E1, available online at http://www.annemergmed.com). All participants for whom antibiotics were stopped on day 5 based on clinical stability criteria ultimately had favorable outcomes through 30 days.

After the initial ED evaluation, 85% of participants in the clinical assessment group were hospitalized and 90% in the

procalcitonin group. A similar small additional proportion of participants in each group was discharged from the ED after a second procalcitonin measurement (if needed) in the procalcitonin group (2%) or reevaluation 6 to 24 hours after randomization in the clinical assessment group (5%). Thus, 114 of 142 participants (80%) in the clinical assessment group compared with 126 of 143 of the procalcitonin group (88%) were hospitalized within 24 hours (difference 8%; 95% CI of the difference –1% to 16%). Overall, median hospital length of stay was 5 days (IQR 3 to 8.25 days; range 0 to 23 days) in the clinical assessment–guided group and 6 days (IQR 4 to 8.25 days; range 0 to 22 days) in the procalcitonin-guided group (difference 1 day; 95% CI –3 to 7 days). After hospitalization, 15 participants (11%) in the clinical assessment–guided group received a new antibiotic prescription with a median duration of 7 days (IQR 3 to 9.5 days; range 1 to 29 days) and 20 participants (15%) in the procalcitonin-guided group received a new antibiotic prescription with a median duration of 10 days (IQR 7 to 10 days; range 1 to 26 days). Serious adverse outcome rates at 30 days were similar between the groups (15% versus 20%, respectively; difference 5%; 95% CI –4% to 14%) (Table 2).

## LIMITATIONS

This study has limitations. Compliance with the procalcitonin algorithm was 76%, which is similar to that in some past procalcitonin trials[3] that demonstrated antibiotic reductions, but lower than that in others.[2] However, these past trials included mixed populations of patients with lower respiratory tract infection, and algorithm adherence has been observed to be inversely related to illness severity and higher in acute bronchitis than in community-acquired pneumonia.[3] Although antibiotic duration in this study was a few days longer than median times for past procalcitonin trials, it was well within reported ranges. Both the procalcitonin algorithm and clinical guidelines are recognized to be imperfect and allow provider judgment. Nonadherence to clinical guidelines also occurred. Although it is possible that greater adherence to either strategy could have led to shorter antibiotic durations, it could have also been associated with worse clinical outcomes. The trial did not have a usual care comparison group because we instead decided to directly compare unique care strategies that had been demonstrated to be associated with safe reduction in antibiotic duration among patients with community-acquired pneumonia and our assessment was that usual care was informed by both strategies. Our finding of similar antibiotic exposure is supported by separate trials demonstrating that both procalcitonin algorithm and clinical assessment–guided care reduced antibiotic duration compared with usual care.[2,3,5] Because this was a pragmatic study, diagnostic testing was at the discretion of the treating physician. We did not collect and report diagnostic testing results, which could affect deviations from recommended care strategies (eg, positive blood culture results). However, we characterized participants, including their severity of illness, and randomization appeared effective at ensuring study group comparability. Our population of ED patients receiving a diagnosis of community-acquired pneumonia was relatively old and had a high hospitalization rate, which, along with the provider familiarity with procalcitonin use and other care patterns, may be different from that in other settings, such as North America. Although we assessed serious adverse outcomes, we did not evaluate the frequency and duration of community-acquired pneumonia symptoms. Some potentially eligible patients were missed during busy periods, which could have introduced selection bias. The study requirement for an ED stay of at least 6 hours for repeated evaluation may have selected patients with more severe disease; however, the proportion of community-acquired pneumonia patients with Pneumonia Severity Index class IV or V was similar to that in past procalcitonin and clinical assessment trials.[2,5] The procalcitonin algorithm requires a second

**Table 2.** Adverse outcomes rates among patients with community-acquired pneumonia in the clinical assessment– and procalcitonin-guided care groups.

| Adverse Outcomes | PCT-Guided Group (n=142), No. (%) | CA-Guided Group (n=143), No. (%) |
|---|---|---|
| All adverse outcomes | 22 (15) | 29 (20)* |
| Death | 2 (1) | 3 (2) |
| ICU admission | 18 (13) | 11 (8) |
| Recurrence/rehospitalization | 19 (13) | 26 (18) |
| Disease-specific complication | 6 (4) | 6 (4) |

*Difference 5%; 95% CI –4% to 14%.

procalcitonin measurement 6 to 24 hours after an initial negative procalcitonin result.[2,3]

## DISCUSSION

Although guideline-based serial clinical assessment did not reduce antibiotic exposure compared with procalcitonin-guided care, this randomized, pragmatic trial demonstrates that, with minimal training, physicians can manage patients with community-acquired pneumonia with clinical assessment and achieve antibiotic duration, efficacy, and safety similar to that with a procalcitonin-testing strategy. To our knowledge, this is the first pragmatic trial to directly compare antibiotic exposure and clinical outcomes among ED patients receiving a diagnosis of community-acquired pneumonia who were randomized to care guided by serial clinical assessments based on IDSA/ATS guidelines or a standard procalcitonin algorithm, in which both groups were managed by physicians with familiarity with and a similar minimal amount of training for each approach. Otherwise, there were no investigation-related interventions that could affect care. Our findings are supported by a recent, large, US, ED-based trial of 1,656 patients with lower respiratory tract infection (community-acquired pneumonia [20%] and other respiratory infections) that did not find a significant difference in antibiotic days between the procalcitonin and guideline-supported clinical care group.[16] However, the study differed from ours in that procalcitonin use was new to clinicians, who were queried by study coordinators about nonadherence to the procalcitonin algorithm.

A meta-analysis of 26 trials involving 6,708 participants with lower respiratory tract infection that compared a procalcitonin algorithm with usual care found significant associated reductions in antibiotic duration, from 8.1 to 5.7 days, and rate of antibiotic-related adverse events, from 22.1% to 16.3%, respectively.[17] Approximately half of these studies were industry sponsored. Serial clinical assessment has not been studied as extensively as procalcitonin use but has also been demonstrated to reduce antibiotic exposure. Uranga et al[5] randomized 312 patients hospitalized with community-acquired pneumonia to have their antibiotics stopped if IDSA/ATS stability criteria were reached at day 5 or to have usual care; median antibiotic duration was significantly reduced, from 10 to 5 days, respectively. IDSA/ATS guidelines recommend antibiotic discontinuation at treatment day 5 if the patient has been afebrile for 48 to 72 hours and has no more than 1 community-acquired pneumonia–associated sign of clinical instability (ie, pulse rate >100 beats/min, respiratory rate >24 breaths/min, systolic blood pressure <90 mm Hg, $Sa_{O_2}$ <90%, or $P_{O_2}$ <60 mm Hg on room air).[7] Among clinical assessment group participants who remained hospitalized, 69% reached clinical stability by day 5, of whom 32% had their antibiotics discontinued. Despite that some procalcitonin-managed participants did not have antibiotics started initially, a significantly greater proportion of participants managed by serial clinical assessments had a total antibiotic duration of less than or equal to 5 days, 22% versus 13%, respectively. However, total antibiotic duration was similar between the groups, largely because of posthospital discharge antibiotic prescription for another 7 to 10 days in both groups. Noting that median hospital stay was approximately 6 days, presuming patients reached IDSA/ATS stability criteria and had low procalcitonin levels before discharge, this practice would appear to be a target for further stewardship efforts. Also, physicians mainly prescribed antibiotic regimens typically used for 7 to 10 days (eg, amoxicillin). In addition to 5-day fluoroquinolone and azithromycin alternatives, studies support effectiveness of 3- and 5-day amoxicillin regimens, which could have also reduced antibiotic duration.[4,8,9]

Previous studies that demonstrated significantly less antibiotic exposure associated with a procalcitonin algorithm compared with usual care had different degrees of active investigator involvement and direction of providers to the best practice of each approach, which may have introduced favorable bias toward the procalcitonin strategy. In the Procalcitonin-Guided Antibiotic Therapy and Hospitalisation in Patients With Lower Respiratory Tract Infections trial, providers who wished to deviate from the procalcitonin algorithm were required to contact the study center.[2] However, this was not required for providers who wished to deviate from clinical antibiotic guidelines. In the Procalcitonin-Guided Antibiotic Therapy in Lower Respiratory Tract Infections in "Real Life" trial, providers were required to justify only procalcitonin algorithm deviations, and study coordinators regularly communicated with providers during the study and, at one site, were responsible for patient enrollment.[3] In contrast, in our trial, physicians were allowed to care for participants without requirements to justify protocol deviations and without study coordinator involvement. Procalcitonin algorithm adherence has been demonstrated to be directly related to familiarity with procalcitonin testing.[3] Therefore, introduction of a new test could justify greater investigator involvement. In our trial, physicians at participating sites were familiar with both approaches and had had availability of procalcitonin testing for at least 3 years. These methods allowed a pragmatic study of each practice under more normal circumstances than past procalcitonin trials.

In our trial, when a hospital physician other than the emergency physician clinically reevaluated the community-

acquired pneumonia diagnosis and antibiotics at 6 to 24 hours, as typically occurs with inpatient admission or primary care follow-up, in 12% of these cases, antibiotics were discontinued. Early clinical reassessment has been demonstrated to safely reduce unnecessary antibiotic use in community-acquired pneumonia.[18] These observations suggest that a significant contributor to antibiotic overuse in community-acquired pneumonia is incorrect diagnosis. Moreover, we found that 80% of participants in the clinical assessment group were hospitalized by 24 hours after ED evaluation versus 88% in the procalcitonin group. Procalcitonin use may increase unneeded care and hospitalizations driven by nonspecific procalcitonin results, which should be studied in future trials.

Guideline-based serial clinical assessment was not superior to procalcitonin-guided care for antibiotic reduction, but appeared to result in comparable outcomes. Because procalcitonin assessments add time and cost to patient care, these findings support strategies to promote better provider understanding and application of clinical guidelines for management of patients with community-acquired pneumonia.

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