Effectiveness and Safety of Procalcitonin-Guided Antibiotic Therapy in Lower Respiratory Tract Infections in “Real Life”

An International, Multicenter Poststudy Survey (ProREAL)

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Background: In controlled studies, procalcitonin (PCT) has safely and effectively reduced antibiotic drug use for lower respiratory tract infections (LRTIs). However, controlled trial data may not reflect real life.

Methods: We performed an observational quality surveillance in 14 centers in Switzerland, France, and the United States. Consecutive adults with LRTI presenting to emergency departments or outpatient offices were enrolled and registered on a website, which provided a previously published PCT algorithm for antibiotic guidance. The primary end point was duration of antibiotic therapy within 30 days.

Results: Of 1759 patients, 86.4% had a final diagnosis of LRTI (community-acquired pneumonia, 53.7%; acute exacerbation of chronic obstructive pulmonary disease, 17.1%; and bronchitis, 14.4%). Algorithm compliance overall was 68.2%, with differences between diagnoses (bronchitis, 81.0%; AECOPD, 70.1%; and community-acquired pneumonia, 63.7%; P < .001), outpatients (86.1%) and inpatients (65.9%) (P < .001), algorithm-experienced (82.5%) and algorithm-naive (60.1%) centers (P < .001), and countries (Switzerland, 75.8%; France, 73.5%; and the United States, 33.5%; P < .001). After multivariate adjustment, antibiotic therapy duration was significantly shorter if the PCT algorithm was followed compared with when it was overruled (5.9 vs 7.4 days; difference, −1.51 days; 95% CI, −2.04 to −0.98; P < .001). No increase was noted in the risk of the combined adverse outcome end point within 30 days of follow-up when the PCT algorithm was followed regarding withholding antibiotics on hospital admission (adjusted odds ratio, 0.83; 95% CI, 0.44 to 1.55; P = .56) and regarding early cessation of antibiotics (adjusted odds ratio, 0.61; 95% CI, 0.36 to 1.04; P = .07).

Conclusions: This study validates previous results from controlled trials in real-life conditions and demonstrates that following a PCT algorithm effectively reduces antibiotic use without increasing the risk of complications. Preexisting differences in antibiotic prescribing affect compliance with antibiotic stewardship efforts.

Trial Registration: isrctn.org Identifier: ISRCTN40854211
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The efficacy, feasibility, and safety of procalcitonin (PCT)-guided antibiotic stewardship in lower respiratory tract infections (LRTIs) and sepsis has been documented in several randomized controlled trials (RCTs). Procalcitonin-guided antibiotic stewardship reduced initial antibiotic prescription rates by 40% to 50% in patients with LRTI presenting to the emergency department7 and by 70% to 80% in ambulatory patients presenting to their general physician13 and reduced total antibiotic exposure in community-acquired pneumonia (CAP) by 40% to 50%. The main effect was by discouraging antibiotic initiation in bronchitis and acute exacerbation of chronic obstructive pulmonary disease and by shortening antibiotic courses in CAP without increased rates of adverse outcomes.1-7

See Invited Commentary at end of article

Most evidence regarding PCT-guided antibiotic stewardship derives from RCTs, with little data outside of controlled study conditions. Results from RCTs may not unconditionally be generalized because of exclusion criteria or
Antibiotic therapy discouraged

0.26-0.5 ng/mL

>0.5 ng/mL

If no antibiotic therapy is initiated:
- Repeat PCT measurement within 6-24 h (also in outpatients if symptoms persist/worsen)
- Differential diagnosis? eg, pulmonary embolism, congestive heart failure, tumor, BOOP, viral, fungal

Antibiotic therapy can be considered for:
1. Admission to the ICU or IMC: (a) respiratory instability (respiratory rate ≥30/min or O₂ saturation <90% with 6 L O₂/min); (b) hemodynamic instability (systolic blood pressure for at least 1 h <90 mm Hg, despite adequate volume replacement or need for vasopressors)
2. Life-threatening comorbidity: (a) imminent death; (b) severe immunosuppression (neutrophils <500/µL for HIV; CD4 <250/µL); (c) chronic infection or other nonrespiratory infection requiring antibiotics (eg, endocarditis, TB)
3. Complications and difficult-to-treat-organisms: LegioneL (antibiotics ≥10 d), abscess, empyema
4. (a) PCT <0.1 ng/mL; CAP PSI V (>130) or CURB-65 ≥3 point; COPD GOLD IV; (b) PCT 0.1-0.25 ng/mL; CAP PSI IV and V (>90); CURB-65 ≥2, COPD GOLD stages III and IV; Sats <90% despite 30 minutes of intensive oxygen therapy

Falsely low PCT: eg, parapneumonic effusion, loculated infection (empyema), early phase of infection, fungal, most severe immunosuppression

If antibiotic therapy is initiated:
- Check PCT on control days 2-3, 4-5, 6-8, and every 2 d after day 8 for guidance of antibiotic therapy
- To stop ongoing antibiotic therapy, use the same cutoff values as above
- For outpatients, duration of antibiotic therapy depends on last PCT value ≥0.25 ng/mL 3 d, ≥0.5 ng/mL 5 d, ≥1 ng/mL 7 d
- For initially very high PCT (eg, ≥5 ng/mL), follow the relative decline of PCT; if patients show clinical improvement
  - Decline ≥80% of peak: stop recommended
  - Decline ≥90% of peak: Stop strongly recommended
- Persistently elevated PCT: suspect complicated course (resistant organism, MOF, abscess…)
- Falsely elevated PCT: eg, severe SIRS and shock, ARDS, trauma, postoperative, tumor (eg, medullary thyroid cancer, SCLC, fungal, malaria

Figure 1. Algorithm for procalcitonin (PCT)-guided antibiotic therapy. This algorithm was available on a password-secured website to all the physicians and study personnel. ARDS indicates acute respiratory distress syndrome; BOOP, bronchiolitis obliterans with organizing pneumonia; CAP, community-acquired pneumonia; COPD GOLD, chronic obstructive pulmonary disease Global Initiative for Chronic Obstructive Lung Disease; CURB-65, confusion, serum urea nitrogen, respiratory rate, blood pressure, and age 65 years or older; HIV, human immunodeficiency virus; ICU, intensive care unit; IMC, intermediate care unit; MOF, multiple organ failure; PSI, Pneumonia Severity Index; SCLC, small-cell lung cancer; SIRS, sepsis inflammatory response syndrome; and TB, tuberculosis.

nonenrollment and are frequently not adequately implemented in daily practice.

In this context, we previously performed a single-center poststudy surveillance to investigate the real-life effectiveness of PCT-guided antibiotic stewardship after completion of the ProHOSP RCT. Median duration of antibiotic treatment was significantly shorter in this survey than in the standard of care ProHOSP control group (6 vs 7 days). Compliance with the prespecified algorithm was excellent (90%), without differences in adverse outcomes. However, physicians had previous experience with the algorithm, which potentially increased adherence.

To assess whether these results also apply to different health care settings, we investigated the effects of PCT guidance in inpatients and outpatients in hospitals and general physician offices in 3 countries with diverse antibiotic-prescribing cultures.

METHODS

PARTICIPANTS AND STUDY DESIGN

This prospective, observational, international, multicenter, quality control survey (ProREAL) monitored initiation and duration of antibiotic therapy, adherence to the published PCT algorithm (Figure 1), and outcome of patients with community-acquired LRTI in centers in Switzerland (n = 10), France (n = 3), and the United States (n = 1) between September 12, 2009, and February 28, 2011. Three of the Swiss hospitals had previously participated in the ProHOSP study and were considered algorithm experienced; all others were considered algorithm naive.

Measurement of PCT levels was recommended in all patients using highly sensitive immunoassays (Kryptor [BRAHMS AG] or miniVidas [bioMérieux]). Both assays provide similar PCT results.

Diagnostic workup and treatment were left to the discretion of the treating physicians. Consecutive patients with LRTI who were seen at an emergency department or a physician’s office were registered by the physician on duty on a password-secured website that displayed the PCT algorithm (Figure 1). In the US center, study nurses screened hospital admission records and enrolled patients within 24 hours. There were no exclusion criteria. Physicians and study personnel were instructed in initial face-to-face 1-hour seminars. Throughout the study, weekly e-mails were sent to local coordinators that contained current enrollment status, encountered problems, and suggested solutions. If necessary, local coordinators or individual physicians were contacted by e-mail or telephone.

DEFINITIONS

Bronchitis, LRTI, acute exacerbation of chronic obstructive pulmonary disease, and CAP were defined according to guidelines. We defined compliance as antibiotic treatment that was initiated and discontinued in accord with the PCT cutoff ranges or, if the PCT levels suggested no antibiotic therapy, with the predefined overruling criteria. Overruling of the algorithm was possible if any of the following criteria were met: admission to the intensive care unit, life-threatening comorbidity, severe immunosuppression, chronic or non-respira-

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tory tract infection requiring antibiotics, complications (ab-
scess and empyema), difficult-to-treat organisms, or high
clinical severity scores (Figure 1). Conversely, noncompli-
ance was defined if antibiotic therapy was initiated or not
discontinued despite low PCT levels in the absence of these pre-
defined overruling criteria, that is, if the algorithm was
overruled based only on clinical judgment.

MONITORING OF PATIENTS

On presentation and during hospitalization, baseline character-
istics, comorbidities, clinical severity scores (CURB-65 [confu-
sion, serum urea nitrogen, respiratory rate, blood pressure, and
age ≥65 years]16 and the Pneumonia Severity Index [PSI]9), course
of PCT levels and antibiotic therapy, length of hospital stay, and
complications were prospectively collected and entered by treat-
ing physicians or study personnel (US site) on the website. Ad-
verse medical outcomes, including all-cause and LRTI-related hos-
pital mortality, intensive care unit admission, disease-related com-
plications (ie, empyema, acute respiratory distress syn-
drome, shock, and requirement for a ventilator or vasopressor sup-
port), and recurrence, were obtained from hospital records and
were documented on the website. Thirty days after enrollment,
telephone interviews were performed by study personnel to iden-
tify adverse outcomes, including death, recurrence, rehospital-
ization, and antibiotic-related adverse effects. Any adverse outcomes and
endpoints included death, recurrence, rehospitalization, or antibi-
otic adverse effects (including Clostridium difficile–associated diar-
rhrea, nausea, vomiting, rash, allergic reactions, abdomi-
nal pain, and candidiasis). For each adverse outcome, 2 mul-
tivariable analyses were performed to assess the safety of ini-
tially withholding antibiotic therapy based on low PCT levels
(<0.25 ng/mL) and to assess the safety of cessation of antibi-
otic use after a decrease in the PCT concentration (≤0.25 ng/mL
or a ≥80% decrease from maximum). Statistical analyses were
performed using commercially available software programs (SAS,
version 9.2 [SAS Institute, Inc] and Epi Info 2002 [Centers for
Disease Control and Prevention]). All the testing was 2-tailed,
and P < .05 was considered statistically significant.

RESULTS

BASELINE CHARACTERISTICS

Of 1810 patients enrolled, 1759 had complete data sets from
the index visit (Swiss: 1361; US: 295; and French: 103). Of 1520
patients (86.4%) with a final diagnosis of LRTI, 1425 (93.8%) had sufficient follow-up information at day
30. Patients with CAP who were overruled correctly ac-
cording to the predefined criteria in the algorithm were
sicker than those treated strictly according to PCT values
(PSI class: 2.8 vs 2.2; CURB-65 score: 1.5 vs 1.2; P < .002),
who, in turn, were sicker than those who were not cor-
rectly overruled, that is, “not compliant” with the algo-
rithm (PSI class: 2.2 vs 1.7; CURB-65 score: 1.2 vs 0.8;
P < .001). Baseline characteristics were similar to those of
patients in the former ProHOSP study7 in the 3 centers
participating in both studies except for a higher severity
of patients with CAP in the ProHOSP group (Table 1).

PRIMARY END POINT

Of 1520 patients with LRTIs, 1208 (79.5%) received at
least 1 antibiotic dose. The overall mean duration of ant-
ibiotic therapy was 6.9 days (inpatients, 7.3 days; out-
patients, 3.5 days; P < .001).

After multivariate adjustment, the predicted mean du-
ration of antibiotic therapy in LRTI was shorter in algorithm-
experienced compared with algorithm-naïve centers (6.0
vs 6.7 days; absolute difference in days [95% CI], −0.71
[−1.25 to −0.17]; P < .01) and if the PCT algorithm was
followed compared with if not (5.9 vs 7.4 days; absolute
difference in days [95% CI], −1.51 [−2.04 to −0.98];
P < .001). Other risk factors for longer antibiotic use du-
ration were CAP (vs bronchitis), renal insufficiency, treatment
in France (vs Switzerland), in-hospital (vs ambulato-
ry) treatment, and higher PSI classes. More detailed results of the multivariable analysis are displayed in Table 2.

Antibiotic therapy was longer when blood cultures
yielded positive results (adjusted regression coefficient,
1.06; 95% CI, 0.13 to 1.99; P = .03) and in patients with
positive sputum culture results (adjusted regression co-
efficient, 2.03; 95% CI, 1.53 to 3.08; P < .001).

Comparing results with those of historic controls, an-
tibiotic therapy duration during ProREAL (6.2 days; 95% CI,
5.8 to 6.7 days) was longer compared with that of the
ProHOSP PCT group (5.0 days; 95% CI, 4.4 to 5.6
days; P = .001) but shorter than in the ProHOSP control

END POINTS

The primary end point was the total duration of antibiotic treat-
ment within 30 days. To calculate antibiotic use dura-
tion, we divided the number of total doses by the number of
daily doses. In case of combination therapy, antibiotic use du-
ration was determined by the duration of the antibiotic that
was given longest; doses of different but simultaneously given
antibiotics were not summed. Secondary end points were du-
ration of antibiotic therapy at the index presentation, adher-
ence to the PCT algorithm, and adverse medical outcomes in
the index hospitalization.

STATISTICAL ANALYSIS

Discrete variables are expressed as number (percentage) and
continuous variables as median (interquartile range), unless
stated otherwise. Frequency comparison was performed using
the χ² test and 2-group comparisons by the t test. All the re-
gression models were adjusted for potential confounders, in-
cluding LRTI diagnosis, country, inpatient or outpatient treat-
ment, sex, PSI score, previous experience with the algorithm,
multilobar involvement in CAP, and different comorbidities (di-
abetes mellitus, malignant disease, cerebrovascular disease, con-
gestive heart failure, renal and hepatic disease, chronic lung
disease, and peripheral arterial disease). A multivariable gen-
eralized linear model was calculated to assess the effect of al-
gorithm compliance and other independent predictors of an-
tibiotic therapy duration. Logistic regression models were
performed to investigate the risk of algorithm compliance, with
adverse outcomes defined as in-hospital complications (in-
cluding acute respiratory distress syndrome, empyema, re-
quirement for vasopressors or mechanical ventilation, admis-
sion to the intensive care unit, and death), any 30-day com-
plication (any of the in-hospital complications, death within
30 days, recurrence of LRTI, or rehospitalization), or antibi-
otic adverse effects (including Clostridium difficile–associated diar-
rhrea, nausea, vomiting, rash, allergic reactions, abdomi-
nal pain, and candidiasis). For each adverse outcome, 2 mul-
tivariable analyses were performed to assess the safety of ini-
tially withholding antibiotic therapy based on low PCT levels
(<0.25 ng/mL) and to assess the safety of cessation of antibi-
otic use after a decrease in the PCT concentration (≤0.25 ng/mL
or a ≥80% decrease from maximum). Statistical analyses were
performed using commercially available software programs (SAS,
version 9.2 [SAS Institute, Inc] and Epi Info 2002 [Centers for
Disease Control and Prevention]). All the testing was 2-tailed,
and P < .05 was considered statistically significant.
group (7.9 days; 95% CI, 7.3 to 8.4 days; \(P < .001\)) for the 3 centers that participated in both studies (Figure 2).

SECONDARY END POINTS

Adherence to the PCT Algorithm

During the entire index presentation (ie, clinic visit, emergency department visit, or entire hospitalization), overall algorithm compliance was 68.2%. Antibiotic therapy followed PCT cutoff ranges on initial presentation in 72.4% of patients and predefined overruling criteria in 8.6% (Figure 1), resulting in overall algorithm compliance of 81.0%. The most important overruling reasons were high clinical severity and respiratory or hemodynamic instability. Overruling due to clinical judgment without prespecified reason occurred in 19.0% of patients.

Algorithm compliance was higher in algorithm-experienced than algorithm-naive centers (\(P < .001\)), higher in outpatients than in inpatients (\(P < .001\)), higher in Switzerland and France than in the US center (\(P < .001\)), and highest in bronchitis and influenza (Figure 3).

**Adverse Medical Outcome**

In-hospital mortality was 5.2%; 10.5% of patients were admitted to the intensive care unit. Overall, the in-hospital complication rate was 19.3%, 30-day mortality was 7.6%, and the recurrence rate was 6.8%. After controlling for comorbidities and severity of disease, withholding antibiotics at initial presentation in patients with low PCT values (\(\leq 0.25\) ng/mL) was not associated with in-hospital complications (adjusted odds ratio [OR], 0.63; 95% CI, 0.30 to 1.31; \(P = .22\)) or any complications within 30 days (adjusted OR, 0.83; 95% CI, 0.44 to 1.55; \(P = .56\)) but with a reduction in the risk of antibiotic-related adverse events (adjusted OR, 0.23; 95% CI, 0.06 to 0.91; \(P = .04\)) in multivariable models (Table 3).

Early cessation of antibiotic therapy according to PCT levels (if the PCT level decreased to \(\leq 0.25\) ng/mL or decreased \(\geq 80\%\) from its maximum) was not associated with in-hospital complications (adjusted OR, 1.10; 95% CI, 0.61 to 1.97; \(P = .76\)) or any complication within 30 days (adjusted OR, 0.61; 95% CI, 0.36 to 1.04; \(P = .07\)) in multivariable logistic models (Table 4).
In this first international multicenter poststudy survey of PCT-guided antibiotic therapy for LRTI, the duration of antibiotic therapy was significantly shortened if the algorithm was followed. The overall mean reduction was approximately 20% (from 7.4 to 5.9 days), which is in the range of that (25%) of a randomized trial using a single PCT value at initial presentation.20 A single PCT measurement in the primary care setting was recently shown to safely reduce the antibiotic treatment rate by 41.6%.13

Multivariable analyses controlling for severity of illness and other confounders confirmed that neither withholding antibiotics on hospital admission in patients with low PCT levels nor discontinuation of antibiotic therapy in patients with appropriate decreases in PCT levels was associated with an increased risk of mortality or of developing other adverse events during hospitalization or over 30 days. The risk of antibiotic-associated adverse events was significantly lower if antibiotics were withheld according to the algorithm. This confirms the safety of PCT-guided antibiotic stewardship outside study conditions and is in accordance with all RCTs and meta-analyses, where there was no difference in outcomes despite strict implementation of the algorithm.21,22

Table 2. Predictors of Antibiotic Therapy Duration From Multivariable Regression

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Regression Coefficient (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compliance</td>
<td>−1.51 (−2.04 to −0.98)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CAP (vs bronchitis)</td>
<td>4.4 (3.3 to 5.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>France (vs Switzerland)</td>
<td>2.22 (1.41 to 3.04)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Outpatient treatment</td>
<td>−2.41 (−3.23 to −1.58)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PSI classes</td>
<td>0.21 (0.07 to 0.35)</td>
<td>.003</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1.21 (0.63 to 1.79)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Previous experience with</td>
<td>−0.71 (−1.25 to −0.17)</td>
<td>.01</td>
</tr>
<tr>
<td>algorithm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multilobar pneumonia</td>
<td>1.18 (0.16 to 2.2)</td>
<td>.02</td>
</tr>
</tbody>
</table>

Abbreviations: CAP, community-acquired pneumonia; CURB-65, confusion, serum urea nitrogen, respiratory rate, blood pressure, and age 65 years or older; PSI, Pneumonia Severity Index.

a Adjusted for compliance, diagnosis, country, treatment site, sex, experience, CURB-65 stage, PSI class, multilobar (in CAP), diabetes mellitus, history of lung cancer, liver insufficiency (transaminases or cholestasis variables >3 times the upper limit of normal or a history of liver cirrhosis or chronic liver disease), history of stroke, congestive heart failure, peripheral vascular disease, and chronic lung disease. The coefficient corresponds to antibiotic therapy days.

b Renal failure was defined as a glomerular filtration rate less than 60 mL/min at initial presentation or a history of chronic renal failure (n = 339; 22.3%).

Table 3. Safety of Initial Withholding of Antibiotic Therapy in Patients With Low PCT Values

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital complications</td>
<td>0.627 (0.299 to 1.314)</td>
<td>.22</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>1.048 (0.243 to 4.513)</td>
<td>.95</td>
</tr>
<tr>
<td>ICU admission</td>
<td>1.248 (0.368 to 4.232)</td>
<td>.72</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>1.701 (0.372 to 7.786)</td>
<td>.49</td>
</tr>
<tr>
<td>Empyema</td>
<td>0.812 (0.040 to 16.457)</td>
<td>.89</td>
</tr>
<tr>
<td>30-day Mortality</td>
<td>1.044 (0.330 to 3.301)</td>
<td>.94</td>
</tr>
<tr>
<td>Recurrences</td>
<td>0.655 (0.246 to 1.748)</td>
<td>.40</td>
</tr>
<tr>
<td>Rehospitalization</td>
<td>0.045 (&lt;0.001 to 0.999)</td>
<td>.98</td>
</tr>
<tr>
<td>Any 30-day complicationc</td>
<td>0.830 (0.444 to 1.550)</td>
<td>.56</td>
</tr>
<tr>
<td>Antibiotic adverse effectsd</td>
<td>0.232 (0.059 to 0.908)</td>
<td>.04</td>
</tr>
</tbody>
</table>

Abbreviations: CURB-65, confusion, serum urea nitrogen, respiratory rate, blood pressure, and age 65 years or older; ICU, intensive care unit; OR, odds ratio; PCT, procalcitonin.

a Odds ratio for adverse events comparing algorithm compliance with algorithm noncompliance on hospital admission in patients with an admission PCT level of 0.25 ng/mL or less adjusted for CURB-65 stage, sex, algorithm experience, PCT value on hospital admission, treatment site, country, diabetes mellitus, and history of lung cancer, liver insufficiency (transaminases or cholestasis variables >3 times the upper limit of normal or a history of liver cirrhosis or chronic liver disease), renal insufficiency (glomerular filtration rate <60 mL/min at initial presentation or a history of chronic renal failure), congestive heart failure, peripheral vascular disease, and chronic lung disease. Only patients without predefined overruling criteria on hospital admission were considered for this analysis.

b In-hospital complications included acute respiratory distress syndrome, empyema, requirement for vasopressors or mechanical ventilation, admission to the ICU, and death.

c Any 30-day complication was defined as any of the in-hospital complications, death within 30 days, recurrence of LRTI, or rehospitalization.

d Antibiotic adverse effects included Clostridium difficile–associated diarrhea, nausea, vomiting, rash, allergic reactions, abdominal pain, and candidiasis.
The finding that CAP and in-hospital treatment were correlated with increasing severity of illness, when physicians might rely on self-perceived levels of experience. This might explain the observation of decreasing compliance from bronchitis to acute exacerbation of chronic obstructive pulmonary disease and CAP. Algorithm compliance was higher in experienced than in naive centers and in Europe than in the United States, probably reflecting a learning curve of the laboratory and the physicians. Therefore, ongoing reinforcement is necessary to increase compliance and the rational use of antibiotics, minimizing antibiotic selection pressure. This also demonstrates the importance of preexisting regional and cultural differences in antibiotic-prescribing habits between Europe and North America, which influence the success of such interventions. Antibiotic-prescribing patterns reflect multilayer decision making, including sociocultural, health care system, legal, and health belief factors. It, thus, is not surprising that compliance was highest in Switzerland, with the lowest antibiotic consumption and resistance rate.

The strengths of this study are its size as the largest single study of PCT-guided antibiotic therapy and its international web-based design. The inclusion of consecutive patients of all different levels of care and experience without exclusion criteria and the relatively small implementation efforts support its generalizability. Although the study design did not permit a direct control group, comparison with historic controls from an RCT performed at the same locations supports the effectiveness of the algorithm.

A potential limitation is the discrepancy between the number of participating centers in Switzerland (n = 10), France (n = 3), and the United States (n = 1). It is, therefore, difficult to make a general conclusion for all countries.

Table 4. Safety of Early Discontinuation of Antibiotic Therapy According to PCT Value After a Decrease in the PCT Value

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital complications</td>
<td>1.095 (0.609 to 1.969)</td>
<td>.76</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>1.498 (0.360 to 6.226)</td>
<td>.58</td>
</tr>
<tr>
<td>ICU admission</td>
<td>0.002 (0.001 to 0.999)</td>
<td>.91</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>0.192 (0.001 to 0.999)</td>
<td>.99</td>
</tr>
<tr>
<td>Empyema</td>
<td>&lt;0.001 (0.001 to 0.999)</td>
<td>.91</td>
</tr>
<tr>
<td>30-d mortality</td>
<td>0.771 (0.328 to 1.814)</td>
<td>.55</td>
</tr>
<tr>
<td>Recurrence</td>
<td>0.939 (0.483 to 1.824)</td>
<td>.85</td>
</tr>
<tr>
<td>Rehospitalization</td>
<td>0.758 (0.097 to 5.951)</td>
<td>.79</td>
</tr>
<tr>
<td>Any 30-d complication</td>
<td>0.607 (0.355 to 1.038)</td>
<td>.07</td>
</tr>
<tr>
<td>Antibiotic adverse effects</td>
<td>1.113 (0.560 to 2.212)</td>
<td>.76</td>
</tr>
</tbody>
</table>

Abbreviations: CURB-65, confusion, serum urea nitrogen, respiratory rate, blood pressure, and age ≥65 years or older; ICU, intensive care unit; OR, odds ratio; PCT, procalcitonin.

# Odds ratio for adverse events comparing discontinuation of antibiotic therapy according to PCT levels (≥0.25 ng/mL or a >80% decrease from maximum) vs algorithm noncompliance adjusted for CURB-65 stage, sex, algorithm experience, PCT value on hospital admission, treatment site, country, diabetes mellitus, and history of lung cancer, liver insufficiency (transaminases or cholestasis variables >3 times the upper limit of normal or a history of liver cirrhosis or chronic liver disease), renal insufficiency (glomerular filtration rate <60 mL/min at initial presentation or a history of chronic renal failure), congestive heart failure, peripheral vascular disease, and chronic lung disease. Only patients without predefined overruling criteria during follow-up were considered for this analysis.

# In-hospital complications included acute respiratory distress syndrome, empyema, requirement for vasopressors or mechanical ventilation, admission to the ICU, and death.

# Any 30-day complication was defined as any of the in-hospital complications, death within 30 days, recurrence of LRTI, or rehospitalization.

# Antibiotic adverse effects included Clostridium difficile-associated diarrhea, nausea, vomiting, rash, allergic reactions, abdominal pain, and candidiasis.

In a single-center pilot survey, we had detected similar results for the Kantonsspital Aarau, Aarau, Switzerland, with extensive previous PCT algorithm experience, where we reported 7 and 6 days of antibiotic therapy in patients with CAP and LRTIs, respectively, who were treated according to the PCT algorithm. In the single-center and the present multicenter surveys, we recruited patients with severe comorbidities and immunodeficiency who were formally excluded from the ProHOSP study. This inclusion at least partially explains why, in the present study, the mean (unadjusted) antibiotic therapy duration in the 3 algorithm-experienced centers was 1.2 days longer than that in the ProHOSP intervention group but 1.7 days shorter than that in the ProHOSP control group. In experienced centers, antibiotic treatment duration was similar to that in the previous single-center pilot study and significantly shorter than that in algorithm-naive centers. These results indicate that PCT safely allows individualized and shortened treatment duration also in real-life conditions in different health care settings.

The finding that CAP and in-hospital treatment were predictors of longer antibiotic treatment is plausible since those patients have a higher likelihood of a bacterial etiology than do patients with bronchitis, who more frequently undergo outpatient treatment. Likewise, its association with increasing severity of illness might explain why renal insufficiency was an independent predictor of longer antibiotic treatment. Renal insufficiency does not prolong the half-life of PCT. Patients with an identified cause had a longer duration of antibiotic therapy than if no causative agent was identified. The PCT levels have been associated with the presence of bacteremia and bacterial load supporting our observation and the validity of our algorithm.

The second important focus of this survey was to evaluate algorithm adherence outside of stringent study conditions in countries with considerably different antibiotic-prescribing cultures and PCT experience. The observed level of compliance is remarkable, especially considering that initial introductory seminars were short, that only 3 of the 14 participating sites were algorithm-experienced, and that 1 of the 3 countries had limited experience with PCT (the United States). In the previous survey, we had achieved overall algorithm compliance of 90% outside of study conditions in a hospital well used to the algorithm. Aujesky et al found that 37.4% of patients with low PSI scores were hospitalized mainly for comorbid illnesses, reflecting the difficulty of implementing guidelines into daily clinical practice and limited confidence in clinical scores. Although the PSI algorithm is more complex than the PCT algorithm, resulting in a lower likelihood of being implemented, we assessed PCT compliance not only at presentation but throughout the entire index presentation, that is, hospitalization in inpatients.

Implementation of algorithms is more challenging with increasing severity of illness, when physicians might rely on self-perceived levels of experience. This might explain the observation of decreasing compliance from bronchitis to acute exacerbation of chronic obstructive pulmonary disease and CAP. Algorithm compliance was higher in experienced than in naive centers and in Europe than in the United States, probably reflecting a learning curve of the laboratory and the physicians. Therefore, ongoing reinforcement is necessary to increase compliance and the rational use of antibiotics, minimizing antibiotic selection pressure. This also demonstrates the importance of preexisting regional and cultural differences in antibiotic-prescribing habits between Europe and North America, which influence the success of such interventions. Antibiotic-prescribing patterns reflect multilayer decision making, including sociocultural, health care system, legal, and health belief factors. It, thus, is not surprising that compliance was highest in Switzerland, with the lowest antibiotic consumption and resistance rate.

The strengths of this study are its size as the largest single study of PCT-guided antibiotic therapy and its international web-based design. The inclusion of consecutive patients of all different levels of care and experience without exclusion criteria and the relatively small implementation efforts support its generalizability. Although the study design did not permit a direct control group, comparison with historic controls from an RCT performed at the same locations supports the effectiveness of the algorithm.

A potential limitation is the discrepancy between the number of participating centers in Switzerland (n = 10), France (n = 3), and the United States (n = 1). It is, therefore, difficult to make a general conclusion for all countries.
tries based on the findings of this survey. Improved PCT assay availability, preferably as a bedside point-of-care test, and reduced assay costs are prerequisites for widespread implementation.

In conclusion, this real-life effectiveness study complements the excellent efficacy and safety record of PCT-guided antibiotic stewardship from many previous RCTs and extends those beyond the stringent study setting. We demonstrate that good compliance with the PCT algorithm is possible in real-life conditions but has to be reinforced to achieve optimal benefit. Regional and cultural differences in preexisting antibiotic-prescribing habits pose a challenge to its successful implementation that requires particular attention.

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REFERENCES

Serum Procalcitonin Levels

It Is All About Confidence

Albrich and colleagues successfully orchestrated an observational, multinational, multicenter, prospective study of the influence of serum procalcitonin (PCT) levels on the care of patients with lower respiratory tract infections (LRTIs). Specifically, does access to PCT levels plus the use of an interpretative advice algorithm influence the duration of antibiotic therapy? The comparison was between patients whose physicians were compliant with the algorithm vs patients whose physicians were noncompliant. Noncompliance was defined as failure to follow the algorithm by either initiation of antibiotic therapy or failure to discontinue therapy despite low PCT levels in the absence of predefined criteria that allowed the algorithm to be overruled. In short, the algorithm advice was overruled and managed based on clinical judgment.

The primary end point was duration of antibiotic therapy. Of 1208 patients who received at least 1 dose of an antibiotic, the mean duration of therapy was 5.9 days when the algorithm was followed and 7.4 days (P < .001) when physicians did not comply with the algorithm. The shorter duration stood the test of various scenarios with community-acquired pneumonia. N Engl J Med. 1997;336(4):243-250.

Variable analyses looking for confounders; of course, some important confounder may have been missed.

Of interest, algorithm compliance was substantially better in those centers that had participated in earlier PCT studies. I suggest that algorithm compliance, or lack thereof, is a direct reflection of the confidence level of physicians in the interpretation of the meaning of serum PCT levels.

The study by Albrich et al is the latest of several studies of patients with LRTIs and PCT treatment guidance. In most studies, compliance with the PCT algorithm shortened the duration of antibiotic therapy. Nonetheless, a healthy skepticism persists. Critics worry about the specificity of an increase in PCT levels for bacterial as opposed to viral infection. Physicians wonder what happens to serum PCT levels if there is dual infection, eg, pneumonia due to Streptococcus pneumoniae concomitant with influenza tracheobronchitis. Why does the serum PCT level increase in patients after aortocoronary bypass surgery or in patients with cardiogenic shock? In short, the serum PCT level help the clinician beyond the usual markers of activation of an innate im-