

# 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-naïve (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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**T**HE 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).<sup>1-12</sup> Procalcitonin-guided antibiotic stewardship reduced initial antibiotic prescription rates by 40% to 50% in patients with LRTI presenting to the emergency department<sup>5</sup> and by 70% to 80% in ambulatory patients presenting to their general physician<sup>13</sup> and reduced total antibiotic exposure in community-acquired pneumonia (CAP) by 40% to

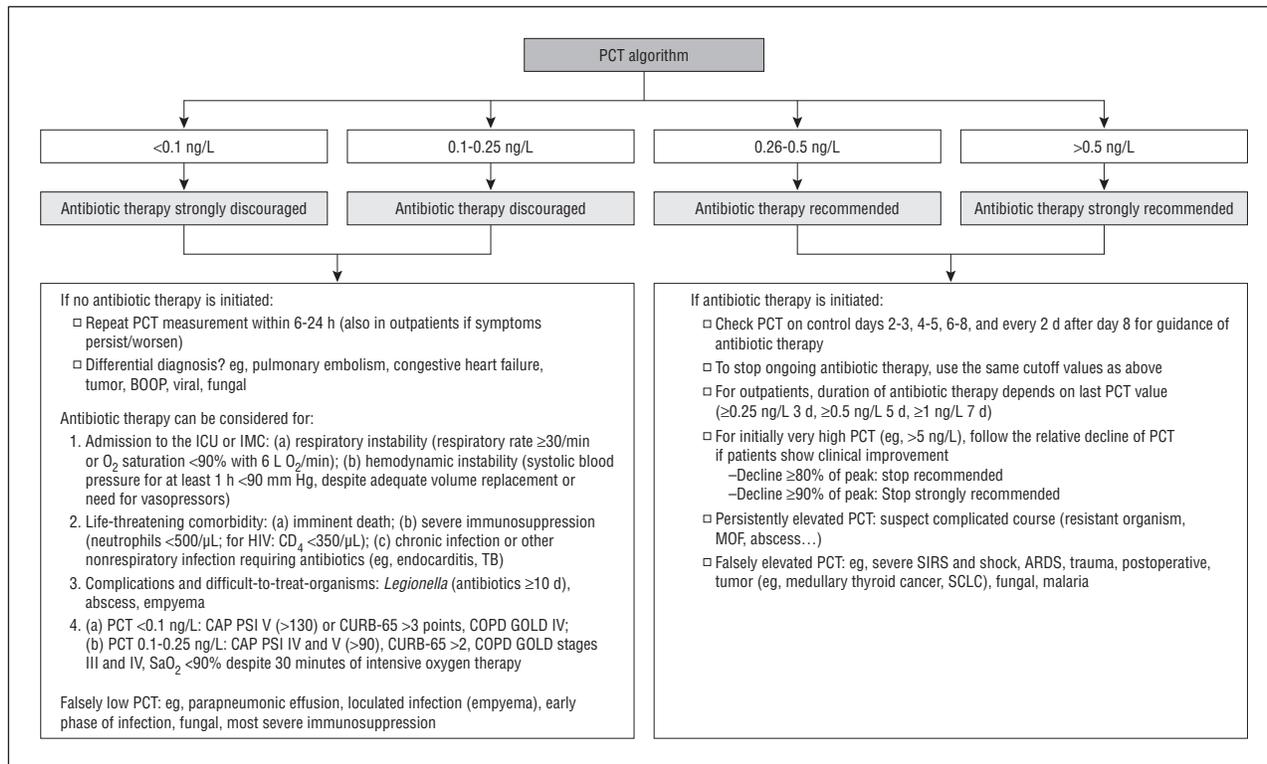
50%.<sup>4</sup> The main effect was by discouraging antibiotic initiation in bronchitis and acute exacerbation of chronic obstructive pulmonary disease and by shortening antibiotic courses in CAP without increased rates of adverse outcomes.<sup>1-7</sup>

### 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

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**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<sup>14</sup> and are frequently not adequately implemented in daily practice.

In this context, we previously performed a single-center poststudy surveillance<sup>15</sup> to investigate the real-life effectiveness of PCT-guided antibiotic stewardship after completion of the ProHOSP RCT.<sup>7</sup> Median duration of antibiotic treatment was significantly shorter in this survey than in the standard of care ProHOSP control group (6 vs 7 days).<sup>15</sup> 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 on inpatients and outpatients in hospitals and general physician offices in 3 countries with diverse antibiotic-prescribing cultures.

ously participated in the ProHOSP study<sup>2,7</sup> 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.<sup>16,17</sup>

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).<sup>3,7</sup> 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.

## 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 previ-

### DEFINITIONS

Bronchitis, LRTI, acute exacerbation of chronic obstructive pulmonary disease, and CAP were defined according to guidelines.<sup>7</sup> 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-

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

## MONITORING OF PATIENTS

On presentation and during hospitalization, baseline characteristics, comorbidities, clinical severity scores (CURB-65 [confusion, serum urea nitrogen, respiratory rate, blood pressure, and age  $\geq 65$  years]<sup>18</sup> and the Pneumonia Severity Index [PSI]<sup>19</sup>), course of PCT levels and antibiotic therapy, length of hospital stay, and complications were prospectively collected and entered by treating physicians or study personnel (US site) on the website. Adverse medical outcomes, including all-cause and LRTI-related hospital mortality, intensive care unit admission, disease-related complications (ie, empyema, acute respiratory distress syndrome, shock, and requirement for a ventilator or vasopressor support), 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 identify adverse outcomes, including death, recurrence, rehospitalization, requirement for additional or repeated antibiotic therapy, and antibiotic-related adverse effects. Any adverse outcomes and repeated antibiotic courses were confirmed with hospital medical records or with general physicians. Informed consent was obtained from all the patients at the US site but was waived by Swiss and French ethics committees.

## END POINTS

The primary end point was the total duration of antibiotic treatment within 30 days. To calculate antibiotic use duration, we divided the number of total doses by the number of daily doses. In case of combination therapy, antibiotic use duration 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 duration of antibiotic therapy at the index presentation, adherence 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  $\chi^2$  test and 2-group comparisons by the *t* test. All the regression models were adjusted for potential confounders, including LRTI diagnosis, country, inpatient or outpatient treatment, sex, PSI score, previous experience with the algorithm, multilobar involvement in CAP, and different comorbidities (diabetes mellitus, malignant disease, cerebrovascular disease, congestive heart failure, renal and hepatic disease, chronic lung disease, and peripheral arterial disease). A multivariable generalized linear model was calculated to assess the effect of algorithm compliance and other independent predictors of antibiotic therapy duration. Logistic regression models were performed to investigate the risk of algorithm compliance, with adverse outcomes defined as in-hospital complications (including acute respiratory distress syndrome, empyema, requirement for vasopressors or mechanical ventilation, admission to the intensive care unit, and death), any 30-day complication (any of the in-hospital complications, death within

30 days, recurrence of LRTI, or rehospitalization), or antibiotic adverse effects (including *Clostridium difficile*-associated diarrhea, nausea, vomiting, rash, allergic reactions, abdominal pain, and candidiasis). For each adverse outcome, 2 multivariable analyses were performed to assess the safety of initially withholding antibiotic therapy based on low PCT levels ( $\leq 0.25$  ng/L) and to assess the safety of cessation of antibiotic use after a decrease in the PCT concentration ( $\leq 0.25$  ng/L or a  $\geq 80\%$  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 according 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 correctly overruled, that is, "not compliant" with the algorithm (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 study<sup>7</sup> 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 antibiotic therapy was 6.9 days (inpatients, 7.3 days; outpatients, 3.5 days;  $P < .001$ ).

After multivariate adjustment, the predicted mean duration 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 duration were CAP (vs bronchitis), renal insufficiency, treatment in France (vs Switzerland), in-hospital (vs ambulatory) 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 coefficient, 2.03; 95% CI, 1.53 to 3.08;  $P < .001$ ).

Comparing results with those of historic controls, antibiotic 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

**Table 1. Baseline Characteristics (Comparison With the ProHOSP Trial)**

Characteristic	ProREAL (All Patients)	Strictly PCT Guided	Correctly Overruled	Not Correctly Overruled	ProREAL (Experienced Centers)	ProHOSP (Centers Also Participating in ProREAL)
Patients enrolled, No.	1810	NA	NA	NA	604	735
Sufficient information at initial visit, No.	1759	NA	NA	NA	604	735
LRTI final diagnosis, No./total No.	1520	805/1520	232/1520	483/1520	549	697
LRTI with sufficient information at 30-d follow-up, No.	1425	744	223	458	549	697
Demographics						
Female sex, No./total No. (%)	781/1759 (44.4)	353/805 (43.9)	90/232 (38.8)	240/483 (49.7)	251/604 (41.6)	304/735 (41.4)
Age, median (IQR), y	71.0 (57.6-81.2)	70 (55.0-80.8)	74.3 (62.0-81.2)	72.4 (58.7-81.3)	70 (58.0-80.0)	71.0 (58.0-81.0)
Final diagnosis, No. (%)						
CAP	945 (53.7)	439 (54.5)	163 (70.3)	343 (71.0)	359 (59.4)	428 (58.2)
Exacerbation of COPD	301 (17.1)	163 (20.2)	50 (21.6)	88 (18.2)	90 (14.9)	147 (20.0)
Acute bronchitis	253 (14.4)	189 (23.5)	16 (6.9)	48 (9.9)	88 (14.6)	122 (16.6)
Influenza	21 (1.2)	14 (1.7)	3 (1.3)	4 (0.8)	12 (2.0)	NA
Other diagnosis (non-LRTI)	242 (13.7)	NA	NA	NA	55 (9.1)	38 (5.2)
Coexisting illnesses, No. (%)						
Preexisting lung disease	675 (38.4)	301 (37.4)	117 (50.4)	174 (36.0)	238 (39.5)	287 (39.0)
Cancer	189 (10.7)	77 (9.6)	33 (14.2)	53 (11.0)	88 (14.6)	91 (12.4)
Coronary heart disease	338 (19.2)	152 (18.9)	52 (22.4)	93 (19.3)	126 (20.9)	137 (18.6)
Congestive heart failure	225 (12.8)	86 (10.7)	41 (17.7)	53 (11)	67 (11.1)	100 (13.6)
Cerebrovascular disease	109 (6.2)	50 (6.2)	17 (7.3)	27 (5.6)	43 (7.1)	51 (6.9)
Peripheral artery disease	104 (5.9)	52 (6.5)	21 (9.1)	16 (3.3)	48 (8.0)	36 (4.9)
Diabetes mellitus	304 (17.3)	143 (17.8)	39 (16.8)	77 (15.9)	114 (18.9)	124 (16.9)
Renal insufficiency	394 (22.4)	184 (22.9)	67 (28.9)	88 (18.2)	172 (28.5)	175 (23.8)
Liver insufficiency	44 (2.5)	20 (2.5)	5 (2.2)	7 (1.5)	19 (3.2)	8 (1.1)
Risk assessment						
Any comorbidity, No. (%)	1254 (71.3)	560 (69.6)	190 (81.9)	337 (69.8)	460 (76.3)	524 (71.3)
PSI class (in CAP), mean/median	2.1/2	2.2/2	2.8/4	1.7/0	2.6/2	3.2/3
CURB-65 points (in CAP), mean/median	1.1/0	1.2/1	1.5/2	0.8/0	1.3/1	1.4/1
Inpatient status (in LRTI), No. (%)	1347 (88.6)	661 (82.1)	227 (97.8)	459 (95)	508 (92.5)	68 (90.7)

Abbreviations: CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; CURB-65, confusion, serum urea nitrogen, respiratory rate, blood pressure, and age 65 years or older; IQR, interquartile range; LRTI, lower respiratory tract infection; NA, not applicable; PCT, procalcitonin; PSI, Pneumonia Severity Index.

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/L) was not associated with in-hospital complications (adjusted odds ratio [OR], 0.63; 95% CI, 0.30 to 1.31;  $P = .22$ ) or with 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/L or decreased  $\geq 80\%$  from its maximum) was not associated with risk of 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**).

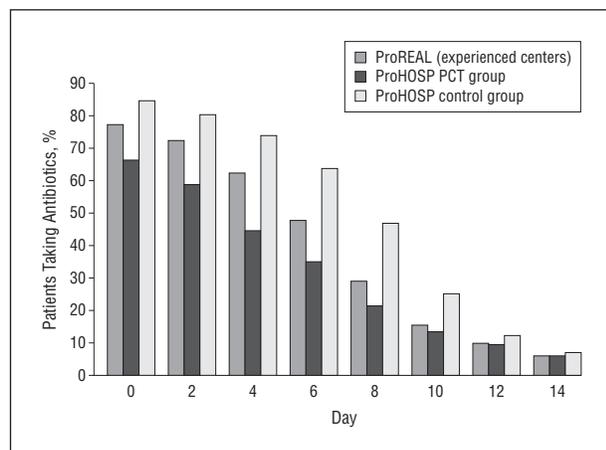
**Table 2. Predictors of Antibiotic Therapy Duration From Multivariable Regression**

Predictor	Regression Coefficient (95% CI) <sup>a</sup>	P Value
Compliance	-1.51 (-2.04 to -0.98)	<.001
CAP (vs bronchitis)	4.4 (3.7 to 5.1)	<.001
France (vs Switzerland)	2.22 (1.41 to 3.04)	<.001
Outpatient treatment	-2.41 (-3.23 to -1.58)	<.001
PSI classes	0.21 (0.07 to 0.35)	.003
Renal failure <sup>b</sup>	1.21 (0.63 to 1.79)	<.001
Previous experience with algorithm	-0.71 (-1.25 to -0.17)	.01
Multilobar pneumonia	1.18 (0.16 to 2.2)	.02

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.

<sup>a</sup>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.

<sup>b</sup>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%).

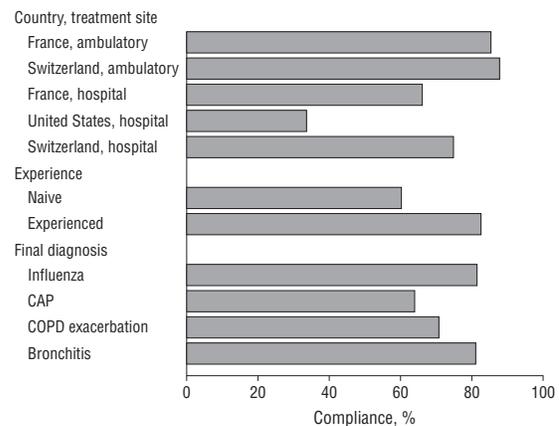


**Figure 2.** Antibiotic exposure compared between real-life experience (ProREAL) and a randomized controlled trial (ProHOSP procalcitonin [PCT] group and control group) (for centers participating in both).

## COMMENT

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 mean overall 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.<sup>20</sup> A single PCT measurement in the primary care setting was recently shown to safely reduce the antibiotic treatment rate by 41.6%.<sup>13</sup>

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



**Figure 3.** Algorithm compliance. CAP indicates community-acquired pneumonia; COPD, chronic obstructive pulmonary disease.

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

Variable	Adjusted OR (95% CI) <sup>a</sup>	P Value
In-hospital complications <sup>b</sup>	0.627 (0.299 to 1.314)	.22
In-hospital mortality	1.048 (0.243 to 4.513)	.95
ICU admission	1.248 (0.368 to 4.232)	.72
Mechanical ventilation	1.701 (0.372 to 7.786)	.49
Empyema	0.812 (0.040 to 16.457)	.89
30-d Mortality	1.044 (0.330 to 3.301)	.94
Recurrences	0.655 (0.246 to 1.748)	.40
Rehospitalization	0.045 (<0.001 to >0.999)	.98
Any 30-d complication <sup>c</sup>	0.830 (0.444 to 1.550)	.56
Antibiotic adverse effects <sup>d</sup>	0.232 (0.059 to 0.908)	.04

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.

<sup>a</sup>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/L 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.

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

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

<sup>d</sup>Antibiotic adverse effects included *Clostridium difficile*-associated diarrhea, nausea, vomiting, rash, allergic reactions, abdominal pain, and candidiasis.

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.<sup>21,22</sup>

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

Variable	Adjusted OR (95% CI) <sup>a</sup>	P Value
In-hospital complications <sup>b</sup>	1.095 (0.609 to 1.969)	.76
In-hospital mortality	1.498 (0.360 to 6.226)	.58
ICU admission	0.002 (<0.001 to >0.999)	.81
Mechanical ventilation	0.192 (<0.001 to >0.999)	.99
Empyema	<0.001 (<0.001 to >0.999)	.91
30-d mortality	0.771 (0.328 to 1.814)	.55
Recurrence	0.939 (0.483 to 1.824)	.85
Rehospitalization	0.758 (0.097 to 5.951)	.79
Any 30-d complication <sup>c</sup>	0.607 (0.355 to 1.038)	.07
Antibiotic adverse effects <sup>d</sup>	1.113 (0.560 to 2.212)	.76

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.

<sup>a</sup>Odds ratio for adverse events comparing discontinuation of antibiotic therapy according to PCT levels ( $\leq 0.25$  ng/L or a  $\geq 80\%$  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.

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

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

<sup>d</sup>Antibiotic adverse effects included *Clostridium difficile*-associated diarrhea, nausea, vomiting, rash, allergic reactions, abdominal pain, and candidiasis.

In a single-center pilot survey,<sup>15</sup> 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 formerly 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.<sup>23</sup> 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<sup>24-26</sup> and bacterial load,<sup>26</sup> 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,<sup>15</sup> we had achieved overall algorithm compliance of 90% outside of study conditions in a hospital well used to the algorithm. Aujesky et al<sup>27</sup> 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,<sup>9</sup> 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,<sup>28,29</sup> 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.<sup>30,31</sup>

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 coun-

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 wide-spread 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

1. Stolz D, Christ-Crain M, Bingisser R, et al. Antibiotic treatment of exacerbations of COPD: a randomized, controlled trial comparing procalcitonin-guidance with standard therapy. *Chest*. 2007;131(1):9-19.
2. Schuetz P, Christ-Crain M, Wolbers M, et al; ProHOSP Study Group. Procalcitonin-guided antibiotic therapy and hospitalization in patients with lower respiratory tract infections: a prospective, multicenter, randomized controlled trial. *BMC Health Serv Res*. 2007;7:102.
3. Christ-Crain M, Stolz D, Bingisser R, et al. Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. *Am J Respir Crit Care Med*. 2006;174(1):84-93.
4. Christ-Crain M, Jaccard-Stolz D, Bingisser R, et al. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. *Lancet*. 2004;363(9409):600-607.
5. Briel M, Schuetz P, Mueller B, et al. Procalcitonin-guided antibiotic use vs a standard approach for acute respiratory tract infections in primary care. *Arch Intern Med*. 2008;168(18):2000-2008.
6. Nobre V, Harbarth S, Graf JD, Rohner P, Pugin J. Use of procalcitonin to shorten antibiotic treatment duration in septic patients: a randomized trial. *Am J Respir Crit Care Med*. 2008;177(5):498-505.
7. Schuetz P, Christ-Crain M, Thomann R, et al; ProHOSP Study Group. Effect of

- procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. *JAMA*. 2009; 302(10):1059-1066.
8. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med*. 1987;106(2):196-204.
  9. Bouadma L, Luyt CE, Tubach F, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *Lancet*. 2010;375(9713):463-474.
  10. Stolz D, Smyrniotis N, Eggimann P, et al. Procalcitonin for reduced antibiotic exposure in ventilator-associated pneumonia: a randomised study. *Eur Respir J*. 2009;34(6):1364-1375.
  11. Hochreiter M, Köhler T, Schweiger AM, et al. Procalcitonin to guide duration of antibiotic therapy in intensive care patients: a randomized prospective controlled trial. *Crit Care*. 2009;13(3):R83.
  12. Schuetz P, Christ-Crain M, Müller B. Procalcitonin and other biomarkers to improve assessment and antibiotic stewardship in infections: hope for hype? *Swiss Med Wkly*. 2009;139(23-24):318-326.
  13. Burkhardt O, Ewig S, Haagen U, et al. Procalcitonin guidance and reduction of antibiotic use in acute respiratory tract infection. *Eur Respir J*. 2010;36(3):601-607.
  14. Juurlink DN, Mamdani MM, Lee DS, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med*. 2004;351(6):543-551.
  15. Schuetz P, Batschwaroff M, Dusemund F, et al. Effectiveness of a procalcitonin algorithm to guide antibiotic therapy in respiratory tract infections outside of study conditions: a post-study survey. *Eur J Clin Microbiol Infect Dis*. 2010;29(3):269-277.
  16. Schuetz P, Christ-Crain M, Huber AR, Müller B. Long-term stability of procalcitonin in frozen samples and comparison of Kryptor and VIDAS automated immunoassays. *Clin Biochem*. 2010;43(3):341-344.
  17. Hausfater P, Brochet C, Freund Y, Charles V, Bernard M. Procalcitonin measurement in routine emergency medicine practice: comparison between two immunoassays. *Clin Chem Lab Med*. 2010;48(4):501-504.
  18. Lim WS, van der Eerden MM, Laing R, et al. Defining community-acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax*. 2003;58(5):377-382.
  19. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med*. 1997;336(4):243-250.
  20. Kristoffersen KB, Sogaard OS, Wejse C, et al. Antibiotic treatment interruption of suspected lower respiratory tract infections based on a single procalcitonin measurement at hospital admission: a randomized trial. *Clin Microbiol Infect*. 2009;15(5):481-487.
  21. Schuetz P, Albrich W, Christ-Crain M, Chastet J, Mueller B. Procalcitonin for guidance of antibiotic therapy. *Expert Rev Anti Infect Ther*. 2010;8(5):575-587.
  22. Schuetz P, Chiappa V, Briel M, Greenwald JL. Procalcitonin algorithms for antibiotic therapy decisions: a systematic review of randomized controlled trials and recommendations for clinical algorithms. *Arch Intern Med*. 2011;171(15):1322-1331.
  23. Meisner M, Schmidt J, Hüttner H, Tschaikowsky K. The natural elimination rate of procalcitonin in patients with normal and impaired renal function. *Intensive Care Med*. 2000;26(suppl 2):S212-S216.
  24. Müller F, Christ-Crain M, Bregenzer T, et al; ProHOSP Study Group. Procalcitonin levels predict bacteremia in patients with community-acquired pneumonia: a prospective cohort trial. *Chest*. 2010;138(1):121-129.
  25. Riedel S, Melendez JH, An AT, Rosenbaum JE, Zenilman JM. Procalcitonin as a marker for the detection of bacteremia and sepsis in the emergency department. *Am J Clin Pathol*. 2011;135(2):182-189.
  26. van Nieuwkoop C, Bonten TN, van't Wout JW, et al. Procalcitonin reflects bacteremia and bacterial load in urosepsis syndrome: a prospective observational study. *Crit Care*. 2010;14(6):R206.
  27. Aujesky D, McCausland JB, Whittle J, Obrosky DS, Yealy DM, Fine MJ. Reasons why emergency department providers do not rely on the Pneumonia Severity Index to determine the initial site of treatment for patients with pneumonia. *Clin Infect Dis*. 2009;49(10):e100-e108.
  28. Harbarth S, Albrich W, Goldmann DA, Huebner J. Control of multiply-resistant cocci: do international comparisons help? *Lancet Infect Dis*. 2001;1(4):251-261.
  29. Harbarth S, Albrich W, Brun-Buisson C. Outpatient antibiotic use and prevalence of antibiotic-resistant pneumococci in France and Germany: a sociocultural perspective. *Emerg Infect Dis*. 2002;8(12):1460-1467.
  30. Albrich WC, Monnet DL, Harbarth S. Antibiotic selection pressure and resistance in *Streptococcus pneumoniae* and *Streptococcus pyogenes*. *Emerg Infect Dis*. 2004;10(3):514-517.
  31. Filippini M, Masiero G, Moschetti K. Socioeconomic determinants of regional differences in outpatient antibiotic consumption: evidence from Switzerland. *Health Policy*. 2006;78(1):77-92.

## INVITED COMMENTARY

# Serum Procalcitonin Levels

## It Is All About Confidence

**A**lbrich and colleagues<sup>1</sup> 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 multi-

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

Of interest, algorithm compliance was substantively 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<sup>1</sup> 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.<sup>2,3</sup> 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 aorticocoronary bypass surgery or in patients with cardiogenic shock? In short, does the serum PCT level help the clinician beyond the usual markers of activation of an innate im-