Effect of Procalcitonin-Based Guidelines vs Standard Guidelines on Antibiotic Use in Lower Respiratory Tract Infections: The ProHOSP Randomized Controlled Trial

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Effect of Procalcitonin-Based Guidelines vs Standard Guidelines on Antibiotic Use in Lower Respiratory Tract Infections

The ProHOSP Randomized Controlled Trial

Philipp Schuetz, MD
Mirjam Christ-Crain, MD
Robert Thomann, MD
Claudine Falconnier, MD
Marcel Wolbers, PhD
Isabelle Widmer, MD
Stefanie Neidert, MD
Thomas Fricker, MD
Claudine Blum, MD
Ursula Schild, RN
Katharina Regez, RN
Ronald Schoenenberger, MD
Christoph Henzen, MD
Thomas Bregenzer, MD
Claus Hoess, MD
Martin Krause, MD
Heiner C. Bucher, MD
Werner Zimmerli, MD
Beat Mueller, MD
for the ProHOSP Study Group

Context In previous smaller trials, a procalcitonin (PCT) algorithm reduced antibiotic use in patients with lower respiratory tract infections (LRTIs).

Objective To examine whether a PCT algorithm can reduce antibiotic exposure without increasing the risk for serious adverse outcomes.

Design, Setting, and Patients A multicenter, noninferiority, randomized controlled trial in emergency departments of 6 tertiary care hospitals in Switzerland with an open intervention of 1359 patients with mostly severe LRTIs randomized between October 2006 and March 2008.

Intervention Patients were randomized to administration of antibiotics based on a PCT algorithm with predefined cutoff ranges for initiating or stopping antibiotics (PCT group) or according to standard guidelines (control group). Serum PCT was measured locally in each hospital and instructions were Web-based.

Main Outcome Measures Noninferiority of the composite adverse outcomes of death, intensive care unit admission, disease-specific complications, or recurrent infection requiring antibiotic treatment within 30 days, with a predefined noninferiority boundary of 7.5%; and antibiotic exposure and adverse effects from antibiotics.

Results The rate of overall adverse outcomes was similar in the PCT and control groups (15.4% [n=103] vs 18.9% [n=130]; difference, –3.5%; 95% CI, –7.6% to 0.4%). The mean duration of antibiotics exposure in the PCT vs control groups was lower in all patients (5.7 vs 8.7 days; relative change, –34.8%; 95% CI, –40.3% to –28.7%) and in the subgroups of patients with community-acquired pneumonia (n=925, 7.2 vs 10.7 days; –32.4%; 95% CI, –37.6% to –26.9%), exacerbation of chronic obstructive pulmonary disease (n=228, 2.5 vs 5.1 days; –50.4%; 95% CI, –64.0% to –34.0%), and acute bronchitis (n=151, 1.0 vs 2.8 days; –65.0%; 95% CI, –84.7% to –37.5%). Antibiotic-associated adverse effects were less frequent in the PCT group (19.8% [n=133] vs 28.1% [n=193]; difference, –8.2%; 95% CI, –12.7% to –3.7%).

Conclusion In patients with LRTIs, a strategy of PCT guidance compared with standard guidelines resulted in similar rates of adverse outcomes, as well as lower rates of antibiotic exposure and antibiotic-associated adverse effects.

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UNNECESSARY ANTIBIOTIC USE importantly contributes to increasing bacterial resistance and increases medical costs and the risks of drug-related adverse events.[1-3] The most frequent indication for antibiotic prescriptions in the northwestern hemisphere is lower respiratory tract infections (LRTIs),which range in severity from self-limited acute bronchitis to severe acute exacerbation of chronic obstructive pulmonary disease (COPD), and to life-threatening bacterial community-acquired pneumonia (CAP).[4] Clinical signs and symptoms, as well as commonly used laboratory markers, are unreliable in distinguishing viral from bacterial LRTI.[5-7] As many as 75% of patients with LRTI are treated with antibiotics, despite the predominantly viral origin of their infection.[8]

An approach to estimate the probability of bacterial origin in LRTI is the measurement of serum procalcitonin (PCT).

For editorial comment see p 1115.

Author Affiliations and Members of the ProHOSP Study Group are listed at the end of this article.
Corresponding Author: Beat Mueller, MD, Department of Internal Medicine, Kantonsspital Aarau, Tellstrasse, CH-5001 Aarau, Switzerland (happy.mueller@unibas.ch).

Evidence from clinical trials suggests that use of clinical algorithms based on PCT cutoff ranges leads to important reductions in antibiotic use.[9-14] However, 4 of these trials were performed in single academic hospital settings, compared PCT-based algorithms with nonstandardized routine care, and were all insufficiently powered to show whether patients treated with PCT-based algorithms do not have higher rates of disease-related complications.

We initiated a large multicenter trial in both academic and nonacademic hospitals in Switzerland to compare whether the use of PCT guidance would be noninferior in terms of adverse medical outcomes and to reduce antibiotic exposure in patients with LRTI compared with treatment based on established, internationally recognized guidelines.

METHODS

Study Design

ProHOSP is an investigator-initiated, multicenter, noninferiority, randomized controlled trial. Details of the trial design have already been published.[15] We consecutively enrolled patients with LRTI presenting to the emergency departments (EDs) of 6 participating tertiary care hospitals and randomized the patients to receive antibiotics based on a PCT algorithm (PCT group) or according to evidence-based guidelines (control group). Allocation of patients was concealed by a study Web site, which provided all study-related information on the treatment of LRTI based on the most recent recommendations.[16-19] To enforce both the guidelines and the PCT algorithm, the treating physician had to follow Web-based instructions before registering and entering baseline data. Local investigators and the medical staff of each hospital were trained in group seminars and received handouts to become familiar with the details of the trial, the correct handling of the PCT algorithm, current guideline recommendations, and the study Web site. The protocol was approved by all local ethical committees, and written informed consent was obtained from all participants. This study adhered to the consolidated standards for the reporting of noninferiority trials.[20]

Patient Population

Between October 2006 and March 2008, 1825 patients with a primary diagnosis of LRTI were treated in the EDs of the 6 participating hospitals. Patients were required to be at least 18 years and admitted from the community or a nursing home with acute LRTI of less than 28 days' duration. Inclusion criteria for LRTI were the presence of at least 1 respiratory symptom (cough, sputum production, dyspnea, tachypnea, pleuritic pain), plus at least 1 finding during auscultation (rales, crepitation), or 1 sign of infection (core body temperature >38.0°C, shivering, or leukocyte count >10 000/μL or <4000/μL) independent of antibiotic pretreatment. CAP was defined as a new infiltrate on chest radiograph.[16-19] COPD was defined by postbronchodilator spirometric criteria, according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.[16,21] In patients with a clinical history of COPD and smoking, lung function testing at the time of inclusion was not mandatory. Acute bronchitis was defined as LRTI in the absence of an underlying lung disease or focal chest signs and infiltrates on chest radiograph, respectively.[17]

Patients were ineligible if they were not able to give written informed consent because of language restriction or severe dementia. Exclusion criteria included patients with active intravenous drug use, severe immunosuppression other than corticosteroid use, life-threatening medical comorbidities leading to possible imminent death, patients with hospital-acquired pneumonia (development of pneumonia ≥48 hours after hospital admission or if they were hospitalized within 14 days before presentation), and patients with chronic infection necessitating antibiotic treatment.

Study Protocol and Intervention

In all patients, PCT was measured using a rapid sensitive assay with a functional assay sensitivity of 0.06 μg/L (Kryptor PCT; Brahms, Hennigsdorf, Germany) and an assay time of less than 20 minutes. The test was performed on-site at the central laboratory of each participating hospital and the results were routinely available around the clock within 1 hour. The PCT levels were communicated in the PCT group by the Web site to the treating physician together with a treatment recommendation for antibiotics based on a PCT algorithm validated in previous studies.[9,11,12,14] According to the PCT algorithm (eFigure 1, available at http://www.jama.com), initiation or continuation of antibiotics was strongly discouraged if PCT was less than 0.1 μg/L and discouraged if levels were 0.25 μg/L or lower. Initiation or continuation of antibiotics was strongly encouraged if PCT was higher than 0.5 μg/L and encouraged if levels were higher than 0.25 μg/L. If antibiotics were withheld, hospitalized patients were clinically reevaluated and PCT measurement was repeated after 6 to 24 hours.

All hospitalized patients were clinically reassessed to follow the resolution of the infection on days 3, 5, and 7 and at discharge. In patients in the PCT group with increased PCT values and antibiotic therapy, PCT measurements were repeated after 3, 5, and 7 days and antibiotic treatment was discontinued using the same cutoff ranges. In patients with high PCT values on admission (ie, >10 μg/L), the algorithm recommended stopping antibiotics if PCT levels decreased by 80% and we strongly recommended stopping antibiotics if PCT levels decreased by 90% of the initial value. In outpatients, the initiation and duration of antibiotic therapy was based on the initial PCT value and patients were reassessed only in case of worsening disease.

Overruling of the PCT algorithm was possible by prespecified criteria, namely in patients with immediate need for intensive care unit (ICU) admission, with respiratory or hemodynamic instability, with positive antigen test for *Legionella pneumophila*, or after consulting with the study center. In patients with severe CAP (pneumonia severity index [PSI][22] IV or V) or COPD (GOLD[23] IV or III) and PCT values of less than 0.1 μg/L or 0.25 μg/L or less, respectively, initial overruling of the algorithm was possible. In case of overruling, a repeated PCT measurement and

early discontinuation of antibiotic therapy after 3, 5, or 7 days was strongly suggested.

In the control group, antibiotic use was in accordance with recommendations from up-to-date guidelines.[16-19] In brief, antibiotic use was encouraged in CAP for 5 to 10 days in uncomplicated cases, at least 14 days in *L pneumophila* CAP, at least 10 days in necrotizing CAP, and in the case of empyema or lung abscess, where drainage was suggested. In COPD, antibiotic therapy was recommended for 5 to 10 days if the patient had either severe COPD (GOLD[23] IV) or purulent sputum, and at least 1 of the following: increased dyspnea and increased sputum volume.[21] In acute bronchitis, antibiotics were strongly discouraged. A short 3- to 5-day course of antibiotics was recommended only in patients with purulent sputum and an additional risk factor (>75 years and fever, chronic heart failure, insulin-dependent diabetes, or serious neurological disorder).[19] Irrespective of patients' allocation, other laboratory test results including white blood cell count and C-reactive protein, usually routinely requested by the treating physician to monitor the resolution of the infection, were allowed by the protocol.

In both groups, the choice of antibiotic regimen was left at the discretion of the treating physician. A switch from intravenous to oral antibiotics was recommended if patients had stable or improving vital signs, resolution of the predominant clinical sign, and if oral intake was possible.[18,19]

End Points

The primary noninferiority end point was a composite of overall adverse outcomes occurring within 30 days following the ED admission. It included death from any cause, ICU admission for any reason, disease-specific complications (ie, persistence or development of pneumonia, lung abscess, empyema, and acute respiratory distress syndrome), and recurrence of LRTI in need of antibiotics with or without hospital readmission.

Predefined secondary superiority end points were antibiotic exposure, including duration of intravenous and oral antibiotic therapy, adverse effects from antibiotic treatment, and length of hospital stay. Outcomes were assessed during the hospital stay by unblinded study physicians and by structured telephone interviews at day 30 by blinded medical students. An independent data and safety monitoring board was established to monitor safety and adverse events during the trial.

Statistical Analysis

The primary study hypothesis was that a PCT algorithm is noninferior to the treatment with enforced guidelines with respect to the overall adverse outcome. To estimate the frequency of the primary end point, we used data from previous intervention trials.[11,12,14] Based on these data, the risk of disease-specific failure was assumed to be at most 20%. To define noninferiority with regard to the primary combined end point, the planning committee agreed on a 7.5% absolute difference as the clinically tolerable upper limit (ie, at worst the risk of an overall adverse outcome in the PCT group was increased by <7.5%). Based on this noninferiority boundary, a minimal sample size of 1002 patients was determined allowing for an overall adverse outcome rate in the control group of at most 20% and aiming for a power of 90%. Instead of a fixed sample size, we predefined a fixed recruitment period of 18 months with the goal to randomize all eligible patients from the 6 participating hospitals during that period and an extension if less than 1002 patients had been recruited.[15] This prospective rule allows for the possibility of a higher number of patients and thus better power for subgroup analyses, while maintaining the integrity of the trial. All secondary end points were superiority end points. No interim analyses were planned or performed during the trial.

The primary analysis population is the full analysis set, which includes all randomized patients following an intention-to-treat principle. A confidence interval (CI) for the difference of the overall adverse outcome rates was calculated based on Cochran statistic using Mantel-Haenszel weights and stratification by type of LRTI.[24] We used multiple imputation by chained equations to impute the primary end point for patients lost to follow-up. Results were aggregated over 10 imputed sets using the Rubin variance formula and the imputation was based on the estimated joint distribution of the randomized treatment group, the diagnosis, all covariates included in the derivation of the PSI score, length of hospital stay, and binary indicators for all components of the primary end point. Because in a noninferiority trial an intention-to-treat analysis is not necessarily conservative, the primary analysis was repeated on the per-protocol population.

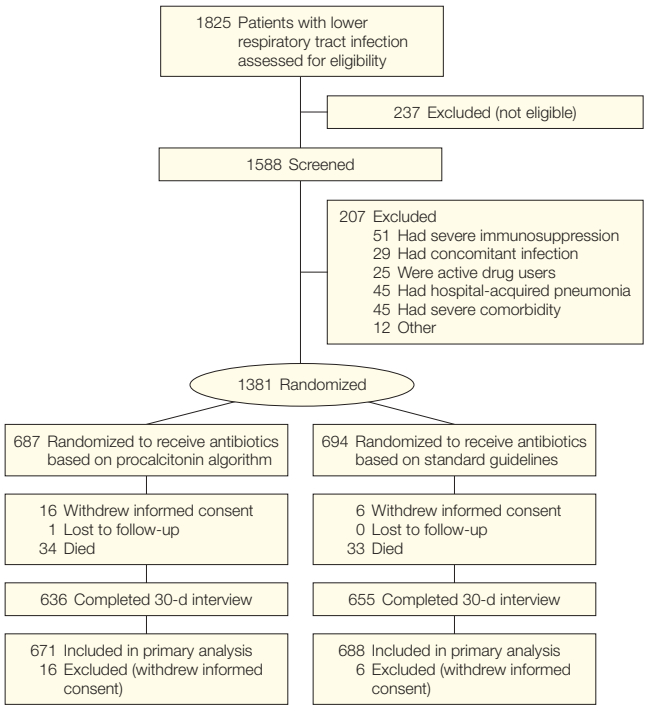
In a second step, the primary end point was modeled with a logistic regression model, adjusted for the following covariates (in addition to the treatment group): age, sex, LRTI subgroup, and center. We also tested for an interaction between treatment group and center. The adjusted analysis was repeated in patients with CAP, with PSI class as an additional covariate. Additionally, Kaplan-Meier curves of the time to the first adverse outcome were calculated. Continuous secondary end points were compared with the Wilcoxon rank sum test; CIs for the relative reduction in antibiotics exposure and length of hospital stay were based on the bootstrap percentile method. For binary secondary end points, we calculated CIs for the risk difference (overall and in LRTI subgroups), according to the method of Agresti and Caffo,[25] and *P* values using the χ^2 test.

All reported CIs were 2-sided 95% intervals, and tests were 2-sided with a 5% significance level. All analyses were performed with R version 2.5.1 (R Foundation for Statistical Computing, Vienna, Austria)[26] and STATA version 9.2 (Stata Corp, College Station, Texas). Multiple imputation was performed with the contributed R package mice.[27]

RESULTS

We randomized a total of 1381 patients; 22 patients withdrew informed consent during the trial and were excluded from all analyses, resulting in 1359 patients for the intention-to-treat analysis (FIGURE 1). Each of the 6 hos-

Figure 1. Flow Diagram of Patients in Trial



pitals contributed between 171 and 265 patients and in total 180 residents and 62 senior residents cared for the patients at the 6 participating sites.

The 2 groups of patients were balanced with regard to baseline characteristics (TABLE 1). Antibiotic pretreatment was present overall in 27% of patients and in 26%, 29%, and 29% of patients with CAP, exacerbation of COPD, and acute bronchitis, respectively. In 11% of patients, systemic corticosteroids mainly for severe COPD were prescribed. In 68% of patients, CAP was diagnosed; 17% had exacerbation of COPD, 11% had acute bronchitis, and 4% had other final non–LRTI diagnoses (other infections [n=15], acute congestive heart failure [n=8], pulmonary embolism [n=7] or tumor [n=7], vasculitis [n=6], other pneumopathy [n=4], other conditions [n=8]). More than 50% of patients with CAP were in high-risk classes according to the PSI score.[22] Overall, 102 patients (7.5%) were treated as outpatients and the median length of stay was 8 days (interquartile range, 4-12). The rate of outpatient treatment was similar in the PCT and control groups overall (6.4% vs 8.6%) and in patients with CAP, exacerbation of COPD, and acute bronchitis. More patients with CAP with low-risk PSI classes I and II were treated as outpatients (20.8%) compared with high-risk PSI classes IV to V (2.4%).

Primary End Point

A total of 103 patients in the PCT group (15.4%) vs 130 patients (18.9%) in the control group reached the primary end point of combined adverse outcome within 30 days of ED admission. The 95% CI for the risk difference (–7.6% to 0.4%) excludes an excess risk in the PCT group of 7.5% or more satisfying the predefined noninferiority criterion and the same holds true for the analysis on the per-protocol population (TABLE 2). Both, the primary end point and mortality were similar or tended to be lower for the PCT group for all LRTI subgroups; 95% CIs for the combined adverse outcome rate and mortality exclude excess risks of more than 2.5% overall and in the subgroup of patients with CAP.

Adjusted analyses confirmed that patients with PCT-guided antibiotic prescription did not have a higher risk of the combined adverse outcome compared with patients in the control group. The odds ratio (OR) for the combined adverse outcome was 0.76 (95% CI, 0.57-1.01) with lower odds in the PCT group for all patients, and the OR for the subgroup of patients with CAP was 0.76 (95% CI, 0.53-1.07). There was no indication of an interaction between study group and center ($P=.64$). Kaplan-Meier curves of the time to the first adverse outcome are shown in eFigure 2 (available at http://www.jama.com).

Secondary End Points

Prescription rates and overall antibiotic exposure were significantly reduced in the PCT group for the whole population as well as in all LRTI subgroups (TABLE 3). The mean duration of antibiotic exposure was less overall (FIGURE 2). The overall reduction in the duration of antibiotics exposure due to PCT guidance ranged between 25.7% and 38.7% in the 6 study sites, respectively. The reductions in antibiotic prescription rates were from 87.7% to 75.4% for all LRTIs, from 99.1% to 90.7% for CAP, from 69.9% to 48.7% for exacerbated COPD, and from 50.0% to 23.2% for acute bronchitis. Reductions in the mean duration of intravenous antibiotic therapy was from 3.8 to 3.2 days for all LRTIs (relative change, –17.1%; 95% CI, –26.6% to –6.5%; $P<.001$), from 4.8 to 4.1 days for CAP, from 1.9 to 1.3 days for exacerbated COPD, and from 1.0 to 0.6 days for bronchitis. Similarly, reductions in the mean duration of oral antibiotic therapy was from 4.9 to 2.5 days for all LRTIs (relative change, –48.5%; 95% CI, –54.7% to –41.5%; $P<.001$), from 5.9 to 3.1 days for CAP, from 3.2 to 1.3 days for exacerbated COPD, and from 1.8 to 0.4 days for bronchitis.

In the 925 patients with CAP, 72 (7.8%) had growth of microorganisms in blood cultures (*Streptococcus pneumoniae* [n=59], *Escherichia coli* [n=2], *Haemophilus influenzae* [n=2], *Staphylococcus aureus* [n=2], *Pseudomonas aeruginosa* [n=1], *Streptococcus* species [n=6]), and

25 patients (2.7%) had a positive urine antigen test for *L pneumophila*. Mean PCT values in patients with CAP with positive blood test cultures (15.3 µg/L) were higher vs patients with CAP without bacterial growth in blood test cultures (3.3 µg/L). In both groups, the mean duration of antibiotic therapy was longer in patients with positive blood test cultures, namely 10.3 vs 7.0 days in the PCT group and 15.1 vs 10.2 days in the control group. Patients with *L pneumophila* CAP had higher mean PCT levels (7.5 vs 4.1 µg/L), but were similarly treated in both groups (12.5 days in the PCT group and 13.0 days in the control group) as recommended by the overruling criteria.

The PCT group showed an absolute decrease of 8.2% (95% CI, –12.7% to –3.7%) in the rate of adverse effects, including nausea, diarrhea, and rash (from 28.1% to 19.8%). This decrease was most prominent in patients with CAP (from 33.1% to 23.5%) (Table 3). The length of hospital stay was similar in both groups for all patients and in all LRTI subgroups.

Adherence With Study Algorithm

In the PCT group, PCT measurements were taken at 4.3 different points overall (4.3 times in CAP, 4.5 times in COPD, and 3.5 times in acute bronchitis). Only 1 outpatient (n=43) in the PCT group had a PCT reassessment at day 3. In 609 patients (90.8%) in the PCT group, antibiotics were initiated and stopped according to the PCT algorithm, including 70 patients (11.5%) in whom the algorithm was overruled based on prespecified criteria (high-risk patients [n=22], instability and ICU admission [n=39], pneumonia due to *L pneumophila* [n=9]). In 62 patients (9.2%) in the PCT group, the algorithm was overruled in violation of the criteria based on the judgment of the treating physician (9.6% in CAP, 10.4% in COPD, and 2.9% in acute bronchitis). The rates of overruling for initiation of therapy and prolonged antibiotic therapy for the different conditions were 5.3% and 20.2% for CAP, 5.3% and 15.9% for exacerbated COPD, and 7.3% and 21.9% for acute bronchitis, respectively. The overruling rate in the control group was 20.6% (20.2% in CAP, 21.2% in COPD, and 29.3% in acute bronchitis). In the subgroup of patients in both study groups in whom the treatment algorithm was not overruled, the mean duration of antibiotic courses was still decreased by 29.3% (from 7.7 to 5.4 days), the prescription rate was decreased from 84.4% to 72.9%, and adverse effects from antibiotics were decreased by absolute 7.2% (from 26.6% to 19.4%).

Table 1. Baseline Characteristics Overall and by Randomization Group[a]

Characteristics	All (N = 1359)	PCT Group (n = 671)	Control Group (n = 688)
Demographics			
Age, median (IQR), y	73 (59-82)	73 (59-82)	72 (59-82)
Male sex, No. (%)	782 (57.5)	402 (59.9)	380 (55.2)
Coexisting illnesses, No. (%)			
Coronary heart disease	282 (20.8)	146 (21.8)	136 (19.8)
Cerebrovascular disease	110 (8.1)	54 (8.1)	56 (8.1)
Renal dysfunction	302 (22.2)	156 (23.3)	146 (21.2)
COPD	533 (39.2)	265 (39.5)	268 (39.0)
Neoplastic disease	167 (12.3)	69 (10.3)	98 (14.2)
Diabetes	231 (17.0)	118 (17.0)	113 (16.4)
Clinical history, No. (%)			
Antibiotics before presentation	362 (26.8)	187 (28.0)	175 (25.8)
Corticosteroids pretreatment	151 (11.4)	76 (11.6)	75 (11.2)
Cough	1164 (88.7)	572 (87.9)	592 (89.4)
Sputum production	678 (50.9)	332 (50.1)	346 (51.8)
Dyspnea	1009 (77.0)	496 (76.2)	513 (77.7)
Fever	782 (57.9)	374 (55.8)	408 (59.9)
Chills	362 (32.0)	182 (32.1)	180 (32.0)
Clinical findings			
Confusion, No. (%)	84 (6.8)	41 (6.7)	43 (7.0)
Respiratory rate, median (IQR), breaths/min	20 (16-25)	20 (16-26)	20 (16-25)
Systolic blood pressure, median (IQR), mm Hg	134 (120-150)	134 (120-150)	134 (120-150)
Heart rate, median (IQR), beats/min	93 (80-106)	93 (80-106)	93 (81-106)
Body temperature, median (IQR), °C	37.8 (37.0-38.6)	37.8 (37.0-38.7)	37.8 (37.0-38.5)
Rales, No. (%)	832 (64.1)	418 (64.9)	414 (63.3)
Laboratory findings, median (IQR)			
PCT, µg/L	0.24 (0.11-1.36)	0.24 (0.12-1.18)	0.24 (0.11-1.60)
C-reactive protein, mg/L	114 (41-220)	115 (38-212)	114 (41-220)
Leukocyte count, cells/µL	11 400 (8400-15 300)	11 600 (8500-15 400)	11 200 (8400-15 200)
Final diagnosis, No. (%)			
CAP	925 (68.1)	460 (68.6)	465 (67.6)
Exacerbation of COPD	228 (16.8)	115 (17.1)	113 (16.4)
Acute bronchitis	151 (11.1)	69 (10.3)	82 (11.9)
Other final diagnosis	55 (4.0)	27 (4.0)	28 (4.0)
Risk assessment in patients with CAP	**(n = 925)**	**(n = 460)**	**(n = 465)**
PSI points overall, median (IQR)	91 (66-115)	91 (67-117)	91 (66-114)
PSI class, No. (%)			
I	90 (9.7)	76 (11.0)	63 (9.3)
II	173 (18.7)	138 (20.1)	124 (18.4)
III	189 (20.4)	147 (21.4)	152 (22.7)
IV	349 (37.7)	243 (35.3)	252 (37.6)
V	124 (13.4)	84 (12.2)	80 (11.9)
Hospitalized patients, No. (%)	1257 (92.5)	628 (93.7)	629 (91.4)
Initial prescription of antibiotics[b]	1060 (84.3)	492 (78.3)	568 (90.3)
Outpatients, No. (%)	102 (7.5)	43 (6.4)	59 (8.6)
Initial prescription of antibiotics[c]	49 (48.0)	14 (32.6)	35 (59.3)

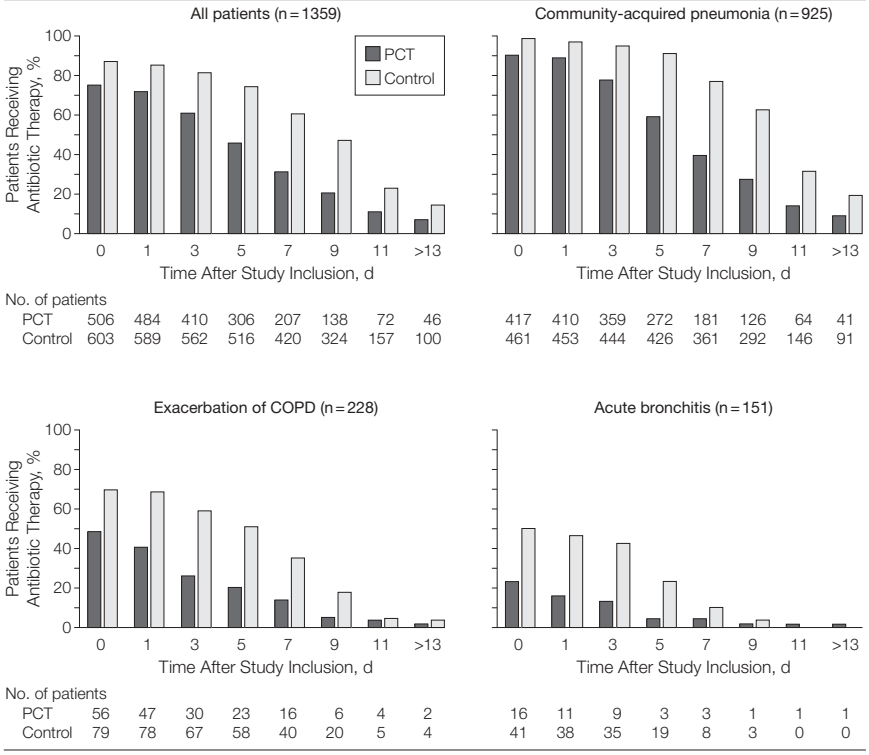
Abbreviations: CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; PCT, procalcitonin; PSI, pneumonia severity index.
[a] See the "Results" section for definition of other final diagnosis. Higher PSI class refers to higher risk for mortality.
[b] $P<.01$.
[c] $P<.001$.

Table 2. Rates of Combined Adverse Outcomes and Mortality by Randomization Group

	No. (%) of Patients		
	PCT Group	Control Group	Risk Difference, % (95% CI)
All patients (intention-to-treat)[a]	**(n = 671)**	**(n = 688)**	
Overall adverse outcome	103 (15.4)	130 (18.9)	–3.5 (–7.6 to 0.4)
Death	34 (5.1)	33 (4.8)	0.3 (–2.1 to 2.5)
ICU admission	43 (6.4)	60 (8.7)	–2.3 (–5.2 to 0.4)
Recurrence/rehospitalization	25 (3.7)	45 (6.5)	–2.8 (–5.1 to –0.4)
Disease-specific complication	17 (2.5)	14 (2.0)	0.5 (–1.1 to 2.0)
Per-protocol population	**(n = 633)**	**(n = 650)**	
Overall adverse outcome	95 (15.0)	123 (18.9)	–3.9 (–8.2 to 0.03)
Death	29 (4.6)	31 (4.8)	–0.2 (–2.6 to 2.0)
Community-acquired pneumonia	**(n = 460)**	**(n = 465)**	
Overall adverse outcome	74 (16.1)	94 (20.2)	–4.1 (–9.1 to 0.9)
Death	24 (5.2)	26 (5.6)	–0.4 (–3.3 to 2.6)
Exacerbation of COPD[a]	**(n = 115)**	**(n = 113)**	
Overall adverse outcome	15 (13.0)	21 (18.6)	–5.3 (–14.8 to 4.4)
Death	4 (3.5)	5 (4.4)	–0.9 (–6.4 to 4.5)
Acute bronchitis	**(n = 69)**	**(n = 82)**	
Overall adverse outcome	6 (8.7)	8 (9.8)	–1.1 (–10.4 to 8.7)
Death	1 (1.4)	0	1.4 (–2.9 to 6.1)
Other diagnoses	**(n = 27)**	**(n = 28)**	
Overall adverse outcome	8 (29.6)	7 (25.0)	4.6 (–18.7 to 27.5)
Death	5 (18.5)	2 (7.1)	11.4 (–7.5 to 28.9)

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; PCT, procalcitonin.
[a] Outcome was missing for 1 patient with exacerbation of COPD. For the calculation of the risk (n and %) in each group, this patient was treated as being without adverse outcome, but estimates for the risk difference are based on multiple imputation of the missing outcome.

Figure 2. Antibiotic Exposure in Patients Receiving Antibiotic Therapy



PCT indicates procalcitonin; COPD, chronic obstructive pulmonary disease.

COMMENT

In this large multicenter trial including patients with LRTI, an algorithm with PCT cutoff ranges was noninferior to algorithm-based clinical guidelines in terms of adverse outcomes and was more effective in reducing antibiotic exposure and associated adverse effects.

Emerging bacterial resistance to multiple antimicrobial agents calls for more efficient efforts to reduce the use of antimicrobial agents in self-limited and nonbacterial diseases and to shorten the duration of antibiotic treatment in bacterial infections.[2] Although several strategies have been proposed to reduce antibiotic overuse as well as misuse, adherence to guidelines in routine clinical care is variable,[28-30] which was also confirmed in this trial. The overruling rates in this trial were lower in the PCT group vs the control group and should be interpreted in the context of our study population with a high number of high-risk patients with CAP (PSI class IV and V) and high rate of ICU admissions.

Higher circulating peak levels and protracted normalization of PCT levels correlate with a more severe systemic infection, mirroring a slower bacterial clearance and a higher virulence of the microorganism.[12,31,32] As shown in 2 previous smaller studies[12,13] and in this study, patients with bacteremic CAP had markedly increased PCT concentrations resulting in a longer duration of treatment. Recommendations for microbiological testing in LRTI remain controversial. Positive bacterial cultures may have a major effect on the treatment of a severely ill patient and are important for epidemiologic studies and surveillance of antibiotic susceptibility patterns. Conversely, the low sensitivity and the infrequent positive effect on clinical care argue against the routine use of blood and sputum cultures in all patients with LRTI.[33,34]

In our trial including patients with different severities of LRTIs, CAP was the most important definite diagnosis. Most patients were referred by their primary care physician, because of the severity of the infection, concomitant important comor-

bidities, or both. This may explain the relatively high antibiotic exposure in patients in the control group treated according to current guidelines. In patients with life-threatening infections such as CAP, the PCT algorithm was expected to reduce antibiotic exposure by shortening the antibiotic courses. Appropriate decrease of the treatment duration is an important aspect of lowering antibiotic-associated costs and minimizing selection pressures for resistant organisms.[33] Conversely, in milder respiratory infections, namely acute bronchitis and upper respiratory tract infections in primary care, initiation of antibiotic therapy is markedly decreased up to 75% by PCT guidance.[9] Point-of-care testing for PCT measurement are becoming available in Europe and in the United States, which enables a more widespread use of this approach in smaller medical clinics and outpatient physician offices. A recent trial has proven the feasibility, efficacy, and safety of a PCT-guided antibiotic stewardship in primary care.[9]

The strengths of our trial are (1) the large cohort of patients with LRTIs of different severity and clinical manifestations representative for patients typically treated in EDs and hospitals, (2) the rigorous follow-up, (3) similar Web-based implementation of both algorithms in each treatment group, and (4) the partially blinded outcome assessment. Our study also has limitations. Composite end points including mortality as the clinically most important component have drawbacks. The combined adverse outcome tended to be lower in the PCT group, but we observed a slightly higher mortality rate, which, however, is at worst 2.5%. Physicians knowing they will be monitored better adhere to guidelines resulting in a possibly lower antibiotic prescription rate compared with the real-life setting (Hawthorne effect). The intervention with PCT testing and physicians' gained experience of reduced antibiotic treatment may have affected antibiotic prescription patterns in the control group (spillover effect). The final decision to withhold or decrease antibiotic treatment was left to the discretion of the attending physician in both groups. Thus, physicians were not obliged to always conform to the study protocol in both groups. However, protocol overruling would result in a "conservative bias," potentially underestimating the benefit of a PCT-guided approach.

Table 3. Antibiotic Exposure, Adverse Effects, and Length of Hospital Stay

	PCT Group	Control Group	Relative Mean Change or Rate Difference % (95% CI)
All patients	**(n = 671)**	**(n = 688)**	
Antibiotic exposure, mean (median [IQR]), d	5.7 (5 [1-8])	8.7 (9 [6-11])	–34.8 (–40.3 to –28.7)
Antibiotic prescription rate, No. (%)	506 (75.4)	603 (87.7)	–12.2 (–16.3 to –8.1)
Adverse effect rate from antibiotics, No. (%)	133 (19.8)	193 (28.1)	–8.2 (–12.7 to –3.7)
Duration in patients with adverse effects, median (IQR), d	3 (1-7)	4 (2-10)	
Length of hospital stay, mean (median [IQR]), d	9.4 (8 [4-12])	9.2 (8 [4-12])	1.8 (–6.9 to 11.0)
Community-acquired pneumonia	**(n = 460)**	**(n = 465)**	
Antibiotic exposure, mean (median [IQR]), d	7.2 (7 [4-10])	10.7 (10 [8-12])	–32.4 (–37.6 to –26.9)
Antibiotic prescription rate, No. (%)	417 (90.7)	461 (99.1)	–8.5 (–11.3 to –5.6)
Adverse effect rate from antibiotics, No. (%)	108 (23.5)	154 (33.1)	–9.6 (–15.4 to –3.8)
Duration in patients with adverse effects, median (IQR), d	3 (2-7)	5 (2-10)	
Length of hospital stay, mean (median [IQR]), d	10.0 (8 [5-13])	9.5 (8 [4-12])	5.3 (–5.1 to 16.8)
Exacerbation of COPD	**(n = 115)**	**(n = 113)**	
Antibiotic exposure, mean (median [IQR]), d	2.5 (0 [0-4])	5.1 (6 [0-8])	–50.4 (–64.0 to –34.0)
Antibiotic prescription rate, No. (%)	56 (48.7)	79 (69.9)	–21.2 (–33.2 to –8.5)
Adverse effect rate from antibiotics, No. (%)	14 (12.2)	18 (15.9)	–3.8 (–12.8 to 5.4)
Duration in patients with adverse effects, median (IQR), d	1.5 (1-4)	2 (1-3.5)	
Length of hospital stay, mean (median [IQR]), d	8.8 (8 [5-11])	9.2 (8 [5-13])	–4.4 (–19.1 to 12.9)
Acute bronchitis	**(n = 69)**	**(n = 82)**	
Antibiotic exposure, mean (median [IQR]), d	1 (0)	2.8 (1 [0-5])	–65.0 (–84.7 to –37.5)
Antibiotic prescription rate, No. (%)	16 (23.2)	41 (50.0)	–26.8 (–40.7 to –11.5)
Adverse effect rate from antibiotics, No. (%)	7 (10.1)	11 (13.4)	–3.3 (–13.5 to 7.5)
Duration in patients with adverse effects, median (IQR), d	1 (1-2)	1.5 (1-5.8)	
Length of hospital stay, mean (median [IQR]), d	5.4 (4 [1-7])	6.1 (4 [0-9])	–10.3 (–37.1 to 27.0)
Other diagnoses	**(n = 27)**	**(n = 28)**	
Antibiotic exposure, mean (median [IQR]), d	4.9 (3 [0-8])	7.7 (4 [1-11])	–36.1 (–68.3 to 23.2)
Antibiotic prescription rate, No. (%)	63.0 (17)	78.6 (22)	–15.6 (–37.9 to 8.7)
Adverse effect rate from antibiotics, No. (%)	4 (14.8)	10 (35.7)	–20.9 (–41.5 to 2.6)
Duration in patients with adverse effects, median (IQR), d	5.5 (4.3-6.8)	3.5 (1.0-8.5)	
Length of hospital stay, mean (median [IQR]), d	10.9 (9 [6-14])	13.4 (11 [5-21])	–19.0 (–42.3 to 15.4)

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; PCT, procalcitonin.

In conclusion, particularly in countries with higher antibiotic prescription rates than Switzerland,[34] PCT guidance will have substantial clinical and public health implications to reduce antibiotic exposure and associated risks of adverse effects and antibiotic resistance.

Author Affiliations: Department of Internal Medicine, Kantonsspital Aarau, Aarau (Drs Schuetz, Christ-Crain, Bregenzer, and Mueller and Mss Schild and Regez); Department of Internal Medicine (Drs Schuetz, Christ-Crain, Thomann, Falconnier, Blum, and Mueller and Mss Schild and Regez) and Basel Institute for Clinical Epidemiology and Biostatistics (Drs Schuetz, Wolbers, and Bucher), University Hospital Basel, Basel; Department of Internal Medicine, Buergerspital, Solothurn (Drs Thomann and Schoenenberger); Department of Internal Medicine, Kantonsspital, Liestal (Drs Falconnier and Zimmerli); Department of Internal Medicine, Kantonsspital, Lucerne (Drs Widmer, Neidert, and Henzen); and Department of Internal Medicine, Kantonsspital, Muensterlingen (Drs Fricker, Hoess, and Krause), Switzerland.

Author Contributions: Drs Schuetz and Wolbers had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Schuetz, Christ-Crain, Wolbers, Fricker, Hoess, Bucher, Zimmerli, Mueller.
Acquisition of data: Schuetz, Christ-Crain, Thomann, Falconnier, Widmer, Neidert, Blum, Schild, Regez, Henzen, Krause, Zimmerli, Mueller.
Analysis and interpretation of data: Schuetz, Wolbers, Fricker, Schoenenberger, Bregenzer, Bucher, Mueller.
Drafting of the manuscript: Schuetz, Wolbers, Mueller.
Critical revision of the manuscript for important intellectual content: Christ-Crain, Thomann, Falconnier, Widmer, Neidert, Fricker, Blum, Schild, Regez, Schoenenberger, Henzen, Bregenzer, Hoess, Krause, Bucher, Zimmerli.
Statistical analysis: Schuetz, Wolbers.
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The ProHOSP Study Group: Rita Bossart, RN, Sabine Meier, Pamela Spreiter, Claudia Baehni, Ayesha Chaudri, Fabian Mueller, Jeannine Haeuptle, Roya Zarbosky, Rico Fiumefreddo, Melanie Wieland, RN, Charly Nusbaumer, MD, Andres Christ, MD, Roland Bingisser, MD, Kristian Schneider, RN, Christine Vincenzi, RN, and Michael Kleinknecht, RN, from the University Hospital Basel; Brigitte Walz, PhD, and Verena Briner, MD, Kantonsspital Lucerne; Dieter Conen, MD, Andreas Huber, MD, and Jody Staehelin, MD, Kantonsspital Aarau; Chantal Bruehlhardt, RN, Kantonsspital Liestal; Ruth Luginbuehl, RN, and Agnes Muehlemann, RN, Buergerspital Solothurn, Ineke lambinon, and Max Zueger, MD, Kantonsspital Muensterlingen.
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