Procalcitonin-Guided Antibiotic Use vs a Standard Approach for Acute Respiratory Tract Infections in Primary Care

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Background: Acute respiratory tract infections are the most common reason for antibiotic therapy in primary care despite their mainly viral etiology. A laboratory test measuring procalcitonin levels in blood specimens was suggested as a tool to reduce unnecessary prescribing of antibiotics. We consider whether antibiotic therapy guided by procalcitonin reduces the use of antibiotics without increasing the restrictions experienced by patients by more than 1 day.

Methods: Fifty-three primary care physicians recruited 458 patients, each patient with an acute respiratory tract infection and, in the physician's opinion, in need of antibiotics. Patients were centrally randomized to either a procalcitonin-guided approach to antibiotic therapy or to a standard approach. For patients randomized to procalcitonin-guided therapy, the use of antibiotics was more or less strongly discouraged (procalcitonin level, ≤0.1 or ≤0.25 μg/L, respectively) or recommended (procalcitonin level, >0.25 μg/L). Follow-up data were collected at 7 days by treating physicians and at 14 and 28 days by blinded interviewers.

Results: Adjusted for baseline characteristics, the mean increase at 14 days in days in which activities were restricted was 0.14 with procalcitonin-guided therapy (95% confidence interval [CI], −0.53 to 0.81 days), which met our criterion of an increase in days in which activities were restricted by no more than 1 day. With procalcitonin-guided therapy, the antibiotic prescription rate was 72% lower (95% CI, 66%-78%) than with standard therapy. Both approaches led to a similar proportion of patients reporting symptoms of ongoing or relapsing infection at 28 days (adjusted odds ratio, 1.0 [95% CI, 0.7-1.5]).

Conclusions: As an adjunct to guidelines, procalcitonin-guided therapy markedly reduces antibiotic use for acute respiratory tract infections in primary care without compromising patient outcome. In practice, this could be achieved with 1 to 2 procalcitonin measurements in patients for whom the physician intends to prescribe antibiotics.

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ACUTE RESPIRATORY TRACT infections are the most common reason for antibiotic therapy in primary care.[1,2] In Europe and the United States, over 50% of acute respiratory tract infections are treated with antibiotics in primary practice, despite their mainly viral etiology.[2,3] Excessive use of antibiotics is associated with increased antibiotic resistance for common bacteria, medicalizing effects (eg, patients with a prescribed antibiotic for a respiratory tract infection will take future respiratory tract tract infections more seriously, probably seek medical advice from a physician, and demand antibiotics), high costs, and adverse reactions.[1,2,4,5] Therefore, the judicious use of antibiotics in primary care is paramount.

Clinical signs and symptoms of bacterial infection and laboratory parameters are often inconclusive.[6,7] The challenge for the primary care physician remains to identify those patients with a bacterial respiratory tract infection for whom antimicrobial treatment is beneficial.[8]

See Invited Commentary at end of article

A new approach is to guide antibiotic therapy based on the level of the biomarker procalcitonin (PCT). Circulating levels of PCT are elevated with a systemic bacterial infection but remain relatively low with a viral infection or with inflammatory diseases.[9] A recent systematic review and meta-analysis found that PCT is superior to C-reactive protein for the diagnosis of bacterial infections.[10] Recently, we found that by using a PCT-based algorithm, both the rate and duration of antibiotic use could be markedly reduced in patients hospitalized with a lower respiratory tract infection.[11-13]

The objective of this trial was to evaluate a PCT-guided diagnostic and therapeutic strategy for acute upper and lower respiratory tract infections in primary care. We assessed whether antibiotic therapy guided by PCT reduces the use of antibiotics without increasing the restriction of activities experienced by patients by more than 1 day compared with a standard therapy based on current guidelines.

METHODS

DESIGN

We conducted a randomized, open, multicenter, noninferiority trial. From December 13, 2004, until April 30, 2006, adult patients with an acute respiratory tract infection and, in their physician's opinion, in need of antibiotics were randomized to either a PCT-guided approach to antibiotic therapy or to a standard approach in which physicians were asked to adhere to current guidelines. Allocation to either intervention was concealed by using a centralized randomization procedure with computer-generated lists produced by an independent statistician. Randomization was in fixed blocks of 4, and a separate randomization list was kept for each physician's practice. A detailed protocol of this trial, including baseline characteristics of participating physicians, has been published.[14] The ethics committee of the University Hospital Basel (Basel, Switzerland) approved the trial protocol. The trial was supervised by an independent monitoring board consisting of a general internist in primary care, an infectious disease specialist, and a pneumologist. All participating physicians and patients gave written informed consent. This report adheres to the consolidated standards for the reporting of noninferiority trials.[15]

PARTICIPANTS

We sent an invitation letter to all primary care physicians in 2 cantons in northwest Switzerland to participate in the trial. Of 345 eligible physicians contacted once, 53 physicians gave written informed consent and were included. Trial physicians consecutively screened adults with symptoms (first experienced within the previous 28 days) of an acute infection of the respiratory tract system. Inclusion criteria for patients were a consultation for common cold, rhinosinusitis, pharyngitis, tonsillitis, tracheobronchitis, otitis media, influenza, acute exacerbation of asthma or chronic obstructive pulmonary disease (COPD), or community-acquired pneumonia (confirmed by chest radiograph); and the physician's intention to prescribe antibiotics on the basis of evidence-based guidelines. Exclusion criteria for patients were antibiotic use within the previous 28 days, psychiatric disorders or inability to give written informed consent, not being available for follow-up, not being fluent in German, severe immunosuppression, cystic fibrosis, active tuberculosis, and the need for immediate hospitalization.[14] Recruitment ceased at a participating practice after 20 patients were recruited or on April 30, 2006, whichever came first.

INTERVENTION

Updated guidelines, adapted to local conditions and reviewed by local experts, were developed by M.B. and H.C.B. based on existing evidence-based US position papers for the treatment of acute respiratory tract infections.[16-19] We distributed these guidelines as a booklet[20] and presented them to all participating physicians in an interactive 2-hour seminar.

When a trial physician intended to give antibiotics to an eligible patient, the physician had to call the study center, and the patient was randomly allocated to PCT-guided or standard antibiotic therapy. Blood samples were collected from all recruited patients and sent by courier to the central laboratory of the University Hospital Basel for PCT measurement. The PCT level was measured using a commercially available time-resolved amplified cryptate emission technology assay (Kryptor PCT; Brahms, Hennigsdorf, Germany). The assay has an improved functional assay sensitivity of 0.06 µg/L (ie, 4-fold above normal reference range; note that with the Kryptor assay used, the normal mean values cannot be determined. These were determined by an experimental assay and, thus, are only comparable in part in absolute numbers[21]).[22] Assay time is 19 minutes with 20 to 50 µL of plasma or serum.

If the patient was randomized to receive PCT-guided therapy, the PCT test result was communicated to the study practice within 2 to 4 hours depending on transportation time of probes delivered to the central laboratory. In patients with PCT levels lower than 0.1 µg/L, a bacterial infection was considered highly unlikely, and the use of antibiotics was discouraged. In patients with a PCT level higher than 0.25 µg/L, a bacterial infection was considered likely and the use of antibiotics was recommended. For PCT concentrations of 0.1 to 0.25 µg/L, a bacterial infection was considered unlikely, and the use of antibiotics was not recommended. The trial physician then decided on the appropriate treatment and informed the patient by telephone. Patients to be given antibiotics were asked to fill a delayed prescription (a prescription issued under a reservation) or to pick up the antibiotic from the practice. The type of antibiotic prescribed was left to the discretion of the physician. When antibiotics were withheld from patients, a second measurement of the PCT level was mandatory within 6 to 24 hours for safety reasons. The use of antibiotics was recommended if this second measurement was higher than 0.25 µg/L or if the PCT level had increased from the first measurement by more than 50% and the patient showed no clinical improvement. All patients given antibiotics based on PCT level were reassessed after 3 days. Discontinuation of antibiotic treatment was then recommended in patients with a PCT level of 0.25 µg/L or lower.[14] For patients randomized to standard therapy, physicians were free to choose the type and duration of antibiotic treatment, but the use of evidence-based guidelines was encouraged.

DATA AND OUTCOMES

We obtained baseline data for all eligible primary care physicians in northwest Switzerland from the registry of the Swiss Medical Association. Trial physicians recorded baseline data on patient signs and symptoms, diagnostic procedures, their diagnosis, and comorbidities; they collected blood samples and documented therapy at each follow-up visit. Seven medical students, blinded to the goal and design of the study, conducted standardized follow-up interviews by telephone at 14 and 28 days after baseline. Over 98% of interviews were completed within 2 days of the supposed interview date. We used Teleform software (Cardwell, Cardiff, Wales) for data entry.

The primary outcome was the number of days, within the first 14 days after baseline, during which a patient's daily activities (work or recreation) were restricted by a respiratory tract infection. Secondary outcomes were antibiotic prescription rate, duration of actual antibiotic treatment (days), degree of discomfort from infection (scored on a scale from 0 [no discomfort] to 10 [a great deal of discomfort]), days of work missed, days with adverse effects from medication (all within 14 days), and the proportion of patients reporting any symptoms of an ongoing or relapsing respiratory tract infection at 28 days after baseline. All serious adverse events (ie, hospitalization for any reason, sepsis, abscess, allergic reaction owing to received

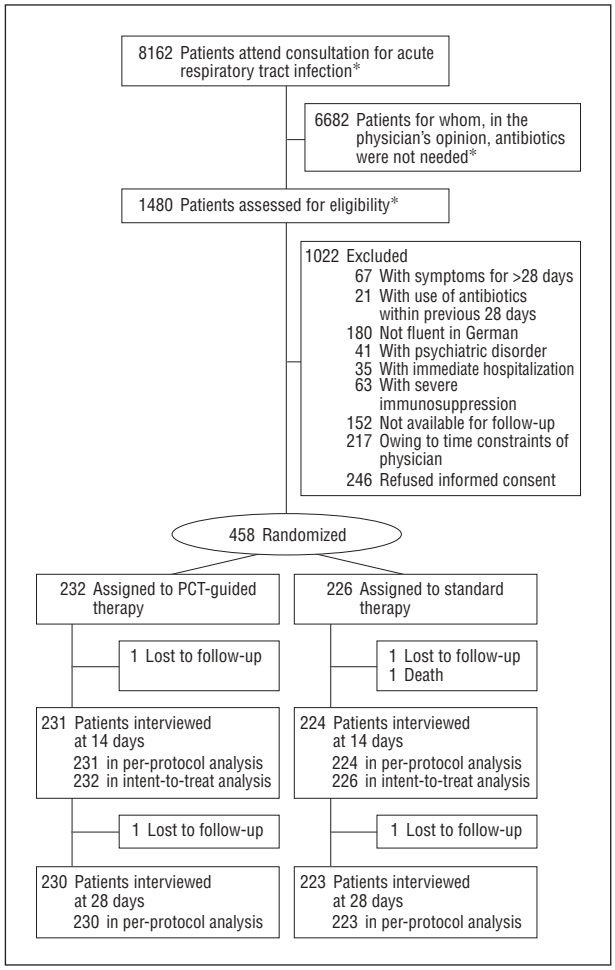

Figure 1. Flowchart of patients. PCT indicates procalcitonin; an asterisk indicates that the number of patients with acute respiratory tract infections screened for inclusion in the trial were estimated from physician self-report.

medication, or death) that occurred within 28 days of baseline were reviewed by an independent monitoring board.

SAMPLE SIZE

In a previous trial,[23] the standard deviation in the number of days in which activities were restricted at 14 days from an acute respiratory tract infection was 4 days for patients prescribed antibiotics. Given this estimate, we required a sample size of 275 per group to show that, at worst, PCT-guided therapy leads to 1 additional day with restrictions relative to standard therapy, assuming a 1-sided type I error rate of 5%, and a type II error rate of 10% (ie, 90% statistical power).[24]

STATISTICAL ANALYSIS

For the primary outcome we report both per-protocol and intention-to-treat analyses. In the per-protocol analysis, missing outcomes and missing covariates remained missing. In the intention-to-treat analysis, missing outcomes were conservatively set to 14 days with restrictions for patients with PCT-guided therapy and zero days with restrictions for patients with standard therapy; missing covariates (5 missing values for the education category and 1 missing value for the degree of discomfort at baseline) were set to their mean value. Using a multivariate, generalized, linear mixed model, we calculated an adjusted 95% confidence interval (CI) for the difference between PCT-guided and standard therapy in the number of days in which activities were restricted by a respiratory tract infection. This model had age, sex, education, any comorbidity, and the baseline score for the degree of discomfort reported by the patient as covariates and had study practice as a random effect. Covariates were selected prior to the analysis in an effort to increase precision and reduce bias.[25] Adding study practice to the model as a random effect acknowledges 2 sources of variation (within- and between-practice variation) and is appropriate when the desired inference is from the practices in this trial to other patients in other practices. The PCT-guided therapy was regarded as noninferior to the standard therapy if the difference between groups in days with restricted activities was, at most, 1 day.

For all secondary outcomes, we performed per-protocol analyses with respect to outcome but with missing covariate values replaced by their mean. For each analysis, we specified a distribution appropriate for each outcome and then used the same generalized linear mixed model as described herein. We used Stata statistical software (version 9.2; Stata Corp, College Station, Texas) for all analyses.

RESULTS

RECRUITMENT AND BASELINE

Data from the Swiss Medical Association suggest that trial physicians were similar to all eligible primary care physicians in northwest Switzerland with respect to characteristics recorded by the association.[14] Trial physicians recruited 458 patients (**Figure 1**). Owing to slower recruitment than expected, we extended the initial recruitment period by 4 months (to April 30, 2006). Baseline characteristics of patients were similar for both PCT-guided and standard therapy (**Table 1**). At baseline, patients had a median of 5 days (interquartile range [IQR], 3-7 days) of restricted activities from an acute respiratory tract infection and rated the degree of discomfort as 6 to 7 (on a scale of 0-10) (IQR, 5-8).

PRIMARY OUTCOME: DAYS WITH RESTRICTED ACTIVITIES FROM INFECTION

Of the 455 patients interviewed at 14 days (per-protocol analysis), both patients with PCT-guided therapy (n=231) and those with standard therapy (n=224) reported a mean of 8.7 days with restricted daily activities (**Table 2**). An adjusted increase of 0.1 days with restricted activities (95% CI, –0.5 to 0.8 days) while receiving PCT-guided therapy met our criterion for noninferiority (**Figure 2**). Noninferiority seemed consistent across different diagnoses of respiratory tract infections (**Table 3**). In a sensitivity analysis, we excluded practices that recruited fewer than 10 patients, leading to a reduced sample of 299 patients recruited at 16 practices. In this reduced sample, the mean number of days with restricted activities were 8.7 and 8.6 for patients with PCT-guided and standard therapy, respectively, with an adjusted increase of 0.2 days with restrictions for patients receiving PCT-guided therapy (95% CI, –0.7 to 1.0 days). In an intention-to-treat analysis with conservative replacement of missing outcomes, the adjusted increase of 0.2 days (95% CI, –0.4 to 0.9 days) with restrictions with PCT-guided therapy still satisfied our noninferiority criterion.

Table 1. Baseline Characteristics of Patients

Characteristic	No. (%)	
	PCT-Guided Therapy Group (n=232)	Standard Therapy Group (n=226)
Age, median [IQR], mean (SD), y	45 [33-63], 48 (18)	46 [35-62], 48 (18)
Women	134 (58)	139 (62)
Educational level, y[a]		
Low (≤5)	30 (13)	52 (23)
Medium (>5 and ≤10)	145 (63)	122 (55)
High (>10)	56 (24)	48 (22)
Days with RAs, median [IQR], mean (SD), No.	4.5 [3-7], 5.8 (4.7)	5 [3-7], 6.5 (4.7)
Degree of discomfort from infection, median [IQR], mean (SD)[b]	6 [5-8], 6.1 (2.6)	7 [5-8], 6.2 (2.4)
Presence of any comorbidity	33 (14)	37 (16)
Chronic lung disease	12 (5.2)	14 (6.2)
Diabetes mellitus	6 (2.6)	7 (3.1)
Heart failure	8 (3.4)	6 (2.6)
Other comorbidities	7 (3.0)	10 (4.4)
Use of diagnostic test other than PCT	190 (82)	176 (78)
PCT, median [IQR], mean (SD), µg/L	0.08 [0.06-0.1], 0.39 (2.7)	0.08 [0.06-0.1], 0.24 (1.3)
CRP, median [IQR], mean (SD), mg/dL[c]	28 [7-71], 51 (65)	34 [10-76], 51 (55)
Diagnosis		
Common cold	13 (5.6)	18 (8.0)
Acute rhinosinusitis	52 (22)	52 (23)
Acute pharyngitis or tonsillitis	42 (18)	33 (15)
Acute laryngitis or tracheitis	8 (3.5)	4 (1.8)
Acute otitis media	0	5 (2.2)
Acute bronchitis	58 (25)	70 (31)
Influenza	3 (1.3)	1 (0.4)
Exacerbated COPD	12 (5.2)	9 (4.0)
Exacerbated asthma	6 (2.6)	3 (1.3)
Community-acquired pneumonia	38 (16)	31 (14)

Abbreviations: COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; IQR, interquartile range; PCT, procalcitonin; RA, restricted activity.
[a] Five missing values led to a reduced sample of 231 patients receiving PCT-guided therapy and 222 patients receiving standard therapy.
[b] One missing value led to a reduced sample of 231 patients receiving PCT-guided therapy. The discomfort scale is 0 to 10.
[c] Eight missing values led to a reduced sample of 230 patients receiving PCT-guided therapy and 220 patients receiving standard therapy.

SECONDARY OUTCOME: ANTIBIOTIC USE

Trial physicians prescribed antibiotics for 58 of the 232 patients (25%) with PCT-guided therapy and for 219 of 226 patients (97%) with standard therapy (percentage decrease while receiving PCT-guided therapy, 72% [95% CI, 66%-78%]; adjusted odds ratio, 0.01 [95% CI, 0.002-0.018]). Among patients with acute exacerbations of COPD or asthma or community-acquired pneumonia receiving PCT-guided therapy, the number of antibiotic prescriptions were reduced by about 40%, whereas among patients with upper respiratory tract infections or acute bronchitis receiving PCT-guided therapy, antibiotic prescriptions were reduced by about 80% (Table 3). The mean duration of antibiotic treatment in patients receiving antibiotics was 6.2 days with PCT-guided therapy and 7.1 days with standard therapy (adjusted decrease with PCT, 1.0 days [95% CI, 0.4-1.7 days]).

In 85% of cases, physicians and patients adhered to the treatment algorithm in the PCT group. Thirty-five patients (15%) received antibiotics despite PCT levels lower than 0.25 µg/L. Thirteen patients in the PCT group in whom antibiotics were initially withheld (those with a PCT level lower than 0.25 µg/L) received an antibiotic based on a PCT level higher than 0.25 µg/L at the second measurement or because of an increase in PCT level from the initial measurement by more than 50% within 24 hours.

OTHER PATIENT OUTCOMES

On average, the degree of discomfort from the infection (on a scale of 0 to 10) decreased from 6.1 and 6.2 at baseline to 1.9 and 1.1 at 14 days with PCT-guided and standard therapy, respectively. The adjusted difference in discomfort at 14 days was 0.8 scale points (95% CI, 0.4-1.2) higher with PCT-guided therapy. For patients with an occupation or employment (n=312), the mean number of days of work missed were similar in both groups: 4.9 and 4.8 days with PCT-guided and standard therapy, respectively (adjusted increase with PCT therapy, 0.3 days [95% CI, –0.5 to 1.2 days]). The mean number of days in which patients experienced adverse effects from medication (abdominal pain, diarrhea, nausea or vomiting, skin rash) were significantly lower with PCT-guided therapy (2.3 days vs 3.6 days with standard therapy; adjusted decrease with PCT, 1.1 days [95% CI, 0.1-2.1 days]). Many more patients reported experiencing diarrhea when receiving standard therapy (**Table 4**). Similar antibiotics were used in both therapies.

After 28 days, symptoms of an ongoing or relapsing respiratory tract infection were reported by 69 of 230 patients (30%) receiving PCT-guided therapy and by 67 of 223 patients (30%) receiving standard therapy (adjusted odds ratio, 1.0 [95% CI, 0.7-1.5]).

Table 2. Summary of Primary and Secondary Outcomes

Outcome	PCT-Guided Therapy Group	Difference (95% CI) Between PCT-Guided and Standard Therapy Groups	Standard Therapy Group
Primary End Points[a]			
Per protocol analysis	n=231		n=224
Days with RAs, mean (SD)	8.7 (3.9)		8.7 (3.8)
Unadjusted difference in days (95% CI)		0.01 (–0.7 to 0.7)	
Adjusted difference in days (95% CI)[b]		0.1 (–0.5 to 0.8)	
Intention-to-treat analysis	n=232		n=226
Days with RAs, mean (SD)	8.7 (3.9)		8.6 (3.9)
Unadjusted difference in days (95% CI)		0.1 (–0.6 to 0.8)	
Adjusted difference in days (95% CI)[b]		0.2 (–0.4 to 0.9)	
Secondary End Points[c]			
Prescribed antibiotics, No. (%)	58 (25)		219 (97)
Percentage difference (95% CI)		–72 (–78 to –66)	
Adjusted odds ratio (95% CI)[b]		0.01 (0.002 to 0.02)	
Days with antibiotics, mean (SD)[d]	6.2 (2.5)		7.1 (2.2)
Adjusted difference in days (95% CI)[b]		–1.0 (–1.7 to –0.4)	
Degree of discomfort from infection score at 14 d, mean (SD)[e]	1.9 (2.7)		1.1 (1.9)
Adjusted difference in score (95% CI)[b]		0.8 (0.4 to 1.2)	
Days with adverse effects within 14 d, mean (SD)[f]	2.3 (4.6)		3.6 (6.1)
Adjusted difference in days (95% CI)[b]		–1.1 (–2.1 to –0.1)	
Days of work missed within 14 d, mean (SD)[g]	4.9 (4.6)		4.8 (4.2)
Adjusted difference in days (95% CI)[b]		0.3 (–0.6 to 1.2)	
Patients with any symptoms of ongoing or relapsing infection at 28 d, No. (%)	69 (30)		67 (30)
Adjusted odds ratio (95% CI)[b]		1.0 (0.7 to 1.5)	

Abbreviations: CI, confidence interval; PCT, procalcitonin; RA, restricted activity.

[a] For the primary outcome, we provide a per-protocol analysis (ie, missing outcomes and missing covariates remain missing) and an intention-to-treat analysis (ie, replacement of missing outcomes by 14 or zero days with restrictions for patients receiving PCT-guided and standard therapy, respectively, and of missing covariates [5 missing values for education category and 1 missing value for degree of discomfort from infection at baseline] by their mean).

[b] Generalized linear mixed model with the physician practice as a random effect and patient covariates as fixed effects (age, sex, education, comorbidity, and symptom score at baseline).

[c] For all secondary outcomes, analyses are per-protocol with respect to outcome, but with any missing covariate replaced by their mean.

[d] Only for those patients who reported to have taken antibiotic medication (n=58 patients receiving PCT-guided therapy, and n=216 patients receiving standard therapy).

[e] The discomfort scale is 0 to 10.

[f] Possible adverse effects were abdominal pain, diarrhea, nausea or vomiting, and skin rash (for details, see Table 4).

[g] For patients with occupation or employment only (n=164 patients receiving PCT-guided therapy, and n=148 patients receiving standard therapy).

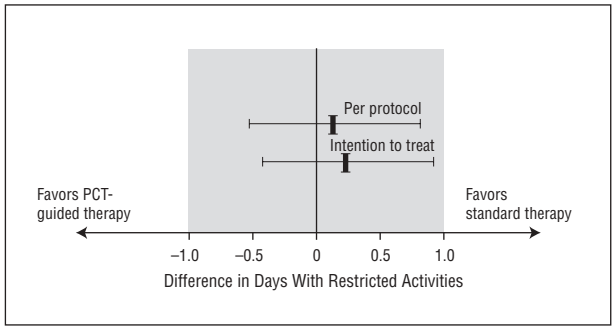

Figure 2. Adjusted difference in number of days with restrictions between groups. The error bars indicate 95% confidence intervals; PCT, procalcitonin.

SERIOUS ADVERSE EVENTS

One patient with exudative tonsillitis developed a peritonsillary abscess while receiving PCT-guided therapy the day after baseline and underwent ambulant surgery. Four patients in each therapy group were hospitalized for pneumonia within 28 days of baseline. In all of these patients, symptoms were completely resolved by day 28, except for a 44-year-old patient with a septic syndrome who was receiving PCT-guided therapy and a 34-year-old patient with a relapse of pneumonia who was receiving standard therapy. An 88-year-old patient receiving standard therapy died of herpes simplex pneumonia 11 days after baseline.

COMMENT

In this primary care trial, PCT-guided therapy was not inferior to standard therapy with respect to the number of days during which a patient's activities were restricted by a respiratory tract infection. The PCT-guided therapy markedly reduced antibiotic use: the overall antibiotic prescription rate was 72% lower, and the duration of antibiotic use was, on average, 1 day shorter than with standard therapy. The rate of patients reporting any symptoms of ongoing or relapsing infection at 28 days was identical for both therapies.

Our trial has strengths and limitations. The strengths of our trial were concealed central randomization of patients, blinding of interviewers, and sufficient power to demonstrate noninferiority in patient outcome for a novel approach to guide antibiotic therapy relative to a standard approach. Our results seem qualitatively consistent across different types of respiratory tract infections.

Table 3. Main Outcomes by Type of Respiratory Tract Infection[a]

Diagnosis	No. (%) PCT-Guided Therapy Group	No. (%) Standard Therapy Group
Community-acquired pneumonia		
Patients, No.	38	31
Prescribed antibiotics	22 (58)	31 (100)
Days with RAs within 7 d	5.4 (1.7)	5.9 (1.6)
Days with RAs within 14 d	9.9 (3.6)	11.0 (3.3)
Acute exacerbation of COPD or asthma		
Patients, No.	18	12
Prescribed antibiotics	10 (56)	11 (92)
Days with RAs within 7 d	5.8 (1.7)	5.4 (1.9)
Days with RAs within 14 d	9.6 (4.1)	9.7 (4.9)
Acute bronchitis		
Patients, No.	58	70
Prescribed antibiotics	11 (19)	69 (99)
Days with RAs within 7 d	5.1 (2.1)	5.2 (1.9)
Days with RAs within 14 d	9.4 (4.2)	9.0 (3.8)
Acute tonsillitis or pharyngitis		
Patients, No.	42	33
Prescribed antibiotics	7 (17)	33 (100)
Days with RAs within 7 d	4.3 (1.5)	3.7 (1.9)
Days with RAs within 14 d	7.2 (3.0)	6.8 (3.2)
Upper respiratory tract infection or influenza (excluding tonsillitis and pharyngitis)		
Patients, No.	76	80
Prescribed antibiotics	8 (11)	75 (94)
Days with RAs within 7 d	4.8 (2.1)	4.7 (2.0)
Days with RAs within 14 d	8.1 (3.8)	8.2 (3.7)

Abbreviations: COPD, chronic obstructive pulmonary disease; PCT, procalcitonin; RA, restricted activity.
[a]Data are given as mean (SD), except where noted.

Table 4. Symptoms Consistent With Adverse Effects From Antibiotic Therapy Among Included Patients

Symptoms	Patients, No. PCT-Guided Therapy Group (n=231)	Patients, No. Standard Therapy Group (n=224)	Median Duration, d PCT-Guided Therapy Group	Median Duration, d Standard Therapy Group
Abdominal pain	40	41	3	3
Diarrhea	47	76	3	3
Vomiting	41	35	2	3
Skin rash	15	14	3	5

Abbreviation: PCT, procalcitonin.

We achieved a high rate of follow-up, and for the primary outcome, we report both per-protocol and intention-to-treat analyses with conservative replacement of missing values in the latter. However, we were not able to blind physicians or patients in our trial. Thus, physicians may have learned from their experience with PCT testing and over the course of the trial refined their ability to select patients in need of antibiotics. Any bias of this sort should be conservative for secondary outcomes such as antibiotic prescription rate and the duration of antibiotic therapy. Some patients randomized to PCT-guided therapy might have been disappointed at not receiving an antibiotic and might therefore have felt restricted for longer by the symptoms of their infection. This bias is likely to be conservative with respect to our primary outcome.

By participating in the trial, physicians demonstrated a high degree of motivation, an interest in improving the treatment of acute respiratory tract infections, and a willingness to commit additional time for patient recruitment and data collection, which may limit the external validity of our results. There were a large number of patients who refused informed consent or were excluded owing to time constraints of physicians, which most likely reflects the high demands of the trial on patients and participating physicians. Moreover, repeated blood sampling with measurement of PCT at a central laboratory might be considered not cost-effective and too time-consuming. However, as a proof-of-concept, patient safety was of utmost importance in this trial. Based on our results, one could argue that, outside the trial, remeasurement of PCT is necessary only in patients who are not improving clinically. A "near-patient" test for PCT, which can be easily applied to a patient at an outpatient clinic or physician's office and should give a rapid result, is in development, and our trial demonstrates the potential value of an accurate test for this biomarker. Country-specific costs of PCT measurement ($10-$30) and potential savings in consumption of other health care resources should be considered to establish cost-effectiveness from the societal perspective. Cost-effectiveness is increased by reducing the number of measurements; by lowering the cost per analysis in settings with high costs for antibiotic agents; by reducing the use of less reliable tests such as C-reactive protein or leukocyte count; by considering potential effects on hospitalization rate and duration; or by including short-term costs for adverse events of antibiotic therapy, such as diarrhea, and long-term costs for a possible increase in antibiotic resistance and its monitoring.

Compared with standard therapy, PCT-guided therapy leads to a slight increase in patient discomfort at 14 days (0.8 scale points on a scale of 0 to 10). This is consistent with findings from systematic reviews[26] and a recent trial[27] that suggest that, for most patients, antibiotics probably provide modest symptomatic relief. This difference in discomfort at 14 days also seems modest in the context of the large decrease in discomfort from baseline to 14 days seen with both therapies (more than 4 scale points). In addition, with PCT-guided therapy, fewer patients experience antibiotic-related adverse effects, in particular, diarrhea.

In previous trials[11-13] using PCT-guided therapy, antibiotic use was markedly reduced in a broad spectrum of patients admitted to our hospital with lower respiratory tract infections. The present trial expands the spectrum to include primary care patients with any type of respiratory tract infection. This is also, to our knowledge, the first PCT trial employing a noninferiority design for a patient-relevant outcome.

Other trials in primary care have successfully reduced antibiotic use by delaying prescribing of antibiot-

ics; prescriptions were filled only when symptoms persisted.[27,28] To a certain extent, delayed prescription of antibiotics is also part of our PCT-based algorithm; delayed prescriptions were filled in cases of elevated PCT levels. The advantage of PCT-guided therapy over a simple delayed prescription should be the additional safety in limiting the risk of septic complications. Although randomized controlled trials are almost always too small to demonstrate safety, data from our trial and previous trials using PCT-guided therapy suggest balanced numbers of serious adverse events between intervention and control groups.[11-13]

Antibiotic prescription rates in Switzerland are low compared with those in the United States[29] or in most other European countries.[30] Northern Switzerland in particular has a low rate of antibiotic resistance, consistent with relatively low overall antibiotic use.[30] In this trial, only 18% of screened patients were considered to be in need of antibiotic therapy, and in a previous trial,[23] the overall antibiotic prescription rate was 19% in patients with respiratory tract infections. Thus, in countries with high prescription rates of 60% to 80%, such as France and the United States,[1-3] the reduction in antibiotic use with PCT-guided therapy could be substantial, in absolute terms, with a major favorable impact on bacterial resistance.[31]

In countries with low antibiotic use, primary care physicians tend to rely on the results of diagnostic tests as a safety measure when making decisions about antibiotic treatment.[32,33] However, in a randomized controlled trial, a C-reactive protein rapid test seemed not to reduce antibiotic prescriptions.[34] Moreover, the reliability of C-reactive protein or leukocyte count for guiding antimicrobial therapy is limited by their protracted response with late peak levels and a suboptimal specificity, especially in patients with systemic inflammation.[7,10] In these respects, PCT seems more accurate than the currently available biomarkers.[10] Measurement of PCT can reassure physicians and patients who are for or against antibiotic treatment and could help to break the vicious circle of medicalizing effects on patients with often self-limiting respiratory tract infections.

In conclusion, this trial suggests that as an adjunct to guidelines, PCT-guided therapy can markedly reduce the use of antibiotics for acute respiratory tract infections in primary care without compromising patient outcome. Future research needs to confirm that a near-patient test of PCT is a safe, valid, and cost-effective tool in primary care, in particular in physician populations with higher rates of antibiotic prescription. In view of the current overuse of antimicrobial therapy for often self-limiting respiratory tract infections, our findings may have important clinical and epidemiological implications.

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INVITED COMMENTARY

Clinicians treating respiratory tract infections in ambulatory settings must reconcile patients' frequent expectations for prescriptions for antibiotics (whether perceived or actual[1]) with evidence that antibiotics confer little, if any, benefit for these common and mostly viral syndromes.[2,3] Lingering concerns about primary bacterial infection, whether self-limited (eg, *Mycoplasma pneumoniae*), life-threatening (eg, *Neisseria meningiditis*[4]), clinically occult, or an impending bacterial superinfection[1] (eg, bacterial sinusitis or pneumonia), also militate against withholding antibiotics. No wonder, then, that the decision to prescribe antibiotics provokes more discomfort among office-based general practitioners than the use of any other class of drugs.[5]

An accurate test for the presence or absence of bacterial infection would therefore be welcomed by many clinicians[6] and, potentially, could lead to marked reductions in antibiotic prescriptions for respiratory tract infections. Although commonly used, C-reactive protein is insufficiently sensitive to rule out bacterial infection,[7] as are the erythrocyte sedimentation rate and white blood cell count.[8] By contrast, serum PCT, a peptide precursor to the calcium-regulating hormone, calcitonin, whose production by diverse bodily tissues leads to rapidly and persistently elevated levels during bacterial infection,[9] may be more accurate in diagnosing bacterial infections among hospitalized patients.[10] Its use in randomized controlled trials led to substantial reductions in antimicrobial use without compromising clinical outcomes among adults hospitalized with severe sepsis or septic shock[11] and exacerbations of chronic obstructive pulmonary disease,[12] adults presenting to a hospital emergency depart-