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Procalcitonin guidance and reduction of antibiotic use in acute respiratory tract infection

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ABSTRACT: Increasing worldwide development of antimicrobial resistance and the association of resistance development and antibiotic overuse make it necessary to seek strategies for safely reducing antibiotic use and selection pressure.

In a first step, in a non-interventional study, the antibiotic prescription rates, initial procalcitonin (PCT) levels and outcome of 702 patients presenting with acute respiratory infection at 45 primary care physicians were observed. The second part was a randomised controlled non-inferiority trial comparing standard care with PCT-guided antimicrobial treatment in 550 patients in the same setting. Antibiotics were recommended at a PCT threshold of 0.25 ng·mL^{-1}. Clinical overruling was permitted. The primary end-point for non-inferiority was number of days with significant health impairment after 14 days.

Antibiotics were prescribed in 30.3% of enrolled patients in the non-interventional study. In the interventional study, 36.7% of patients in the control group received antibiotics as compared to 21.5% in the PCT-guided group (41.6% reduction). In the modified intention-to-treat analysis, the numbers of days with significant health impairment were similar (mean 9.04 *versus* 9.00 for PCT-guided and control group, respectively; difference 0.04; 95% confidence interval -0.73–0.81). This was also true after adjusting for the most important confounders. In the PCT group, advice was overruled in 36 cases. There was no significant difference in primary end-point when comparing the PCT group treated as advised, the overruled PCT group and the control group (9.008 *versus* 9.250 *versus* 9.000 days; p=0.9605).

A simple one-point PCT measurement for guiding decisions on antibiotic treatment is non-inferior to standard treatment in terms of safety, and effectively reduced the antibiotic treatment rate by 41.6%.

KEYWORDS: Antibiotic policy, respiratory tract infections, therapy

The increasing worldwide development of microbial resistance together with the decreasing numbers of launches of new antimicrobial agents is a subject of major concern [1, 2]. Clearly, the primary care setting is the place with the highest antibiotic use and, therefore, selection pressure [3]. Conversely, it is well known that patients with symptoms of acute respiratory infection are particularly subject to excessive antibiotic overuse [4, 5]. This is due to the limited value of clinical signs for the diagnosis of upper and lower respiratory tract infections, including community-acquired pneumonia, the preference of physicians for supposedly safe treatment selections, and patients' expectations and requests. In view of the, at best, marginal benefits of antibiotic treatment of acute upper and lower respiratory tract infections [6], antibiotic overuse is of major concern.

Since the first pilot study published in 2004 [7], procalcitonin (PCT)-guided strategies for antibiotic treatment decision have gained much attention. For example, it could be shown that this strategy might be feasible in guiding antibiotic treatment in patients with acute exacerbations of chronic obstructive pulmonary disease (COPD) [8], as well as treatment duration in patients with community-acquired pneumonia [9] and severe infectious diseases in the intensive care unit [10].

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Most recently, this strategy was also evaluated in primary care in patients with symptoms of acute respiratory infections, also supporting the potential for substantial reductions in antibiotic use in this patient population [11].

Most of these landmark interventional trials were performed by one Swiss study group particularly engaged in this issue. Thus there is a need to reproduce this principle in other regions and settings. Moreover, shortcomings, such as intervention biases, must be overcome. In the present trial, it was investigated whether a very simple one-point PCT measurement in all consecutive patients with symptoms of acute respiratory infection presenting in primary care reduces antibiotic use compared to routine management and is non-inferior in terms of safety.

METHODS

Study description

The present study consisted of two parts. The first part was a non-interventional observational trial in order to document the prescription of antibiotics of primary care physicians in patients presenting with symptoms of respiratory tract infection. PCT levels were determined subsequently in order to estimate the potential for restriction of antimicrobial treatment.

The second part was a randomised controlled non-inferiority trial comparing the outcome of patients receiving routine care with that of those undergoing PCT-guided antimicrobial treatment.

Patient selection in both studies

The criteria for inclusion and exclusion of patients were identical in both parts of the study. Patients who were aged $\geqslant$18 yrs, suffered from symptoms of an acute respiratory tract infection according to the clinical diagnosis of the investigator and provided written informed consent were included. No attempt was made to standardise the clinical diagnosis using predefined diagnostic criteria. However, physicians were asked to make a distinct diagnosis of upper or lower respiratory tract infection.

Criteria for exclusion included: treatment with antibiotics during the previous 2 weeks, chronic liver disease, major surgery that had required hospitalisation during the last 4 weeks, autoimmune or systemic disorders, dialysis, medullary C-cell carcinoma, and other inflammatory diseases.

Both parts of the study were approved by the ethical committee of Hanover Medical School (MHH; Hanover, Germany). All participating patients provided written informed consent prior to inclusion.

In both studies, the instruction of the study centres took place during an investigators' meeting at the MHH and an additional briefing of the team at the physician's office through employees of the MHH. The trials were monitored and supervised by the Dept of Pulmonary Medicine (MHH).

Protocol of the non-interventional part of the study

All patients underwent clinical investigation. Patients who required antimicrobial treatment according to clinical judgment received a prescription. Physicians were free to decide on the kind and dosage of the prescribed antibiotics.

A venous EDTA blood specimen was taken from each patient, which was collected, centrifuged and deep-frozen until batch analysis of PCT by employees of the MHH. The results were not reported to the physicians.

Protocol of the interventional part of the study

An overview of the interventional study protocol is given in figure 1. All patients were investigated as in the first part of the study. Patients who required antimicrobial treatment according to clinical judgment received a prescription with the request to redeem the prescription only after they had been told to do so by telephone. If the final decision was made against antibiotics, the patient was asked to return the prescription to the MHH in a pre-addressed pre-paid envelope. Physicians were free to decide on the kind and dosage of the prescribed antibiotics.

Preceding studies [7–9, 11], as well as the first part of the present study, had shown that a PCT level of <0.25 ng·mL^{-1} indicates that a relevant bacterial infection of the respiratory tract is unlikely. Therefore, it was decided to use this value as a threshold for the prescription of antibiotics. According to the PCT level being below or above the threshold and the initial

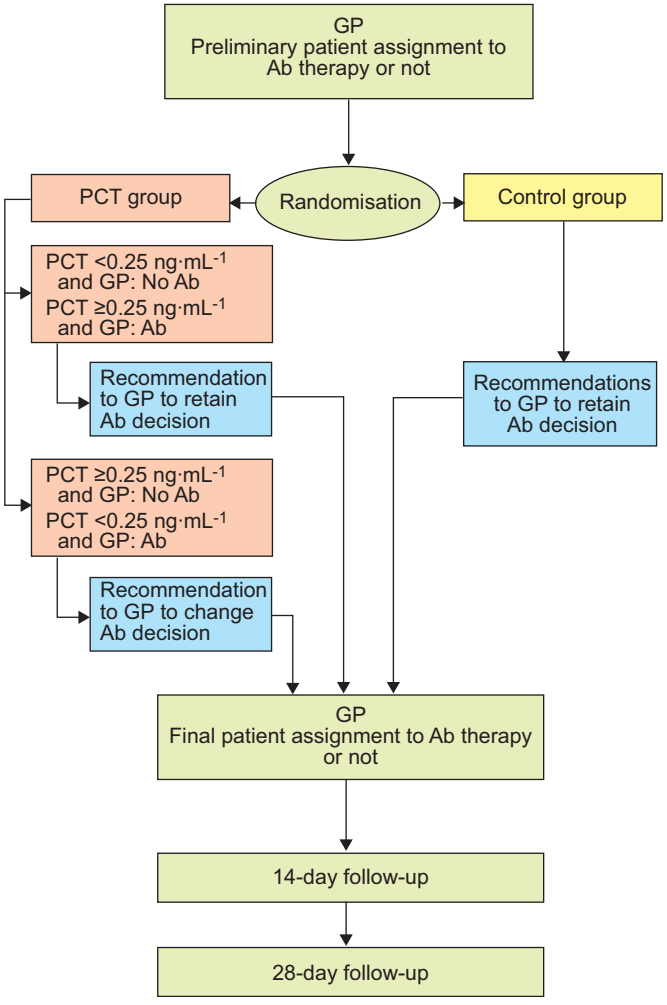

FIGURE 1. Protocol of the second interventional study. GP: general practitioner; Ab: antibiotic; PCT: procalcitonin.

decision of the treating physician regarding the prescription of an antibiotic, a recommendation to retain or change the initial decision was faxed to the physician by the central laboratory. Neither the result of the randomisation nor the exact PCT concentration was conveyed to the physician. The time from blood collection to result transfer was $\leqslant$4 h.

In view of the recommendation, the physician made their final decision regarding the prescription of an antibiotic and informed the patient accordingly by telephone. The physician was permitted to overrule the recommendation, but was asked to indicate the reasons behind this decision.

Follow-up clinical investigations were undertaken by employees of the MHH blinded to the study aim and the content of the study protocol on days 14 and 28 after inclusion in the study. These checks were executed through structured telephone interviews. They included questions on the following: persistence of symptoms of respiratory tract infection, impairment during everyday life and/or leisure activities due to the respiratory tract infection, need for additional physician contact, need for new or additional antibiotic treatment, duration and adverse effects of antibiotic treatment, and requirement for hospitalisation.

Further details about participating general practices, recruitment performance, study periods, blood sample handling, the randomisation procedure, data recorded and PCT measurement are provided in the online supplementary material.

End-points and power calculations for the interventional part of the study

The primary end-point was number of days with impairment during everyday life and/or leisure activities due to the respiratory tract infection within the first 14 days according to self-assessment. The secondary end-points included: frequency of prescription of antimicrobial treatment; number of days of antibiotic intake; number of days with antibiotic-induced side-effects; symptoms of a respiratory tract infection on days 14 and 28; revisit to the physician's office with a respiratory tract infection within 28 days; change of antibiotics within 28 days; hospitalisation within 28 days; and mortality within 28 days.

In two previous trials [7, 11], the SD for the number of days with significant health impairment due to acute respiratory tract infection at 14 days was 4 days. Given this estimate, and assuming a 5% type I (one-sided) and a 10% type II error rate, *i.e.* a power of 90%, a sample size of 275 per group was required to show that PCT-guided therapy leads to not more than an additional 1 day with significant health impairment compared to standard therapy. Calculations were performed using PASS 2005 software (NCSS, Kaysville, UT, USA).

Statistical analysis

For the primary outcome, the number of days with significant health impairment due to acute respiratory tract infection at 14 days, a modified intention-to-treat analysis is reported. The modification concerned the exclusion of patients who fulfilled the exclusion criteria (see, for example, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline topic E9, *Statistical Principles for Clinical Trials* [12]).

For the primary outcome, missing values were not replaced. In a sensitivity analysis, missing values for the primary outcome were replaced either as worst case for all (*i.e.* assuming 14 days with health impairment, scenario 1) or as worst case for PCT-guided and best case for standard therapy (*i.e.* assuming 14 days with health impairment for PCT-guided and 0 days for standard therapy).

Using univariate ANOVA, an adjusted 95% confidence interval (CI) was calculated for the difference between PCT-guided and standard therapy in the number of days with significant health impairment due to acute respiratory tract infection at 14 days. The multivariable model included age, sex, body mass index (BMI), the presence of comorbid conditions (diabetes mellitus, heart failure or COPD), smoking, alcohol and overall number of symptoms observed (symptom score), as well as the study practice, as covariates. PCT-guided therapy was regarded as non-inferior to standard therapy if the upper limit of the 95% CI for the difference between groups in number of days with significant health impairment was $<$1 day.

For the secondary outcome variables, the nonparametric Kruskal–Wallis test (continuous variables) and Pearson's Chi-squared test with simulated p-values (categorical variables) were applied. PCT-guided therapy was regarded as non-inferior to standard therapy if no significant increase was observed. Unless specified otherwise, results are reported for follow-up at 28 days.

PCT-guided therapy was regarded as effective for reduction of antibiotic use if the frequency of prescribed antibiotic therapy, number of days with antibiotics and number of days with antibiotic-induced side-effects were significantly lower than under standard therapy.

R version 2.5.1 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS and SPSS16.0 (SPSS, Inc., Chicago, IL, USA) were used for all analyses.

RESULTS

Non-interventional part of the study

Patient population

Overall, 702 patients were recruited; 41% were male and their mean age was 42.4 yrs (range 18.1–92.1 yrs). According to the clinical judgment of the attending physician, 31% had upper and 86% lower respiratory tract infection. Chest radiography was performed in only 4.3%, and no patient was hospitalised.

Follow up at day 28

Of the patients, 22.5% revisited the physician. Three were subsequently hospitalised (one had malignant glioblastoma) and 63.8% were incapable of working for a mean of 6.3 days (range 1–28 days). No patient died.

Antimicrobial treatment

A total of 189 (26.9%) patients were treated with antibiotics. An additional 24 (3.4%) received antibiotics during follow-up. Thus overall 213 (30.3%) received antibiotics during the course of their illness.

PCT value distribution

The median PCT concentration was 0.050 ng·mL^{-1} (interquartile range (IQR) 0.031–0.070 ng·mL^{-1}), whereas 643 (91.6%)

patients had PCT levels of <0.1 ng·mL^{-1}, 53 (7.5%) of 0.1–0.25 ng·mL^{-1} and only six (0.9%) of >0.25 ng·mL^{-1}. Of these six patients, only two received antibiotics. Thus, provided that the outcome would be similar, the potential for reduction of antimicrobial treatment was found to be 99.1%.

Interventional part of the study

Patient population

Overall, 571 patients provided informed consent, but 21 were excluded due to meeting exclusion criteria. These were: prior use of antibiotics (n=1), small cell bronchial cancer (n=1), autoimmune disease (n=6), systemic disease (n=7), other inflammatory disease (n=1), severe liver cirrhosis (n=1), portal hypertension (n=1), loss of sample (n=1), and withdrawn consent (n=2). Results are reported for the final analysis set of 550 patients. The baseline clinical characteristics, comorbid conditions and clinical symptoms are listed in tables 1 and 2 of the online supplementary material. These were comparable in both groups. The clinical diagnoses assigned after initial evaluation are listed in table 1. Overall, 34.5 and 37.1% of episodes were classified as lower respiratory tract infections in the PCT and control group, respectively.

Results of PCT determination

The total median PCT level was 0.056 (IQR 0.034) ng·mL^{-1}, with no significant differences between groups (PCT *versus* control group: 0.054 (0.032) *versus* 0.057 (0.034) ng·mL^{-1}; p=0.795). A total of 495 (90.0%) patients exhibited PCT levels of <0.1 ng·mL^{-1}, 53 (9.6%) of 0.1–0.25 ng·mL^{-1} and only two (0.4%) of ⩾0.25 ng·mL^{-1}, both in the control group.

Proportion of patients receiving antimicrobial treatment

After initial clinical evaluation, 84 (30.5%) patients were assigned to antibiotics in the PCT group and 89 (32.4%) in the control group (p=0.701). In the PCT group, the advice following PCT determination was not to give antibiotics in any patient; however, the advice was overruled in 36 (13.1%) patients. The reasons for overruling included: signs of infection (n=14), patient's request (n=5), results of chest radiography (n=2), purulent sputum (n=1), strong cough (n=1), purulent tonsillitis (n=1), severe obstructive bronchitis (n=1), and not specified (n=11).

Up to days 14 and 28, an additional nine and five patients in the PCT group received antibiotics in the group with an initial decision not to treat, and eight and one patient in the group not treated following recommendation after PCT measurement, a total of 59 (21.5%) patients on antibiotics as opposed to 101 (36.7%) in the control group (p=0.0005) (tables 2 and 3). Only one out of two patients in the control group with a PCT level of ⩾0.25 ng·mL^{-1} received an antibiotic. Thus, in spite of overruling, the PCT strategy permitted at least for a 41.6% reduction in antibiotic use.

Macrolides, aminopenicillin and doxycyclin accounted for 81% of prescriptions. Fluoroquinolones were only administered in 7.6%. There were no significant differences in terms of antibiotic selection between the two groups (table 3 of online supplementary material).

Primary end-point

All patients were treated according to the protocol. In the modified intention-to-treat analysis, excluding patients not meeting the inclusion criteria and not replacing missing values (n=1 missing in the PCT group and n=3 in the control group), the numbers of days with significant health impairment were similar (mean 9.04 *versus* 9.00 for PCT-guided and control group, respectively; difference 0.04; 95% CI -0.73–0.81). This was also true after adjusting for age, sex, BMI, symptom score, comorbid conditions, smoking, alcoholism and study site (9.10 *versus* 8.89; difference -0.21; 95% CI -0.53–0.95) (fig. 2).

Sensitivity analysis for primary end-point

When missing values were replaced by worst case for all (14 days' impairment) or by worst for PCT and best for control, the difference between PCT-guided and control group in number of days with impairment was -0.05 (95% CI -0.81–0.71, or mean of 9.06 days for PCT-guided *versus* 9.11 days for control) and 0.25 (95% CI -0.52–1.03; 9.06 days for PCT-guided and 8.80 days for control), respectively. The non-inferiority margin was, therefore, only slightly overdrawn for the second extreme scenario.

TABLE 1 Diagnosis of primary care physicians after initial clinical evaluation

	Total	PCT	Control	p-value
Subjects n	550	275	275	
Acute sinusitis	141	78	63	0.170
Otitis media	13	4	9	0.256
Pharyngitis	54	26	28	0.886
Tonsillitis	25	14	11	0.677
Laryngitis	43	24	19	0.527
Influenza	8	5	3	0.728
Common cold	318	159	159	1.000
Acute bronchitis	186	91	95	0.793
Pneumonia	3	0	3	0.250
AECOPD	6	2	4	0.689
AE-asthma	3	2	1	1.000

Data are presented as absolute numbers. PCT: procalcitonin; AECOPD: acute exacerbation (AE) of chronic obstructive pulmonary disease.

TABLE 2 Initial clinical decisions, procalcitonin (PCT)-guided recommendations and final clinical decisions in the intervention group

Initial decision	PCT determination	Reassessment	
		14 days	28 days
No antibiotic (n=191)			
<0.25 ng·mL^{-1} PCT	191	182	177
⩾0.25 ng·mL^{-1} PCT			
Antibiotic (n=84)			
<0.25 ng·mL^{-1} PCT	36	44	45
⩾0.25 ng·mL^{-1} PCT			

Data are presented as absolute numbers.

TABLE 3 Patients without and with antibiotics at different time-points

Without antibiotics	
After initial examination	191 (69.5)
Recommendation	191+84=275 (100.0)
After PCT determination	191+48=239 (86.9)
Up to day 14	222 (80.7)
Up to day 28	215 (78.2)#
With antibiotics	
Up to day 28	59 (21.5)

Data are presented as n (%). #: one patient lost to follow-up.

In the PCT group, advice was overruled in 36 cases. There was no significant difference in primary end-point when comparing the PCT group as advised, the PCT group overruled, and the control (9.008 *versus* 9.250 *versus* 9.000 days; p=0.9605).

Secondary end-points

After 28 days, the number of patients with persisting respiratory symptoms, respiratory reassessment rates for any cause or for respiratory symptoms, and hospitalisation rates were not different when comparing the PCT group and controls. No patient died. This was also true when comparing the PCT group treated as advised (initially without antibiotics and overruled (initially or up to day 28)) (table 4).

The number of days of antibiotic intake, number of days with antibiotic-induced side-effects and change of antibiotics within 28 days did not differ in the subgroups receiving antimicrobial treatment (table 4).

DISCUSSION

The main results of the present study are as follows. 1) Although the rate of patient treatment with antibiotics was consistently relatively low (~30%), there is huge potential for further reduction of antibiotic treatment. 2) A simple PCT-guided strategy of decisions on antibiotic treatment, including the option of clinical overruling, is non-inferior to standard treatment in terms of safety, and effectively reduced the antibiotic treatment rate by 41.6%.

The primary end-point of non-inferiority as regards number of days of impairment was met in the modified intention-to-treat analysis, and this result remained robust in a subsequent sensitivity analysis handling four missing cases at disadvantage to the PCT strategy. Finally, all secondary end-points at 28 days were also met, increasing confidence in the safety of the PCT strategy.

The present study confirms and extends a previous report demonstrating that a PCT-guided strategy leads to reduced antibiotic use without compromising patient outcome [11]. Several important differences to the previous study in study design deserve comment. First, the present study comprised a non-interventional part in order to reflect the real-life practice of antibiotic prescription in patients with symptoms of respiratory tract infection. The proportion of patients treated with antibiotics in this part of the study was very similar to that in the control arm of the interventional part (30.3 and

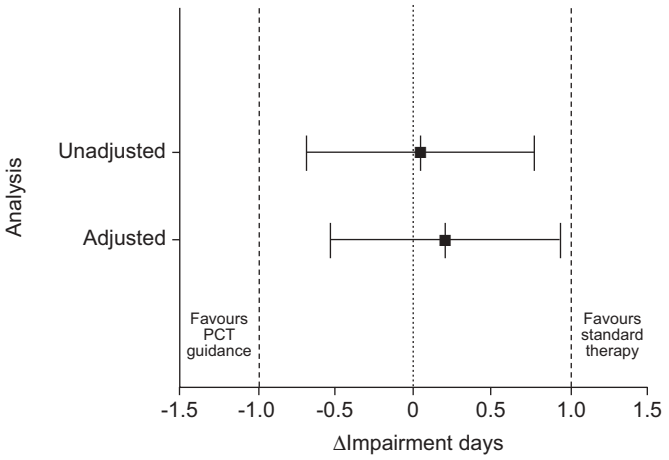

FIGURE 2. Primary end-point analysis at 14 days: number of days with significant health impairment. Data are presented as difference (Δ); horizontal bars represent the 95% confidence interval (CI); ------: Δ of 1 day. Procalcitonin (PCT)-guided therapy was regarded as non-inferior to standard therapy if the upper limit of the 95% CI was <1 day.

36.7%), increasing the validity of the comparator to the intervention. Secondly, patients were included consecutively, prior to clinical examination and any decision to treat with antibiotics. Therefore, the rate of patients finally treated with antibiotics was consistently much lower (30.3 and 36.7 *versus* 97% in the previous study). However, despite this absence of pre-selection, the PCT-guided strategy still reduced antibiotic use by almost a half (41.6%). Thirdly, the previous study included extensive training of the participating physicians in terms of not only briefing but also teaching in evidence-based guidelines. This intervention might open a bias towards antibiotic restriction. In the present study, any intervention affecting routine clinical attitudes was avoided, thus minimising any intervention bias. Fourthly, it was decided to rely on one cut-off for antibiotic decisions (PCT of >0.25 ng·mL^{-1}), thereby simplifying the decision algorithm in clinical practice. It could be shown that even this higher threshold is safe, obviating the need for an intermediate threshold (0.1–0.25 ng·mL^{-1}), with its inherently ambiguous treatment recommendations. Finally, in contrast to the previous study permitting a second PCT measurement, the PCT-guided strategy in the present study was limited to one PCT measurement in order to keep the study design closer to a realistic clinical setting, *i.e.* more cost-effective and less time-consuming. This strategy was shown to be equally safe.

Indeed, these differences account for important extensions of our confidence in PCT-guided strategies to reduce antibiotic use. It was possible to capture robust data on antibiotic prescription in primary care. The present study design permitted elimination of the potential artefact of extensive antibiotic prescription rates by including all consecutive patients prior to a decision for antibiotic treatment and minimisation of the intervention bias that is particularly problematic in nonblinded studies. Moreover, it mirrored more closely routine settings by simplifying treatment algorithms and reducing numbers of measurements.

Even so, the use of PCT in a population with such a mild illness might be questioned. However, we argue that the

TABLE 4 Secondary end-points in patients treated with antibiotics, initially and up to day 28

	Control group	PCT group			p-value#
		All	As advised	Overruled	
Lost to follow-up	3	1			
Ab prescription at baseline and during follow-up	101	59	23	36	**0.0005**
Time on Ab days	7.7±3.3	7.8±2.8	8.6±2.9	7.3±2.6	0.680
Ab side-effects					
Subjects	16	11	3	8	0.331
Time days	6.1±3.7	5.6±2.2	5.6±1.5	5.6±2.5	0.940
Time incapable of working days	3.9±4.9	4.3±4.8	4.2±4.7	4.9±5.2	0.066
RTI symptoms					
At day 14	132 (48.0)	120 (43.6)	107 (45.0)	13 (35.1)	0.296
At day 28	87 (31.6)	76 (27.6)	67 (28.1)	9 (24.3)	0.298
Reassessment for any cause	107 (38.9)	108 (39.3)	92 (38.5)	16 (44.4)	1.000
Reassessment with RTI symptoms	65 (23.6)	63 (22.9)	54 (22.6)	9 (25.0)	0.917
Ab change during follow-up	3	1	1	0	
Hospitalisation	1	0	0	0	
Mortality	0	0	0	0	

Data are presented as mean±SD, n (%) or absolute number. PCT: procalcitonin; Ab: antibiotic; RTI: respiratory tract infection. #: PCT *versus* control.

setting selected in the present study implies a major potential for the reduction of antibiotic use, and the findings of both parts of the study clearly support this notion. Another concern may be the limited data on the operative characteristics of PCT in primary care. Notwithstanding, it is important to realise that the strength of the PCT-guided strategy is related to its ability to predict patients in need of antibiotics (and those who can safely be treated without them), thereby obviating the many limitations inherent to the validation of diagnostic tests in patient populations with mild illness.

An important common issue in both studies is the permissibility of clinical overruling when applying PCT-guided strategies. Although overruling was observed in only a minority of patients in both studies (15% in the previous study and 13% in the present one), no physician would feel comfortable without this option when caring for their patients. Some of these decisions were reported to have been made at the patient's request. Such behaviour may be subject to further intervention strategies to convince patients of the advantages of not using antibiotics [13–16]. It would be important to examine the remaining decisions to treat with antibiotics after such interventions in more detail in order to obtain information about possible true underlying clinical differences. A further substantial reduction in antibiotic use beyond the level achieved in the present study will only be possible by paying attention to those patients assigned to antibiotics despite PCT levels below the chosen threshold.

A limitation of the present study is the absence of PCT levels above the cut-off value in the intervention group. This finding is a result of the strength of the study design, which included all consecutive patients with symptoms of acute respiratory infection, not only those judged to be in need of antibiotics. Indeed, the number of patients with a diagnosis of pneumonia was very low. The number of patients above the threshold of 0.25 $ng \cdot mL^{-1}$ was not explicitly reported in the previous study. However, both studies together make it probable that values above this threshold are relatively rare and most probably not a safety problem in a PCT-guided strategy for reducing antibiotic use. Clinical overruling may still permit for compensation of potential errors following PCT-guided algorithms.

It is concluded that a PCT-guided strategy applied in primary care in unselected patients presenting with symptoms of acute respiratory infection reduces antibiotic use by 41.6% without compromising patient outcome. It is simple enough, in terms of treatment algorithm and measurement procedure, to be applied in routine settings. Further reductions beyond the gains of this PCT-guided strategy seem possible, but require physician and patient education programmes and an investigation into the reasons behind clinical overruling.

CLINICAL TRIAL

This study is registered at ClinicalTrials.gov (trial numbers NCT00827060 and NCT00688610).

STATEMENT OF INTEREST

Statements of interest for O. Burkhardt, S. Giersdorf, U. Haagen, O. Hartmann, S. Ewig, K. Wegscheider and T. Welte can be found at www.erj.ersjournals.com/misc/statements.dtl

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