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A simple procalcitonin-guided strategy results in safe reductions of antibiotic use in patients with symptoms of acute respiratory tract infections in primary care

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ABSTRACT

Background. Worldwide increasing development of antimicrobial resistance and the association of resistance development and antibiotic overuse force to look for strategies to safely reduce antibiotic use and selection pressure.

Methods. In a first step we observed in a non-interventional study the antibiotic prescription rates, initial values for Procalcitonin and the outcome of 702 patients presented with ARTI at 45 primary care physicians. The second part was a randomized, controlled non-inferiority trial comparing standard care with PCT-guided antimicrobial treatment in 550 patients in the same setting. Antibiotics were recommended at a threshold of PCT 0.25 ng/mL. Clinical overruling was allowed. The primary endpoint was non-inferiority for days with significant health impairment after 14 days.

Results. Antibiotics were prescribed in 30.3% of the 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, days with significant health impairment were similar (average 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 the most important confounders. In the PCT group, advice was overruled in 36 cases. There was no significant difference in primary endpoint when comparing the PCT group as adviced, the PCT group overruled, and the control (9.008 versus 9.250 versus 9.000 days, p = 0.9605).

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

The increasing development of microbial resistance worldwide together with decreasing launches of new antimicrobial agents is subject to major concern (1,2). Clearly, the primary care setting is the place with the highest antibiotic use and, therefore, selection pressure (3). On the other hand, it is well known that particularly patients with symptoms of acute respiratory infection are 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 infections including community-acquired pneumonia, the preference of physicians for supposedly safe treatment selections, and patient's expectations and requests. In view of the at best marginal benefits of antibiotic treatment of acute upper and lower respiratory infections (6), antibiotic overuse is of major concern.

Since the first pilot study published in 2004 (7), PCT-guided strategies for antibiotic treatment decisions have gained much attention. E.g., it could be shown that this strategy might be feasible in guiding antibiotic treatment in patients with acute exacerbations of COPD (8) as well as treatment duration in patients with community-acquired pneumonia (9) and severe infectious diseases in the ICU (10). Most recently, this strategy was also evaluated in primary care in patients with symptoms of acute respiratory infections, supporting the potential for substantial reductions in antibiotic use also 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 as well. Moreover, shortcomings such as intervention biases must be overcome. In this trial, we 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 study consisted of two parts. The first part was a non-interventional observational trial in order to document the prescriptions of antibiotics of primary care physicians in patients presenting with symptoms of respiratory tract infections. PCT values were determined subsequently in order to estimate the potential for restrictions of antimicrobial treatment.
The second part was a randomized, controlled non-inferiority trial comparing the outcome of patients receiving routine care with those undergoing PCT-guided antimicrobial treatment.

Patient selection in both studies

Criteria for inclusion and exclusion of patients were identical in both parts of the study. Patients who were at least 18 years old, suffered from symptoms of an acute respiratory tract infection according to clinical diagnosis of the investigator and gave written informed consent were included. No attempt was made to standardize the clinical diagnosis by predefined diagnostic criteria. However, physicians were asked to make a distict diagnose of upper or lower respiratory infection.

Criteria for exclusion were: pretreatments with antibiotics during the last two weeks, chronic liver diseases, major surgery that required hospitalization during the last four weeks, autoimmune or systemic disorders, dialysis, medullary C-cell-carcinomas, and other inflammatory diseases.

The study was approved in both parts by the ethical committee of the “Medizinische Hochschule Hannover”, Germany (Hanover Medical School, MHH). All participating patients gave written informed consent prior to inclusion. In both studies the instruction of the study centers 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 department of pneumology of the MHH.

Protocol of the non-interventional part of the study

All patients received a clinical investigation. Patients who required antimicrobial treatment according to clinical judgment received a prescription. Physicians were free to decide on 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 procalcitonin 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 phone. If the final decision was made against antibiotics, the patient was asked to return the prescription in a pre-addressed and pre-paid envelope to MHH. Physicians were free to decide on kind and dosage of the prescribed antibiotics.

Preceding studies (7-9,11) as well as the first part of the study had shown that a PCT value < 0.25 ng/ml indicates that a relevant bacterial infection of the respiratory tract is unlikely. Therefore, we decided to use this value as a threshold for the prescription of antibiotics. According to the PCT value below or above the threshold and the initial decision of the treating physician regarding the prescription of an antibiotic, a recommendation was faxed by the central laboratory to the physician to retain or change the initial decision. Neither the result of the randomization nor the exact PCT value were conveyed to the physician. The time from blood collection to the result transfer was no longer than 4 hours.

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

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

Further details about participating general practices, recruitment performance, study periods, blood sample handling, randomization procedure, data recorded and procalcitonin measurement are provided in the online supplement.

Endpoints and power calculations for the interventional part of the study

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

In two previous trials (7,11), the standard deviation 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 (1-sided) and a 10% type II error rate, i.e. a power of 90%, we required a sample size of 275 per group to show that PCT-guided therapy leads to not more than one additional day with significant health impairment compared to the standard therapy. Calculations were performed using the software PASS 2005 (NCSS, Kaysville, Utah).

Statistical Analysis

For the primary outcome, the number of days with significant health impairment due to acute respiratory tract infection at 14 days, we report a modified intention-to-treat analysis. The modification concerned the exclusion of patients who did fulfil the exclusion criteria (see e.g. ICH guidelines E9 'Statistical Principles for Clinical Trials') (12).

For the primary outcome, missing values were not replaced. In a sensitivity analysis, missing values in 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 zero days for standard therapy).

Using a univariate analysis of variance, we calculated an adjusted 95% confidence interval (CI) 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, BMI, the presence of comorbidities (diabetes mellitus, heart failure or COPD), smoking, alcohol and the 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% confidence interval for the difference between groups in days with significant health impairment was below 1 day.

For the secondary outcome variables, the non-parametric Kruskal-Wallis test (continuous variables) and Person's Chi^2 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. If not further mentioned, 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, days with antibiotics and days with antibiotics induced side effects were significantly lower than under standard therapy.

We used R (version 2.5.1, http://www.r-project.org) and SPSS (SPSS Inc., Chicago, Illinois) and SPSS16.0 (SPSS Inc., Chicago, Illinois, USA) for all analyses.

RESULTS

Non interventional part of the Study

Patient population

Overall, 702 patients were recruited. 41% were male, mean age was 42.4 years (range 18.1-92.1). According to the clinical judgment of the attending physician, 31% had upper and 86% lower respiratory tract infection. A chest radiograph was performed in only 4.3%, no patient was hospitalized.

Follow up at day 28

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

Antimicrobial treatment

189 patients (26.9%) 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 value was 0.050 (IQR 0.031-0.070), whilst 643 patients (91.6%) had PCT values < 0.1 ng/mL, 53 (7.5%) had values 0.1 – 0.25 ng/mL, and only six patients (0.9%) had values > 0.25 ng/mL. 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 gave informed consent, but 21 were excluded because of meeting exclusion criteria. These were: prior 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), consent withdrawn (n=2). Results are reported for the final analysis set of 550 patients. The clinical baseline characteristics, comorbidities and the clinical symptoms are listed in tables 1 and 2 (online supplement). 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 value was 0.056 (IQR 0.034) ng/mL, with no significant differences between groups (PCT group: 0.054 (IQR 0.032) versus control group 0.057 (IQR 0.034) ng/mL, p = 0.795). 495 patients (90.0%) had PCT values < 0.1 ng/mL, 53 (9.6%) had values 0.1 – 0.25 ng/ml, only two patients (0.4%) had a value ≥ 0,25 ng/mL, both in the control group.

Proportion of patients receiving antimicrobial treatment

After initial clinical evaluation, 84 patients (30.5%) were assigned to antibiotics in the PCT group and 89 patients (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 patients (13.1%). The reasons for overruling included: signs of infection (n=14), patient's request (n=5), result of chest radiograph (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 9 and 5 patients in the PCT group received antibiotics in the group with initial decision not to treat, and 8 and 1 patient in the group not treated following recommendation after PCT measurement, summing up to 59 patients (21.5%) on antibiotics, as opposed to 101 (36.7%) in the control group (p = 0.0005) (tables 2a and b). Only 1 of 2 patients in the control group

with PCT ≥ 0,25 ng/mL received an antibiotic. Thus, in spite of overruling the PCT strategy allowed at least for a 41.6% reduction of antibiotics.

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 in both groups (table 3 online supplement).

Primary endpoint

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 and n=3 missing in the PCT and control group, respectively), days with significant health impairment were similar (average 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, gender, BMI, symptom score, comorbidities, smoking, alcoholism, and study site (9.1 versus 8.89, difference - 0.21, 95% CI -0.53 – 0.95) (figure 2).

Sensitivity analysis for primary endpoint

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 days with impairment was -0.05 (95% CI -0.81 – 0.71, or average days 9.06 for PCT-guided versus 9.11 for control) and 0.25 (95% CI -0.52 – 1.03, 9.06 for PCT-guided and 8.80 for control), respectively. The non-inferiority margin was therefore only slightly overdrawn for the second, extreme scenario.

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

Secondary endpoints

After 28 days, number of patients with persisting respiratory symptoms, respiratory reassessment rates for any cause, for respiratory symptoms, and hospitalization rates were not different when comparing PCT group and controls. No patient died. This was also true when comparing the PCT group treated as adviced (initially without antibiotics and overruled (initially or up to day 28) (table 3).

The days of antibiotic intake, days with antibiotic-induced side-effects and change of antibiotics within 28 days was not different in the subgroups receiving antimicrobial treatment (table 3).

DISCUSSION

The main results of the present study are as follows: 1) although the rate of patients treated with antibiotics was consistently relatively low (around 30%), there is a 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 antibiotic treatment rate by 41.6%.

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

Our 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, our study comprised a non-interventional part in order to reflect 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 36.7%), increasing the validity of the comparator to the intervention. Second, 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 preselection, the PCT-guided strategy still reduced antibiotic use by almost one half (41.6%). Third, the previous study included an extensive training of the participating physicians not only in terms of briefing but also of teaching in evidence based-guidelines. This intervention might open a bias towards antibiotic restriction. In our study, any intervention on routine clinical attitudes was avoided,

thus minimizing any intervention bias. Forth, we decided to rely on one cut-off for antibiotic decisions (PCT > 0.25 ng/ml), thereby simplifying the decision algorithm in clinical practice. We could show that even this higher threshold is safe, obviating the need for an intermediate threshold (0.1 – 0.25 ng/ml) and its inherent ambiguous treatment recommendations. Finally, in contrast to the previous study allowing for a second PCT measurement, the PCT-guided strategy in our 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.

In fact, these differences account for important extensions of our confidence in PCT-guided strategies to reduce antibiotic use. We were able to capture robust data on antibiotic prescription in primary care. Our study design allowed to eliminate the potential artefact of extensive antibiotic prescription rates by including all consecutive patients prior to a decision for antibiotic treatment and to minimize the intervention bias which is particularly problematic in non-blinded studies. Moreover, it mirrored more closely routine settings by simplifying treatment algorithms and reducing measurements.

Even so, one might question the use of PCT in a population with such a mild illness. However, we argue that the setting selected in our 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 operative characteristics of PCT in primary care. Notwithstanding, it is important to realize 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), thereby obviating the many limitations inherent to the validation of diagnostic tests in patient populations with mild illness.

An important issue in common of both studies is to allow for clinical overruling when applying PCT-guided strategies. Although overruling was observed in only

a minority of patients in both studies (15% in the previous and 13% in our study), no physician would feel comfortable without this option when caring for his patients. Some of these decisions were reported to have been made on patient's request. Such behaviour may be subject to further intervention strategies to convince patients about the advantages not to use antibiotics (13-16). The remaining decisions to treat with antibiotics after such interventions would be important to be examined more in detail in order to get information about possible true clinical differences behind. A further substantial reduction of antibiotic use beyond the level achieved in our study will only be possible paying attention to those patients assigned to antibiotics despite PCT-values below the threshold.

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

We conclude 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 also in routine settings. Further reductions beyond the gains of this PCT-guided strategy seem possible but require physician and patient education programs and an investigation about the reasons behind clinical overruling.

Word count for body of the manuscript: 3.428

REFERENCES

(1) Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, Scheld M, Spellberg B, Bartlett J. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. Clin Infect Dis. 2009; 48: 1-12

(2) http://www.rivm.nl/earss/

(3) van de Sande-Bruinsma N, Grundmann H, Verloo D, Tiemersma E, Monen J, Goossens H, Ferech M; European Antimicrobial Resistance Surveillance System Group; European Surveillance of Antimicrobial Consumption Project Group: Antimicrobial drug use and resistance in Europe. Emerg Infect Dis. 2008; 14: 1722-1730

(4) Goossens H, Ferech M, Vander Stichele R, Elseviers M; ESAC Project Group: Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. Lancet 2005; 365: 579-578

(5) Gonzales R, Malone DC, Maselli JH, Sande MA: Excessive antibiotic use for acute respiratory infections in the United States. Clin Infect Dis. 2001; 33: 757-762

(6) Smucny J, Fahey T, Becker L, Glazier R: Antibiotics for acute bronchitis. Cochrane Database Syst Rev. 2004; 4:CD000245

(7) Christ-Crain M, Jaccard-Stolz D, Bingisser R, Gencay MM, Huber PR, Tamm M, Müller B: Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. Lancet. 2004; 363: 600-607.

(8) Stolz D, Christ-Crain M, Bingisser R, Leuppi J, Miedinger D, Müller C, Huber P, Müller B, Tamm M: Antibiotic treatment of exacerbations of COPD: a randomized, controlled trial comparing procalcitonin-guidance with standard therapy.Chest. 2007; 131: 9-19

(9) Christ-Crain M, Stolz D, Bingisser R, Müller C, Miedinger D, Huber PR, Zimmerli W, Harbarth S, Tamm M, Müller B: Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial.Am J Respir Crit Care Med. 2006; 174: 84-93

(10) Nobre V, Harbarth S, Graf JD, Rohner P, Pugin J : Use of procalcitonin to shorten antibiotic treatment duration in septic patients: a randomized trial. Am J Respir Crit Care Med. 2008; 177: 498-505

(11) Briel M, Schuetz P, Mueller B, Young J, Schild U, Nusbaumer C, Périat P, Bucher HC, Christ-Crain M: Procalcitonin-guided antibiotic use vs a standard approach for acute respiratory tract infections in primary care. Arch Intern Med. 2008; 168: 2000-2007

(12) European Medicine Agency. Statistical principles for clinical trials. …

(13) Macfarlane JT, Holmes WF, Macfarlane RM: Reducing reconsultations for acute lower respiratory tract illness with an information leaflet: a randomized controlled study of patients in primary care. Br J Gen Pract. 1997; 47: 719-722

(14) Dowell J, Pitkethly M, Bain J, Martin S: A randomised controlled trial of delayed antibiotic prescribing as a strategy for managing uncomplicated respiratory tract infection in primary care. Br J Gen Pract 2001; 51: 200-205

(15) Macfarlane J, Holmes W, Gard P, Thornhill D, Macfarlane R, Hubbard R: Reducing antibiotic use for acute bronchitis in primary care: blinded, randomised controlled trial of patient information leaflet. BMJ 2002; 324: 91-94

(16) Little P, Rumsby K, Kelly J, Watson L, Moore M, Warner G, Fahey T, Williamson I: Information leaflet and antibiotic prescribing strategies for acute lower respiratory tract infection: a randomized controlled trial. JAMA. 2005; 293: 3029-3035

Table 1. Diagnosis of primary care physicians after initial clinical evaluation

AE = acute exacerbation

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

Table 2 a and b.

a. Initial clinical decisions, PCT guided recommendations, and final clinical decisions in the intervention group

	Initial clinical decision: no antibiotic: n = 191		
PCT ng/mL	after PCT determination	after reassessment up to 14 days, n =9	after reassessment up to 28 days, n = 5
< 0.25	191	182	177
≥ 0.25	-	-	-
	Initial clinical decision: antibiotic: n = 84		
PCT ng/mL	after PCT determination	after reassessment up to 14 days, n = 8	After reassessment up to 28 days, n = 1
< 0.25	36	44	45
≥ 0.25	-	-	-

b. Resulting numbers of patients without and with antibiotics at different time points

Patients …	n	%
… without antibiotics after initial examination	191	69.5
… recommended to withhold antibiotics	191 + 84 = 275	100.0
… without antibiotics after PCT determination	191 + 48 = 239	86.9
… without antibiotics up to day 14	222	80.7
… without antibiotics up to day 28	215*	78.2
… with antibiotics up to day 28	59	21.5

*1 patient was lost to follow-up

Table 3.
Secondary endpoints in patients treated with antibiotics initially and up to day 28

Follow up 28 days					
	Control group lost to follow up n=3	**PCT group** lost to follow up n=1			**p value** PCT vs Control
		all	**as adviced by PCT**	**PCT over ruled**	
Abx prescriptions at baseline and during follow up	**101**	**59**	23	36	**0.0005**
Days on Abx - mean (SD)	**7.7 (3.3)**	**7.8 (2.8)**	8.6 (2.9)	7.3 (2.6)	0.680
Days with side effects due to Abx therapy - mean (SD)	**6.1 (3.7) n=16**	**5.6 (2.2) n=11**	5.6 (1.5) n=3	5.6 (2.5) n=8	0.940 0.331
Days incapable of working - mean (SD)	**3.9 (4.9)**	**4.3 (4.8)**	4.2 (4.7)	4.9 (5.2)	0.066
Patients with RTI symptoms	**87 (31.6%)**	**76 (27.6%)**	67 (28.1%)	9 (24.3%)	0.298
Patients with RTI symptoms at follow up day 14	132 (48.0%)	120 (43.6%)	107 (45.0%)	13 (35.1%)	0.296
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
Abx change during follow up	**3**	**1**	1	0	
Hospitalisation	**1**	**0**	0	0	
Mortality	**0**	**0**	0	0	

Figure 1.
Protocol of the second interventional study

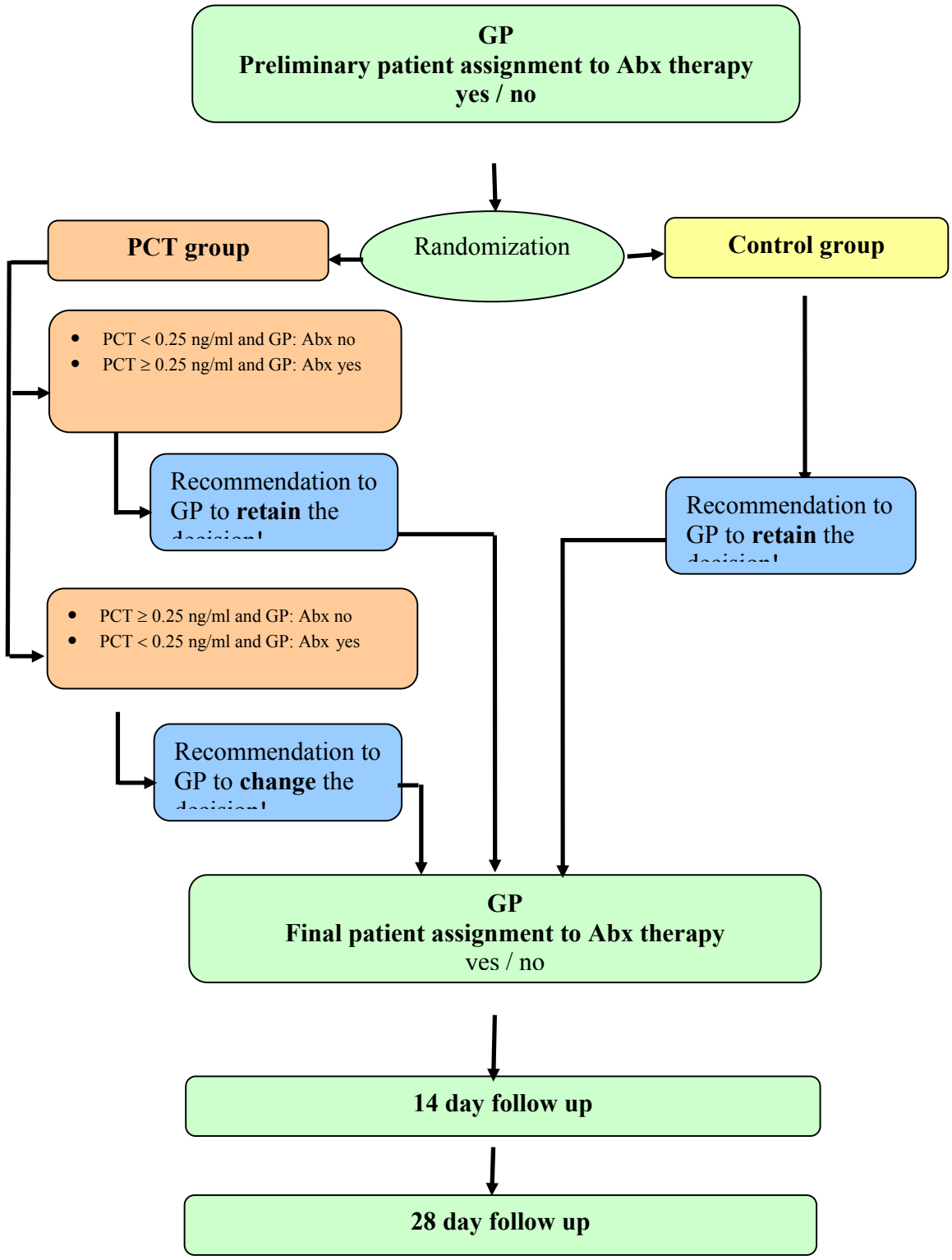
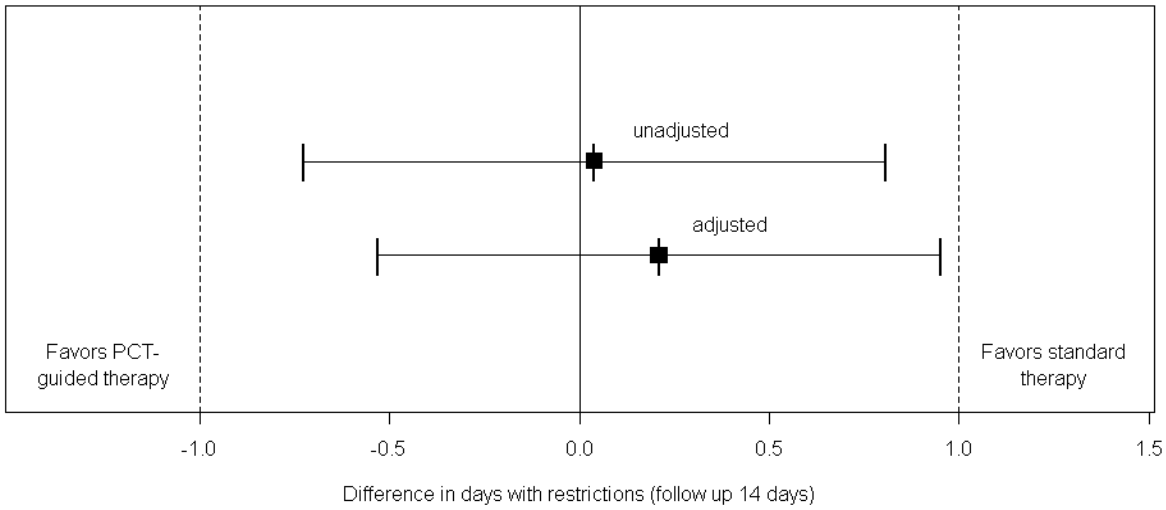


Figure 2.
Primary endpoint analysis at 14 days: days with significant health impairment



Authors Contributions:

Olaf Burckhardt and Tobias Welte conducted the study and were responsible for the study development, data documentation, data interpretation, and the finalisation of the manuscript

Santiago Ewig was responsible for data interpretation and the preparation of the final manuscript

Ulrike Haagen und Sven Giersdorf advised during studyconductind, were responsible for Procalcitonin measurements, statistical analysis, and corrections of the manuscript

Karl Wegscheider was mainly responsible for the statistical analysis

Conflict of Interest Statement:
Tobias Welte has received research grants and fees for lectures from BRAHMS AG.
Olaf Burckhardt has received research grants fromBRAHMS AG
Santiago Ewig has received fees for lectures from BRAHMS AG
Karl Wegscheider hasreceived researchgrants from BRAHMS AG
Ulrike Haagen and Sven Giersdorf are employees of BRAHMS AG, the manufacturer of the assay B.R.A.H.M.S PCT sensitive KRYPTOR, B.R.A.H.M.S AG, Henningsdorf, Germany.