PART I
PROCALCITONIN-GUIDED THERAPY

CHAPTER 5

PROCALCITONIN-GUIDED ANTIBIOTIC THERAPY IN PATIENTS WITH FEVER IN A GENERAL EMERGENCY DEPARTMENT POPULATION: A MULTICENTER NONINFERIORITY RANDOMIZED CLINICAL TRIAL (HITEMP STUDY)

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ABSTRACT

Introduction

Importance: Procalcitonin(PCT)-guided therapy may reduce the number of antibiotics prescribed, but the effect in a general emergency department(ED) population is unclear.

Objective: To determine efficacy, safety, accuracy and economic consequences of PCT-guided therapy in ED patients with fever.

Methods

Design: Noninferiority randomized multicenter clinical trial of PCT-guided therapy versus standard care.

Setting: Two Dutch hospitals.

Participants: Adult patients with fever(≥38.2°C/100.8°F) in triage. Exclusion criteria: no written informed consent, specific immunocompromised conditions, pregnancy, moribund patients, patients who were within 72 hours after surgery or who required primary surgical intervention.

Intervention: Randomization between PCT-guided therapy and standard care. In the PCT-guided group, a single PCT value was available to the treating physician in the ED. The treatment protocol advised antibiotics when PCT level was ≥0.5µg/L.

Main Outcomes and Measures: Primary outcomes. Efficacy: number of patients who were prescribed antibiotics. Safety: composite safety outcome. Accuracy: AUC of PCT and CRP in diagnosing suspected and confirmed bacterial infections. Secondary outcome. Economic consequences: medical and non-medical costs.

Results

A total of 551 patients were included. Efficacy(n=551): PCT-guided therapy did not reduce the number of patients who received antibiotics compared to the control group, 200(73%) versus 212(77%) of patients received antibiotics(p=0.28). Multivariable logistic regression analysis: OR 0.83(95% CI0.53–1.30) for prescription of antibiotics using PCT-guided therapy. Safety(n=526): No statistically significant difference in composite safety outcome between groups (p=0.12). PCT-guided therapy was noninferior to standard care, upper limit of the one-sided 95% CI was 0.46.

Accuracy(n=529): PCT ≥0.5µg/L for confirmed bacterial infections: sensitivity 0.52(95% CI0.45–0.60), specificity 0.74(95% CI0.68–0.78). AUC of confirmed bacterial infections: PCT 0.681(95% CI0.633–0.730), CRP 0.619(95% CI0.569–0.669). AUC of suspected and confirmed bacterial infections: PCT 0.683(95% CI0.635–0.731), CRP 0.695(95% CI0.646–0.744).

Economic consequences: The total average costs per person: € 5386 for patients in the control group, € 4853 for patients in the PCT-guided group, mean difference was -€533(95% CI -€1570-€505).

Conclusion
PCT-guided therapy did not reduce antibiotics in a general ED population with fever. PCT-guided therapy was noninferior to standard care by means of safety. Although the accuracy of PCT for bacterial infections was higher than CRP, it was still poor. Future studies should focus on more accurate diagnostic modalities of bacterial infections.

Trial Registration Dutch trial register: NTR4949.
http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=4949

INTRODUCTION

In patients with bacterial infections, the treatment goal is to provide optimal antimicrobial therapy in accordance with antibiotic stewardship guidelines[1]. However, in the emergency department(ED), antimicrobial treatment is often initiated before a definitive diagnosis is made, since bacterial infections cannot always be ruled out using routine biomarkers such as C-reactive protein(CRP)[2].
When considering antibiotic treatment in patients with a suspected bacterial infection, ED physicians face a dilemma: On the one hand, antibiotics have to be prescribed sparingly, because overuse of antibiotics increases antibiotic resistance and raises healthcare costs[3,4]. On the other hand, withholding antibiotics from patients with bacterial infections and sepsis increases mortality[5,6]. Consequently, patients with suspected infections are often given antibiotics in the ED – a decision based on empirical grounds, rather than on a definitive diagnosis[2,7-9].
For the correct diagnosis of bacterial infection, accurate diagnostic modalities are crucial. Procalcitonin(PCT) is a biomarker with a higher diagnostic accuracy than CRP for bacterial infections in specific adult patient populations[10-12]. PCT can be applied in an algorithm that determines whether antibiotic treatment is necessary, a strategy known as PCT-guided therapy[13]. PCT-guided therapy reduces antibiotics in various clinical settings, such as in primary care and intensive care units(ICU)[13,14]. In the ED, PCT-guided therapy reduces antibiotics in subpopulations of patients with respiratory complaints and patients with suspected community acquired pneumonia(CAP), without increase in adverse events[12,15,16]. However, the effect of PCT-guided therapy in a general ED population remains unclear, because previous ED studies either used specific patient groups, or lacked statistical power[12,15-17]. Furthermore, current evidence on the economic consequences of PCT-guided therapy is incomplete, as studies so far have mainly been retrospective model-based studies, limited to hospital costs[18-21].

The aim of this study was to determine if PCT-guided therapy can be used for a general ED population of patients with fever, by determining the efficacy, safety, diagnostic accuracy, and economic consequences of this strategy.

METHODS

Study design

The HiTEMP study(Higher diagnostic accuracy and cost-effectiveness using procalcitonin in the treatment of emergency medicine patients with fever) was performed in a tertiary referral hospital, Erasmus University Medical Center(EMC) in Rotterdam, and in the Jeroen Bosch hospital(JBZ) in 's-Hertogenbosch, both in the Netherlands. The study was a multicenter, randomized clinical trial with a noninferiority design. The study design has been published previously[22]. In brief, patients were randomized in ED triage between standard care(control group) and PCT-guided therapy(PCT-guided group) and were followed up for 90 days, by ways of medical database review, telephone interviews and general practitioner(GP) inquiry. This study was approved by the Erasmus University Medical Center ethics review board(NL44227.078.13).

Study population

ED patients with a temperature of ≥38.2°C(100.8°F) were eligible. The temperature of 38.2°C was based on the epidemiology of fever in ED patients[23]. Patients were excluded if they had specific immunocompromised conditions, defined as neutropenia with absolute neutrophil count of <0.5x109cells/L, current chemotherapy, or post-solid organ transplantation. Furthermore, pregnant patients, moribund patients and patients with a diagnosis that required primary surgical intervention, or who were within 72 hours after surgery were excluded.

Intervention

PCT levels were determined in all patients. However, only PCT levels of patients in the PCT-guided group were available to the ED physician. A bacterial infection was deemed unlikely when PCT was <0.5µg/L, and antibiotics were discouraged. When PCT was ≥0.5µg/L, a bacterial infection was likely and antibiotics were encouraged. All treating physicians were trained in interpreting PCT values. Following institutional guidelines, patients with suspected infections and systemic inflammatory response syndrome(SIRS) received a single dose of broad-spectrum antibiotics within one hour after ED arrival. This was no main outcome measure, because this treatment took place before laboratory results were available.

Primary outcomes

The efficacy of PCT-guided therapy was defined as the reduction in percentage of patients who were prescribed antibiotic therapy in the ED.

Safety was assessed with a composite safety endpoint(CSE) consisting of 30-days mortality, ICU admission within 30 days after ED visit, and return visits to the ED within 14 days as indication of treatment failure.

Accuracy was defined as the accuracy of PCT and CRP in diagnosing confirmed bacterial infections only, and confirmed and suspected bacterial infections combined. Confirmed bacterial infections were defined as clinically significant positive blood cultures and focus cultures. Suspected bacterial infections were determined by chart review with predefined clinical criteria, by two independent physicians(supplement 1). In case of disagreement, a third physician was referee.

Secondary outcomes

Efficacy of PCT-guided therapy for patients with respiratory sources of infections was assessed in a subgroup analysis, in order to compare results with studies on PCT-guided therapy in this specific subgroup. Secondary safety outcome measures were hospital admission, length-of-hospital-stay and length-of-ICU-stay. We calculated the percentage of protocol nonadherence. Secondary accuracy outcome was accuracy of PCT and CRP in diagnosing bacteremia.

The economic analysis with cost-minimization design included hospital and societal costs. Medical costs included ED visits, PCT testing, antibiotics administered in ED and first three days of antibiotic treatment, hospital and ICU admissions, and general practitioner(GP)consultations. Non-medical costs were defined as productivity losses, which comprised costs of absence from work(absenteeism), reduced productivity while at work(presenteeism), and productivity losses related to unpaid work. Costs of productivity losses were assessed using the iMTA Productivity Cost Questionnaire(iPCQ)[24]. The time horizon for this analysis was 30 days, except for the out-of-hospital medical costs, which was 90 days.

Statistical analysis

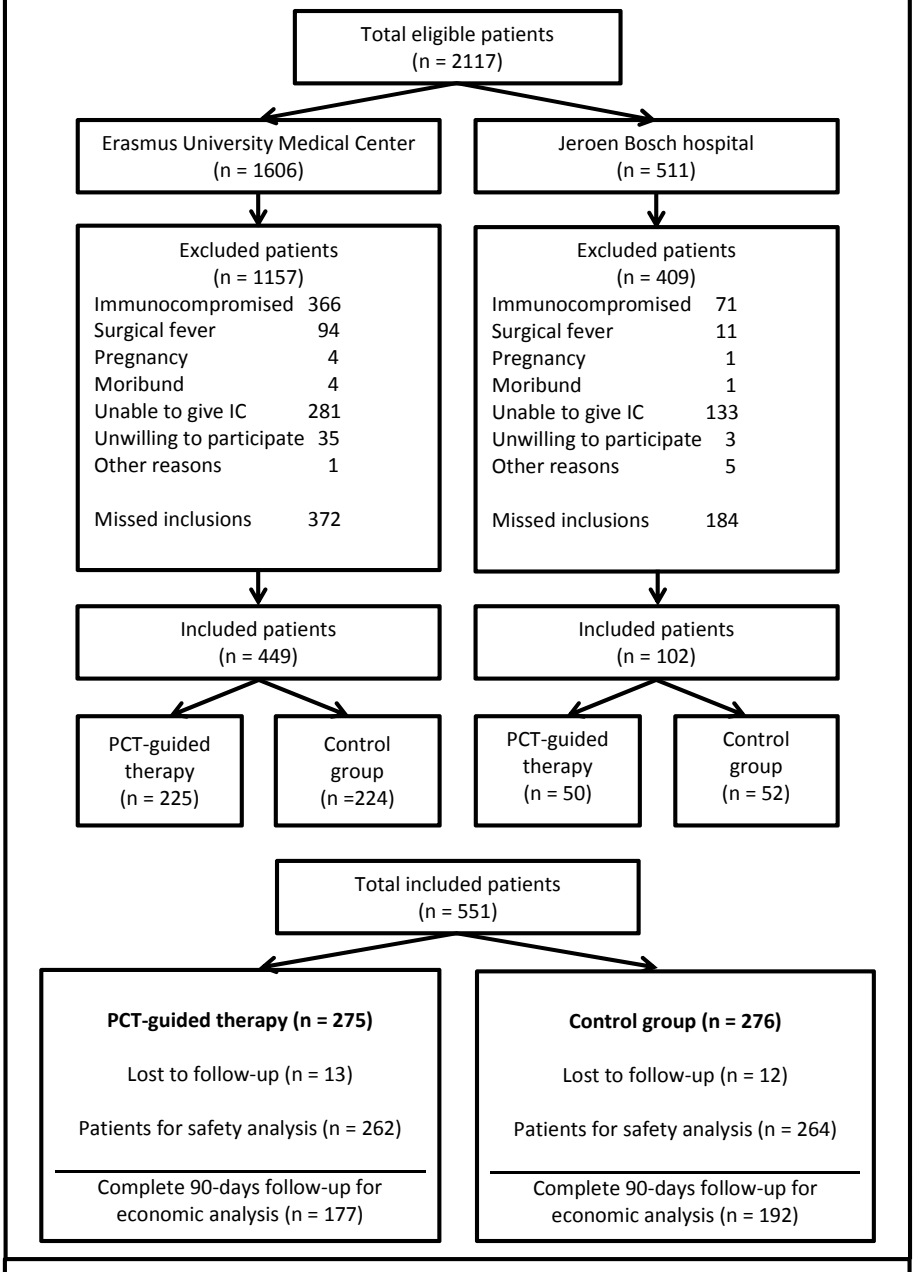
Efficacy was determined using multivariable logistic regression analysis with stepwise backward selection of variables, with a p-value cut-off of 0.05. Age, sex, temperature, medication use, comorbidity, PCT and CRP levels and other variables were considered as independent variables in this analysis. This analysis was performed according the intention-to-treat principle. PCT-guided therapy was deemed noninferior if the upper limit of the one-sided 95 confidence interval(95% CI) for the difference in the CSE between the PCT-guided group and the control group was not higher than 7.5 percentage points. The 95% CI was calculated according to the method described by Agresti and Caffo[25]. The study was powered for the CSE, based on the noninferiority margin of 7.5%. The calculated sample size was 550 patients. Accuracy was reported in three ways. First, as sensitivity and specificity, with binomial proportion CIs calculated using the Clopper-Pearson method. Second, as a receiver operator characteristic curve(ROC) curve. Third, using multivariable logistic regression, corrected for the independent variables age, sex, PCT and CRP levels, temperature, comorbidity, and other variables with $p < 0.1$ for the difference between groups. We accounted for non-linear effects of PCT with logarithmic transfor-

mation. Differences in secondary outcomes were analyzed with Fisher's exact test for dichotomous variables, the independent samples T-test for normally distributed variables, and the Mann-Whitney U test for continuous variables that were not normally distributed. We calculated the optimal cut-off of PCT for confirmed bacterial infections with the Youden's index[26]. Cost-minimization: Costs were derived from the Dutch guidelines for economic evaluations in healthcare[27]. For medical costs, the quantities for each resource used were multiplied by standard unit prices.
Non-medical costs were calculated by multiplying the number of hours of productivity losses by an average hourly wage, for patients who were employed, and by multiplying the number of hours of inability to do unpaid work by standard housekeeper replacement costs for all patients. We calculated mean values for all cost categories and for total costs for both the PCT-guided and control groups. Mean differences between the groups and, using nonparametric bootstrapping, 95% CIs were calculated. All costs were reported in Euros(€). Unless otherwise specified, all statistical tests were two-sided with a significance level of 0.05. Statistical analyses were performed with the statistical package for the social sciences(SPSS v.23), IBM corporation, and Excel, Microsoft corporation.

RESULTS

Between August 2014 and January 2017, 2117 patients were screened for inclusion. Of these 2117 patients, 551 patients were included, of whom 449 in EMC and 102 in JBZ(figure 1). There were 372 missed inclusions in EMC, and 184 in JBZ. Missed inclusions were eligible patients who were not randomized because physicians were unable to perform the randomization procedure due to time constraints. All 551 cases were included in the intention-to-treat analysis for efficacy. There were 25(5%) patients lost-to-follow-up after 30 days, making the number of patients for the safety analysis 526. Patients who were lost-to-follow-up could not be contacted by telephone, and there was no response from their GP. PCT results were unavailable for 19 patients, of whom 8 in the PCT-guided group. This was due to failure to obtain blood samples in the ED. For three additional patients, no CRP result was available, making the number of cases for the accuracy analyses 529. Baseline characteristics are reported in table 1.

Figure 1. Flowchart



IC: informed consent, N: number of patients, PCT: procalcitonin

Table 1. Baseline characteristics

		All (n = 551)	Control group (n= 276)	PCT-guided group (n = 275)
Demographic characteristics				
Age	median [IQR]	63 [43 - 71]	62 [44 - 73]	61 [43 - 70]
Female sex	n (%)	253 (46)	122 (44)	131 (48)
Vital signs at presentation				
Temperature	median [IQR]	38.8 [38.4 - 39.2]	38.8 [38.4 - 39.2]	38.8 [38.4 - 39.3]
Heart rate	median [IQR] n = 550	105 [92 - 119]	105 [92 - 119]	105 [90 - 118]
Systolic bloodpressure	median [IQR] n = 549	130 [118 - 145]	130 [118 - 145]	130 [117 - 145]
Diastolic bloodpressure	median [IQR] n = 549	75 [67 - 85]	75 [67 - 85]	75 [67 - 85]
Respiratory rate	median [IQR] n = 410	20 [17 - 25]	22 [18 - 25]	20 [16 - 25]
Comorbidity				
Diabetes	n (%)	97 (18)	51 (19)	46 (17)
Malignancy	n (%)	106 (19)	44 (16)	62 (23)
HIV	n (%)	17 (3)	10 (4)	7 (3)
Current medication use				
Current antibiotics use (before ED v	n (%)	88 (16)	40 (15)	48 (18)
Steroids	n (%)	78 (14)	37 (13)	41 (15)
Oral anticoagulants	n (%)	64 (12)	31 (11)	33 (12)
Acetylsalicylic acid	n (%)	67 (12)	33 (12)	34 (12)
Biomarkers				
PCT in mcg/L	median [IQR] n = 532	0.26 [0.10 - 0.96]	0.26 [0.10 - 1.00]	0.28 [0.10 - 0.93]
CRP in mg/L	median [IQR] n = 548	62 [19 - 150]	67 [21 - 159]	57 [17 - 132]
Leukocytes in count*10^9 cells/L	median [IQR]	12.0 [8.5 - 15.6]	11.7 [8.6 - 14.9]	11.6 [8.3 - 16.0]
Diagnosis				
Confirmed bacterial infections	n (%)	198 (36)	103 (37)	95 (35)
Confirmed viral infections	n (%)	41 (7)	20 (7)	21 (41)
Confirmed fungal infections	n (%)	1 (0)	0 (0)	1 (0)
Confirmed parasite infections	n (%)	1 (0)	0 (0)	1 (0)
Confirmed non-infectious fever	n (%)	37 (7)	14 (3)	23 (4)
Bacteremia	n (%)	99 (18)	57 (21)	42 (15)
Categories of fever by focus				
- Skin and soft tissue	n (%)	47 (9)	27 (10)	20 (7)
- Respiratory tract	n (%)	212 (39)	102 (37)	110 (40)
- Urogenital tract	n (%)	108 (20)	54 (20)	54 (20)
- Abdominal	n (%)	69 (13)	36 (13)	33 (12)
- Central nervous system	n (%)	4 (1)	1 (0)	3 (1)
- Other source	n (%)	13 (2)	9 (3)	4 (2)
- Fever without source	n (%)	60 (11)	33 (12)	27 (10)
- Non infectious fever	n (%)	37 (7)	15 (5)	22 (8)
Initial ED treatment				
Antibiotics in ED because of SIRS	n (%)	283 (51)	148 (54)	135 (49)

CRP: C-reactive protein, ED: emergency department, HIV: human immunodeficiency virus, IQR: interquartile range, PCT: procalcitonin

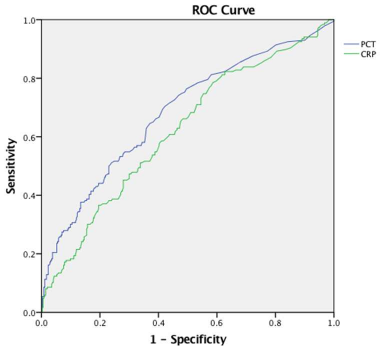
Primary outcomes

Efficacy: 200(73%) of patients in the PCT-guided group received antibiotics, compared to 212(77%) of patients in the control group (p = 0.28)(table 2). PCT-guided therapy did not reduce the probability of antibiotics prescription, odds ratio(OR) 0.83(95% CI 0.53–1.30) when corrected for age, sex, temperature, medication use, comorbidity and PCT and CRP levels. No other independent variables had significant effect(table 3).

Safety: There was no significant difference in the CSE between groups(table 2). The upper limit of the one-sided 95% CI for the difference in the CSE between the PCT-guided group and the control group was 0.46, which was below the defined noninferiority margin of 7.5, making PCT-guided therapy noninferior to standard care by means of safety.

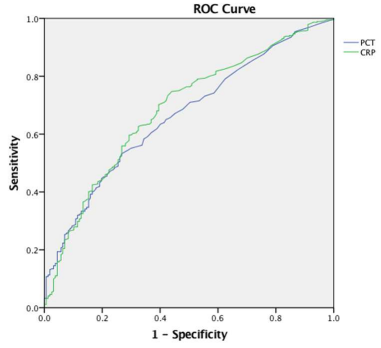
Figure 2. ROC curves

ROC curve of PCT and CRP for confirmed bacterial infection (n = 529)



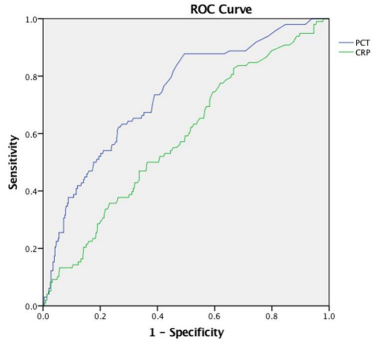
PCT AUC 0.681 (95%CI 0.633 – 0.730)
CRP AUC 0.619 (95%CI 0.569 – 0.669)

ROC curve of PCT and CRP for confirmed and suspected bacterial infection (n = 529)



PCT AUC 0.683 (95%CI 0.635 – 0.731)
CRP AUC 0.695 (95%CI 0.646 – 0.744)

ROC curve of PCT and CRP for bacteremia (n = 529)



PCT AUC 0.736 (95%CI 0.681 – 0.790)
CRP AUC 0.585 (95%CI 0.523 – 0.646)

AUC: Area under curve, CRP: C- reactive protein, PCT: Procalcitonin, ROC curve: Receiver operator characteristic curve

Accuracy: For confirmed bacterial infections only, sensitivity of PCT ≥0.5µg/L was 0.52(95% CI 0.45–0.60), and specificity 0.73(95% CI 0.68–0.78). The ROC curve of PCT yielded an AUC of 0.681(95% CI 0.633–0.730), which was higher than the AUC of CRP, 0.619(95% CI 0.569–0.669) (figure 2).

Multivariable logistic regression analysis showed an OR of PCT of 1.37(95% CI 1.20–1.56), corrected for age, sex, temperature, comorbidity, CRP level and leukocyte count (table 3). This OR showed that a 1% relative increase in PCT level increases the odds for a patient having a bacterial infection 0.37.
For confirmed and suspected infections combined, sensitivity of PCT ≥0.5µg/L was 0.43(95% CI 0.38–0.48), and specificity 0.85(95% CI 0.77–0.89). The AUC of PCT was 0.683(95% CI 0.635–0.731), and was lower than the AUC of CRP, 0.695(95% CI 0.646–0.744). The OR of PCT of 1.29(95% CI 1.09–1.53), corrected for age, sex, temperature, comorbidity, CRP level and leukocyte count.

Table 3. Multivariable analysis of prescription of antibiotics and confirmed and suspected bacterial infections

Efficacy outcome: multivariable logistic regression analysis

Dependent variable:	All patients (n = 551)* Antibiotics prescribed Odds ratio (95% CI)	Subgroup analysis of patients suspected and Antibiotics prescribed Odds ratio (95% CI)
Randomisation (PCT-guided group)	**0.83 (0.53 - 1.30)**	**1.29 (0.59 - 2.82)**
Age (years)	1.04 (1.02 - 1.05)	1.04 (1.02 - 1.06)
Female	0.99 (0.63 - 1.56)	1.14 (0.51 - 2.55)
Temperature (degrees Celcius)	2.37 (1.50 - 3.75)	2.11 (0.94 - 4.74)
Comorbidity: malignancy	1.74 (0.88 - 3.45)	3.81 (0.75 - 19.35)
Comorbidity: diabetes	0.96 (0.48 - 1.91)	0.98 (0.29 - 3.38)
Comorbidity: HIV	1.76 (0.46 - 6.85)	2.31 (0.35 - 15.24)
Medication use: previous antibiotics	3.12 (1.45 - 6.71)	2.31 (0.74 - 7.19)
Medication use: steroids	1.07 (0.55 - 2.10)	3.48 (1.11 - 10.88)
Medication use: oral anticoagulants	1.09 (0.50 - 2.37)	2.69 (0.60 - 11.94)
Medication use: acetylsalicyl acid	2.05 (0.86 - 4.88)	2.86 (0.60 - 13.65)
PCT level (µg/L)	1.18 (1.00 - 1.38)	1.19 (0.74 - 1.90)
CRP level (mg/L)	1.01 (1.00 - 1.01)	1.01 (1.00 - 1.02)

* Multivariable logistic regression analysis with predefined variables. No additional baseline variables met criteria for

Accuracy outcomes: multivariable logistic regression analysis

Dependent variable:	All patients (n = 529)** Confirmed bacterial infections Odds ratio (95% CI)	All patients (n = 529)** Confirmed and suspected bacterial infections Odds ratio (95% CI)
Logarithmic PCT level	**1.37 (1.20 - 1.56)**	**1.29 (1.08 - 1.52)**
CRP level (mg/L)	1.00 (1.00 - 1.01)	1.01 (1.00 - 1.01)
Age (years)	1.01 (1.00 - 1.03)	1.03 (1.02 - 1.04)
Female	0.77 (0.52 - 1.14)	0.59 (0.38 - 0.92)
Temperature (degrees Celcius)	1.67 (1.17 - 2.37)	2.18 (1.41 - 3.36)
Comorbidity: malignancy	1.62 (1.00 - 2.64)	2.06 (1.06 - 4.00)
Comorbidity: diabetes	1.00 (0.59 - 1.70)	1.65 (0.85 - 3.22)
Comorbidity: HIV	0.70 (0.21 - 2.36)	0.70 (0.21 - 2.25)
Leukocyte count (10^9 cells/L)	1.00 (0.99 - 1.02)	1.02 (0.99 - 1.05)

**Multivariable logistic regression analysis with predefined variables, with the addition of leukocyte count.

CI: confidence interval, CRP: C-reactive protein, n: number, PCT: procalcitonin.

Secondary outcomes

In the subgroup analysis of patients with respiratory sources of infections(n = 212), 83(75%) of patients in the PCT-group received antibiotics, compared to 73(72%) patients in the control group (p=0.76). The OR for prescription of antibiotics was 1.29(95% CI 0.59–2.82) (table 3).

In the total population, there were no statistically significant differences in individual endpoints of the CSE (n=526), second ED visit within 14 days (p=0.20), ICU admission within 30 days after ED visit(p=1.00) and 30-days mortality (p=0.11), nor in endpoints hospital admission(p=0.10), length-of-hospital-stay(p=0.25) and length-of-ICU-stay(p=0.32)(table 2).

Protocol nonadherence was 49%(n=529), which consisted of 232 patients who received antibiotics with PCT<0.5µg/L, and 26 patients who did not receive antibiotics with PCT≥0.5µg/L (supplement 2).

A total of 89(48%) of patients with a confirmed bacterial infection(n=186) had PCT<0.5µg/L (supplement 2). Of these 89 patients, 12 patients did not receive antibiotics. Of these 12 patients, two patients suffered adverse events, one return visit to the ED, and one ICU admission. The AUC of PCT for bacteremia was 0.736(95% CI 0.681–0.790), the AUC of CRP for bacteremia was 0.585(95% CI 0.523–0.646). The OR of PCT for bacteremia was 1.37(95% CI 1.20–1.56), corrected for age, sex, temperature, comorbidity, CRP level. No additional variables met criteria for inclusion (supplement 3).

The calculated optimal cut-off of PCT for confirmed bacterial infection was 0.25µg/L. Sensitivity of PCT ≥0.25µg/L was 0.70(95% CI 0.63–0.77), and specificity 0.58(95% CI 0.52–0.63).

A total of 369 patients had a complete follow-up for the cost-minimization analysis, 177(64%) in the control group and 192(70%) in the PCT-guided group. The total average costs per person were €4853 for patients in the PCT-guided group and €5386 for patients in the control group, with a mean difference of -€533 (95% CI -€1570 to €505).

Table 4: Economic analysis

	PCT-guided group (n = 192)		Control group (n = 177)		Difference	
	Mean	Standard deviation	Mean	Standard deviation	Mean	95% CI
Hospital costs	**€ 3899**	**€ 4704**	**€ 4162**	**€ 4680**	**€ 263-**	**-€ 1225 to € 698**
PCT testing	€ 56	€ -	€ -	€ -	€ 56	€ 56 to € 56
Antibiotics administered in ED	€ 7	€ 12	€ 8	€ 15	€ 1-	-€ 3 to € 2
Antibiotics first three days	€ 82	€ 136	€ 73	€ 135	€ 9	-€ 18 to € 37
ED admission	€ 275	€ 63	€ 278	€ 68	€ 3-	-€ 16 to € 11
Admission university hospital	€ 2966	€ 3714	€ 3330	€ 4087	€ 364-	-€ 1162 to € 435
Admission non-university hospital	€ 261	€ 885	€ 235	€ 911	€ 25	-€ 158 to € 209
ICU admission	€ 252	€ 1838	€ 239	€ 1762	€ 13	-€ 356 to € 382
Costs of extramural care	**€ 89**	**€ 117**	**€ 109**	**€ 144**	**€ 20-**	**-€ 47 to € 6**
General practitioner visit	€ 54	€ 75	€ 74	€ 102	€ 20-	-€ 38 to -€ 1
General practitioner house call	€ 34	€ 91	€ 35	€ 98	€ 1-	-€ 20 to € 18
Productivity costs	**€ 866**	**€ 1742**	**€ 1115**	**€ 2118**	**€ 249-**	**-€ 644 to € 147**
Costs of absenteeism from work	€ 632	€ 1628	€ 830	€ 1875	€ 198-	-€ 557 to € 160
Costs of productivity loss while at w	€ 28	€ 142	€ 42	€ 223	€ 14-	-€ 52 to € 24
Replacement for unpaid work	€ 206	€ 521	€ 243	€ 694	€ 37-	-€ 162 to € 88
Total costs	**€ 4853**	**€ 4969**	**€ 5386**	**€ 5168**	**€ 533-**	**-€ 1570 to € 505**

ED: Emergency department, ICU: intensive care unit, PCT: procalcitonin

DISCUSSION

Our study showed that PCT-guided therapy did not reduce the number of febrile patients who were prescribed antibiotics in the ED. PCT-guided therapy was noninferior to standard therapy regarding the CSE. PCT was more accurate in the diagnosis of confirmed bacterial infections than CRP, but the accuracy was poor. For confirmed and suspected infections, the accuracy of PCT was lower than the accuracy of CRP, which suggests that, in patients with suspected infections, PCT results can be incongruent with clinical judgement. PCT-guided therapy did not result in a statistically significant costs reduction.

Our findings are in contrast with other studies on PCT-guided therapy in the ED[10,12,15,16,28,29]. These studies reported antibiotic reductions of 13 to 39 with PCT-guided therapy, in adult patient populations of patients with lower respiratory tract infections, CAP and COPD. However, in our study, we found no difference in the number of antibiotics prescriptions; not in the total cohort, nor in the subgroup analysis of patients with respiratory infections. We speculate that physicians based treatment decisions on clinical judgement and other diagnostic modalities instead of PCT advice in conflicting situations.

The essence of PCT-guided therapy is to reduce antibiotics in patients without bacterial infections. For this strategy to work, PCT levels have to identify patients without bacterial infections accurately, and on top of that, physicians have to trust the results. In the ProHOSP study, Schuetz et al.[12] reported that PCT-guided therapy significantly reduced antibiotics prescriptions in ED patients with suspected CAP. The authors suggested that Swiss physicians' experience with PCT resulted in an increased adherence to PCT advice in the ProHOSP study, because physicians in Switzerland were used to working with PCT. Physicians in Dutch EDs did not have extensive previous clinical experience with the PCT biomarker before this study started. However, we hypothesize that this lack of previous clinical experience, and possible concomitant lack of trust in the accuracy of PCT results, cannot be the only explanation for our findings. Following the 49% PCT-guided therapy protocol nonadherence, we presume that, in a general ED population, PCT is insufficient as a single biomarker in the diagnosis of bacterial infections, and that clinical judgement and other diagnostic modalities are crucical for physicians in order to prevent undertreatment. This was also suggested by Kristoffersen et al., who found a PCT-guided therapy protocol nonadherence of 41% [30].

Although PCT was more accurate for confirmed bacterial infections than CRP and although an increase in PCT level made the presence of a patient having a confirmed infection more likely, a single cut-off of PCT ≥0.5µg/L resulted in an erroneous treatment advice to withhold antibiotics in 89(49%) patients with a confirmed bacterial infection. This cut-off value was higher than in other ED and primary care studies[12,14,15]. The calculated optimal cut-off of PCT for confirmed bacterial infec-

tions, ≥0.25μg/L, had a sensitivity of 0.70, and coincidentally corresponded with the cut-off used in these studies. Out of 253 patients with PCT levels of ≥0.25μg/L, 55 patients(28%) had a confirmed bacterial infection. PCT levels, both with the cut-off of ≥0.5μg/L and with the calculated optimal cut-off of ≥0.25μg/L for confirmed bacterial infections resulted in false negative outcomes in respectively 89(17%) and 55(10%) patients(supplement 2). From these findings we conclude that a single PCT result gave inaccurate treatment advice and should not be used as only criterion to start or withhold antibiotics in a general ED population.

The accuracy of PCT for bacterial infections in our study is lower than in two recent meta-analyses on the accuracy of PCT in the ED (e.g. an AUC of PCT for bacteremia of 0.736 in our study versus 0.84 reported by Jones et al.)[31,32]. This may be due to the fact that our patient population was designed to resemble a general ED population, thereby making it a heterogeneous group with only 36 of patients with a confirmed bacterial infection. Studies with highly selected populations such as the ProHOSP study, consisted of higher percentages of bacterial infections, with 68 of patients having a CAP12.

In the PCT-guided group, patients were admitted to the hospital less often, and had a lower absolute 30-days mortality. Although both findings did not meet the criteria for statistical significance, we speculate that physicians may have used PCT as a biomarker for disease severity. On the one hand, low PCT results may have influenced physicians not to admit patients to the hospital. On the other hand, high PCT results may have prompted physicians to treat patients more aggressively, resulting in a reduction in 30-days mortality. Shehabi et al.[33] described that a single PCT level at ICU admission was predictive of sepsis severity. The value of PCT in disease severity in a general ED patient population has not yet been determined.

The economic analysis demonstrated that there was no statistically significant difference in costs between groups. This was contrary to our hypothesis that PCT-guided therapy reduced overall costs. Hospital admissions and consequent productivity losses account for the highest expenses. Future biomarker strategies that can reduce hospital admissions may reduce healthcare costs.

Limitations

We used body temperature as sole inclusion criterion. This was both a strength and a weakness of the study. A strength, because it was an objective measurement and makes the results generalizable to all ED patients with fever. A weakness, because fever is not a perfect marker of infectious disease. The use of this inclusion criterion resulted in a selection bias, where patients with infectious diseases and normothermia or hypothermia were not eligible for inclusion. Patients with altered mental status and severely ill patients were de facto excluded, because these patients were unable to give written informed consent. Therefore, the results are not generalizable for the entire adult ED patient population.

CONCLUSION

PCT-guided therapy was noninferior to standard care by means of safety, but did not reduce the prescription of antibiotics in patients with fever in a general ED population. In this heterogeneous patient population, PCT was more accurate in the diagnosis of confirmed bacterial infections than CRP, but the accuracy of PCT for bacterial infections was poor.
Future studies should focus on more accurate diagnostic modalities of bacterial infections to reduce antibiotics prescriptions in the ED. Furthermore, PCT-guided therapy may be used for assessing disease severity.

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Supplement 1. Criteria for confirmed and suspected infections

Confirmed infections

Confirmed bacterial infections:
Positive culture result for bacteria (from an otherwise sterile location), positive Legionella or pneumococcus urine test. ³
(Coagulase negative Staphylococcus bacteremia is considered as contamination and not as infection.)

Confirmed viral infections:
Positive viral PCR or serology. *

Confirmed fungal infections:
Positive blood culture or PCR.

Confirmed parasitical infections:
Positive blood culture or PCR, positive blood smear for malaria.

Suspected infections

Suspected bacterial infections:
Negative findings in cultures and PCR.
Positive infiltrate on chest x-ray with as at least 1 respiratory symptom (cough, sputum, dyspnea, tachypnea, pleuritic pain), plus either rales or crepitation on auscultation, shivering, leukocytosis. Positive image modality: infiltrate, abscess. Positive urine nitrite, with positive leukocytes in urine and leukocytosis, or with dysuria complaints in history. Skin: local red and painfull swelling. Abscess found on endoscopy. CSF analysis one of the following criteria: high opening pressure (>18cm H_2O), pleiocytosis (> 5.109/L), elevated protein level (>0.4 g/L), low glucose (<2.5 mmol/L), low glucose CSF/blood ratio (< 0.4), high lactate (>4.2 mmol/L). ERCP findings suggestive of cholangitis. Clinical improvement with antibiotics treatment, when no highly suspected other cause is present.

Suspected viral infections:
Negative findings in cultures and PCR.
History mentions flu-like symptoms. Dry cough. Pathognomic findings of viral infections, such as, but not limited to Koplik spots. Improvement without antibiotics.

Noninfectious fever:
Negative findings in cultures and PCR.
Negative image modality findings suspected for infection. Confirmed or highly likely other diagnosis. Improvement without antibiotics.

Unknown:
Negative findings in cultures and PCR.
Insufficient clinical data in medical chart to determine suspected infection category.

*when a patient has both a confirmed bacterial and viral infection, it is considered a bacterial infection because this has treatment consequences.

CSF: cerebrospinal fluid. ERCP: endoscopic retrograde cholangiopancreatoscopy. PCR: polymerase chain reaction diagnostics.

Supplement 2: Accuracy of PCT for confirmed and suspected infection:

Total number of patients in whom PCT levels were available:		**n = 529**				
Cut-off value: PCT <0.5µg/L	**n =**	**341**	**PCT ≥0.5µg/L**	**n =**	**188**	**Total**
Confirmed bacterial infection:	**n =**	**89**	**Confirmed bacterial infection:**	**n =**	**97**	**186**
Received antibiotics:	n =	77	Received antibiotics:	n =	92	169
Not received antibiotics:	n =	12	Not received antibiotics:	n =	5	17
No confirmed bacterial infection:	**n =**	**252**	**No confirmed bacterial infection:**	**n =**	**91**	**343**
Received antibiotics:	n =	155	Received antibiotics:	n =	70	225
Not received antibiotics:	n =	97	Not received antibiotics:	n =	21	118
Sensitivity of PCT ≥0.5µg/L for confirmed bacterial infections:			0.52 (95% CI 0.45 - 0.60)			
Specificity of PCT ≥0.5µg/L for confirmed bacterial infections:			0.73 (95% CI 0.68 - 0.78)			
Cut-off value: PCT <0.5µg/L	**n =**	**341**	**PCT ≥0.5µg/L**	**n =**	**188**	**Total**
Confirmed and suspected bacterial infection:	**n =**	**216**	**Confirmed and suspected bacterial infection:**	**n =**	**164**	**380**
Received antibiotics:	n =	190	Received antibiotics:	n =	152	342
Not received antibiotics:	n =	26	Not received antibiotics:	n =	12	38
No confirmed and suspected bacterial infection:	**n =**	**125**	**No confirmed and suspected bacterial infection:**	**n =**	**24**	**149**
Received antibiotics:	n =	42	Received antibiotics:	n =	10	52
Not received antibiotics:	n =	83	Not received antibiotics:	n =	14	97
Sensitivity of PCT ≥0.5µg/L for confirmed and suspected bacterial infections:			0.43 (95% CI 0.38 - 0.48)			
Specificity of PCT <0.5µg/L for confirmed and suspected bacterial infections:			0.84 (95% CI 0.77 - 0.89)			
Optimal cut-off value: PCT <0.25µg/L	**n =**	**253**	**PCT ≥0.25µg/L**	**n =**	**276**	**Total**
Confirmed bacterial infection:	**n =**	**55**	**Confirmed bacterial infection:**	**n =**	**131**	**186**
Received antibiotics:	n =	48	Received antibiotics:	n =	121	169
Not received antibiotics:	n =	7	Not received antibiotics:	n =	10	17
No confirmed bacterial infection:	**n =**	**198**	**No confirmed bacterial infection:**	**n =**	**145**	**343**
Received antibiotics:	n =	117	Received antibiotics:	n =	108	225
Not received antibiotics:	n =	81	Not received antibiotics:	n =	37	118
Sensitivity of PCT ≥0.25µg/L for confirmed and suspected bacterial infections:			0.70 (95% CI 0.63 - 0.77)			
Specificity of PCT <0.25µg/L for confirmed and suspected bacterial infections:			0.58 (95% CI 0.52 - 0.63)			

N: number of patients, PCT: procalcitonir

Supplement 3: Multivariable analysis of bacteremia

Multivariable logistic regression analysis

	All patients (n = 529)*
Dependent variable:	Bacteremia Odds ratio (95% CI)
Logaritmic PCT level	**1.37 (1.20 - 1.56)**
CRP level (mg/L)	1.00 (1.00 - 1.01)
Age (years)	1.01 (1.00 - 1.03)
Female	0.77 (0.52 - 1.14)
Temperature (degrees Celcius)	1.67 (1.17 - 2.37)
Comorbidity: malignancy	1.62 (1.00 - 2.64)
Comorbidity: diabetes	1.00 (0.59 - 1.70)
Comorbidity: HIV	0.70 (0.21 - 2.36)

Multivariable logistic regression analysis with predefined variables. No additional baseline variables met criteria for inclusion in analysis.

CI: confidence interval, CRP: C-reactive protein, n: number, OR : Odds ratio, PCT: procalcitonin.