PART I
PROCALCITONIN-GUIDED THERAPY

CHAPTER 3

PROCALCITONIN-GUIDED ANTIBIOTIC THERAPY IN PATIENTS PRESENTING WITH FEVER IN THE EMERGENCY DEPARTMENT

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ABSTRACT

Introduction
In the emergency department (ED), patients with fever often receive antibiotics, because physicians have difficulties in determining the etiology of fever. Procalcitonin is a novel biomarker for bacterial infections. We investigated if PCT-guided antibiotic therapy reduced the antibiotic prescription rate in febrile emergency department (ED) patients.

Methods
Undifferentiated febrile ED patients were randomized to either PCT-guided therapy or standard-of-care. In the PCT-guided group, a single PCT measurement was added to standard laboratory results. In the PCT-guided therapy group, antibiotic treatment was recommended when PCT was ≥0.5µg/L.
The primary outcome was number of patients who received antibiotics in the ED.

Results
107 Patients were included. Fewer antibiotics were prescribed in the PCT-guided therapy group (80% vs 92% (p= 0.08)). Differences were observed in ICU admission (14(24%) vs 4 (8%) (p=0.03)); mortality (0 (0%) vs 2 (4%) (p=0.12)); temperature (median 38.8 (IQR 38.2 – 39.2) vs median 39.0 (IQR 38.7 – 39.5)) (p=0.03)) and CRP level (mean 138 mg/L (SD 120) vs 179 mg/L (SD 146) (p=0.02)) between PCT-guided therapy and standard-of-care. Mean length of hospital stay was 8 days in both groups. In multivariate regression analysis, PCT-guided therapy resulted in a trend towards reduction of the proportion of patients who received antibiotics (OR 0.47 (95%CI 0.13 – 1.66)).

Discussion
Although no statistically significant reduction in number of patients who received was found, the findings in this study suggest that PCT-guided therapy may reduce antibiotics prescriptions in febrile patients from an undifferentiated adult ED population. PCT-guided therapy may be an important tool in antimicrobial stewardship. Larger trials are needed to validate the value of PCT in the ED.

INTRODUCTION

Antibiotics are the mainstay of treatment of bacterial disease. With the increasing use of antibiotics, resistance of microorganisms is on the rise[1]. The surviving sepsis campaign states that, when patients have a suspected infection with systemic inflammatory response syndrome (SIRS), broad-spectrum antibiotics have to be administered within one hour[2]. This increases the rate of antibiotic prescriptions in the emergency department (ED)[3,4], and may also contribute to further resistance for antibiotics. Antimicrobial stewardship stands for targeted and effective antibacterial therapy, with special attention for the initiation and timely ending of antibiotics use. The goal of antimicrobial stewardship is to contain the increasing resistance of microorganisms[5,6]. Procalcitonin (PCT) is a novel biomarker, which has a higher sensitivity and specificity in the diagnosis of bacterial infection compared to the current standard diagnostic tests available in the ED[7-10]. PCT is a precursor protein of calcitonin. Unlike calcitonin, which is only produced in the C-cells of the thyroid gland, procalcitonin can be produced ubiquitously throughout the human body. The production of PCT is upregulated by pro-inflammatory cytokines like interleukin -1 (IL-1), IL-2, IL-6 and tumor necrosis factor alpha, and directly by bacterial endotoxins and lipopolysaccharide. Interferon gamma, a cytokine associated with viral infections, reduces the upregulation of PCT. Furthermore, an increase in PCT levels can be monitored within 4 to 6 hours after start of infection[11-13]. CRP is an acute phase protein, synthesized exclusively in the liver. CRP levels increase during inflammatory states, but are not specific for bacterial infections and take more time, 6 to 48 hours after start of infection, to be detectable compared to PCT[12,14]. These characteristics give PCT a theoretical advantage over CRP. Previously, we showed that the addition of PCT to the current diagnostic workup of patients presenting with fever helps to discriminate between infectious and non-infectious causes[15].
Moreover, recent primary care and ED based interventional PCT-guided therapy studies reported a reduction in antibiotics use in patients suspected of lower respiratory tract infections[9,16,17]. However, since these studies were limited to specific patient populations, the results are not generalizable to febrile patients without a strong suspicion of a specific infection. Therefore, this study addresses all febrile ED patients, a heterogeneous and more challenging group, in order to determine the value of PCT-guided therapy in this emergency department clinical setting.

The objective of this study was to investigate if PCT-guided therapy reduced unnecessary antibiotics prescription in an undifferentiated febrile ED population.

METHODS

Design
Single center, randomised controlled trial of patients visiting the ED of the Slotervaart Hospital in Amsterdam, the Netherlands. The hospital board of medical ethics approved the study protocol. All patients gave written informed consent.

Setting
The Slotervaart hospital in Amsterdam is a general teaching hospital with 410 beds.

Population
All non-pregnant patients, between 18 and 85 years of age, who presented at the ED with fever and gave written informed consent, were eligible for inclusion.

Design
All eligible patients were asked to participate in the study. After inclusion, patients were randomized to either a PCT-guided therapy arm or a standard-of-care arm, using a computer program. In all patients, blood samples and two sets of blood cultures were obtained. Samples for bacterial and viral cultures and polymerase chain reaction (PCR) were taken from the suspected focus of infection, as judged by the treating physician. In both groups, PCT was determined. PCT results were only available to the physician in the ED in the PCT-guided therapy group. With all available laboratory results, physicians filled out a standard case report form on which was reported whether antibiotics were indicated and whether antibiotics were prescribed. The PCT treatment algorithm recommended withholding antibiotics when PCT was <0.5 µg/L, and recommended prescribing antibiotics with PCT levels ≥0.5 µg/L. This treatment algorithm was described Bouadma et al[18]. Physicians were allowed to prescribe antibiotics in case of low PCT levels if this was according to their clinical judgement. There were no predetermined criteria for disregarding the treatment algorithm.

Outcomes
The primary outcome was the number of patients who received antibiotics. Secondary outcomes were hospital and intensive care unit (ICU) admission and length of stay, and mortality. A definite diagnosis of all patients was reported retrospectively, both by an independent physician and by the primary investigator, blinded for PCT results, and was based on culture results and all diagnostic tests available.

Data analysis
We determined differences in variables between the standard-of-care group and the PCT-guided group using Chi-squared tests for dichotomous variables and Stu-

Table 1: Baseline characteristics and calculated differences of the study population				
	PCT guided	Standard-of-care	Total	p-value*
n	59	48	107	
Female sex, n (%)	20 (34%)	18 (38%)	38 (35%)	p = 0.70
Age, median year (SD)	60 (20)	60 (17)	603 (18)	p = 0.55
Temperature, median ˚C(IQR)	38.8 (38.2 – 39.2)	39.0 (38.7 – 39.5)	38.9 (38.4 – 39.3)	**p = 0.03**
ICU admission, n (%)	14 (24%)	4 (8%)	18 (17%)	**p = 0.03**
Mortality, n (%)	0 (0%)	2 (4%)	2 (2%)	p = 0.12
Hospitalization, n (%)	55 (93%)	42 (88%)	97 (91%)	p = 0.31
Diabetes Mellitus, n (%)	14 (24%)	9 (19%)	23 (22%)	p = 0.53
Immunocompromised, n (%)	6 (10%)	6 (13%)	12 (11%)	p = 0.70
Malignancy, n (%)	10 (17%)	6 (13%)	16 (15%)	p = 0.52
Length of stay, median days (IQR)	6 (3 – 9)	7 (3 – 9)	6 (3 – 9)	p = 0.76
PCT, median µg/L (SD)	0.33 (4.6)	0.39 (5.0)	0.38 (4.7)	p = 0.83
CRP, median mg/mL (SD)	108 (120)	165 (146)	127 (133)	**p = 0.02**
Antibiotics prescribed	47 (80%)	44 (92%)	91(85%)	**p = 0.08**
Antibiotics indicated	50 (85%)	40 (83%)	90 (84%)	p = 0.84
Bacterial infection confirmed	20 (34%)	18 (38%)	38 (36%)	p = 0.70
Abbrevations list: N: number. SD: standard deviation. IQR: Inter quartile range. ICU: intensive care unit. * Students' T-test for continuous variables, Chi-squared test for dichotomous variables.				

dent's T-tests for continuous variables. Variables age and gender, together with variables with significant differences between groups ($p<0.1$) were included in multivariate binominal logistic regression analysis.

RESULTS

Patients were included from May 2010 to May 2012. A total of 342 patients were eligible for inclusion; A total number of 107 patients were included and randomised, 14 patients were excluded because data were incomplete and irretrievable. Of the eligible patients, 221 were not included due to logistical problems.

Primary outcome

In the PCT-guided group, significantly fewer antibiotics were prescribed compared to the standard-of-care group (80% vs. 92%, respectively; $p=0.08$; 13% reduction). The groups did not differ by number of confirmed bacterial infections. A total of 15 patients (25%) in the PCT-guided group received antibiotics despite of their low PCT measurement (PCT <0.5 µg/L).

Secondary outcomes

There was no difference in length of hospital stay or mortality. Yet, significantly more patients in the PCT-guided group were admitted to the intensive care unit, (24% vs. 8%, respectively). Furthermore, the patients in the standard-of-care group had a measured temperature and CRP level that were significantly higher. Consequently, standard therapy was compared to PCT-guided therapy in multivariate logistic regression analysis. The determinants ICU admission, temperature and CRP level had a significant effect in univariate logistic regression and were corrected for in multivariate binomial logistic regression analysis. PCT-guided therapy reduced the rate of antibiotics prescribed, OR 0.47 (95%CI 0.13 – 1.66).

There were 73 (68%) patients with bacterial infections, 22 (21%) patients with viral infections, 1 (1%) patient with a parasitic infection, and 14 (13%) patients with a non-infectious cause of fever.

The types of infections were: respiratory infections in 49 (46%) patients, urinary tract infections in 19 (18%) patients, skin and soft tissue infections in 10 (9%) patients, bloodstream infections in 6 (6%) patients, digestive tract infections in 4 (4%) patients, meningo-encephalic infections in 2 (2%) patients, and other febrile disease, including thyrotoxicosis, malignant neuroleptic syndrome and polymyalgia rheumatic in 17 (15%) patients.

Table 2. Types of infection and most common identified pathogens

Infection	Total of patients (n, %)	Specified infection	(n)	Clinical diagnosis only (n)	Proven by culture (n)	Most common identified pathogens*	(n)
Pneumonia/respiratory infection	49 (46%)	Bacterial	35	22	13	Streptococcus sp. E. Coli M. Mycoplasma H. Influenzae	4 2 2 2
		Viral	14	2	12	Influenza A virus Human rhinovirus Para-influenza virus	5 5 2
Urinary tract infection	19 (18%)	Bacterial	19	13	6	E. Coli P. Aegurinosa K. pneumoniae	8 4 3
Bloodborne infection	6 (6%)	Bacterial	4	-	4	Streptococcus sp. S. Aureus P. Aegurinosa	2 1 1
		Viral	1	-	1	Dengue virus	1
		Parasitic	1	-	1	P. Falciparum	1
Gastro-intestinal infection	4 (4%)	Bacterial	1	-	1	E. Coli (ESBL), K. Pneumoniae (ESBL), P. Aegurinosa	1
		Viral	3	3	-	-	-
Skin and soft tissue infection	10 (9%)	Bacterial	9	6	3	S. Aureus Streptococcus sp. P. Aegurinosa	1 1 1
		Viral	1	-	1	Herpes Simplex	1
Viral respiratory infection with bacterial superinfection	3 (3%)	-	-	-	3	Influenza A virus, M. Pneumoniae Influenza A virus, S. Aureus Para-influenza virus, S. Pneumoniae	1 1 1
Meningo-encephalic infections	2 (2%)	Bacterial	2	1	1	Streptococcus sp. (meningitis) *(CT-confirmed cerebral abscess)*	1 1
No specific suspected infection	5 (5%)	-	-	-	-	-	-
Other	9 (9%)	-	-	-	-	Tumor fever Thyreotoxicosis Malignant neuroleptic syndrome Appendicitis Urea crystal arthritis (gout) Diverticulitis Polymyalgia rheumatica	3 1 1 1 1 1
Total* of infections	107 (100%)	Bacterial	73	42	31		
		Viral	22	5	17		
		Parasitic	1	-	1		
		Other	14				

*In some cultures, multiple microorganisms were present.

Abbrevations: E. Coli : Escherichia Coli, M.Mycoplasma: Mycobacterium Mycoplasma, H. Influenzae: Haemophilus Influenzae, P. Aegurinosa: Pseudomonas Aegurinosa, K.Pneumoniae: Klebshiella Pneumoniae, P. Falciparum: Plasmodium Falciparum, S. Aureus: Staphylococcus Aureus.

N: number. Sp: Species. ESBL: extend spectrum beta-lacatamase. CT: computer tomography.

DISCUSSION

In this randomized clinical trial, we showed that PCT-guided antibiotic therapy for undifferentiated febrile patients in the ED did not result in a significant reduction in prescription of antibiotics, but did show a trend towards reduction of the initiation of unnecessary antibiotic therapy. A recent review of literature[7] shows that the PCT intervention studies in primary care, ED and ICU settings use only subgroups of patients. These studies mainly focus on respiratory tract infections and sepsis. Our study is the first study that included an adult ED population with fever, irrelevant of suspected underlying pathology. Because no selection of patients was made, besides fever, the use of PCT-guided therapy may be expanded beyond patients with specific suspected pathology in the ED.

We demonstrated a trend towards reduction of the initiation of unnecessary antibiotic therapy. Reduction in number of antibiotic prescriptions has been reported for specific patient populations in the ED[17,19-24]. Also, antibiotic reduction in patients with suspected respiratory tract infections and fever has been reported in general practice when PCT-guided antibiotic therapy is used[9]. In the proHOSP study[16] the authors reported a significant reduction in the prescription of antibiotics in patients with lower respiratory tract infections. Furthermore, there were similar rates for adverse events in mortality and ICU admittance.

This is the first PCT-guided therapy study carried out in adult ED patients in the Netherlands, a country known for its restrictive antibiotics prescription policy[25,26]. Other ED based studies were performed in Switzerland[16,20,23], Denmark[24], China[22], and one international multicenter trial in Switzerland, France and the United States[17]. The lower rate of reduction of antibiotic prescription in the current study may be partly explained by the higher threshold of Dutch physicians to prescribe antibiotics.

In the ICU setting, PCT is used as a marker to discontinue antibiotic treatment[18,27,28]. In PCT-guided therapy trials based in the ICU, researchers had access to serial measurements of PCT. However, in this ED based study, a single measurement was used to either start or not to start antimicrobial therapy. Although this resulted in a lower rate of reduction of antibiotic use compared to ICU-based studies, it is nonetheless an interesting result, because PCT can change antibiotic policy in a real-life ED setting in a safe and timely manner.

The study population consisted mainly of patients with respiratory and urinary tract infections. This is in accordance with other ED-based studies, both in the Netherlands and internationally[10,29,30]. As the type of infection in febrile patients is not always clear to the ED physician, the use of fever as sole inclusion criterion reflects the real-life clinical situation.

In the PCT-guided therapy group, there were significantly more ICU admissions, and patients had a higher temperature. Because the patients were randomized, these differences were due to chance. However, this means that the PCT-guided therapy

group may have consisted of generally sicker patients. We performed a statistical correction for this difference; however, the differences between groups may have influenced the results. In a similar population, PCT-guided therapy could therefore reduce the proportion of antibiotic prescriptions even more.

Limitations

There were some limitations in this study. First of all, the sample size was small. A number of 221 patients were not included because of logistical problems in the ED. Patients were not included due to unfamiliarity of the physicians with the study, despite several hospital-wide information sessions. This was because all specialties in the Slotervaart hospital had their own ED consultants. Therefore, eligible patients were not always asked to participate. After inclusion, 14 patients had to be excluded because of incomplete data. In the PCT-guided therapy group, there was a 25% rate of antibiotic prescription with a low PCT level. Patients with a low PCT result were still prescribed antibiotics. This may be attributable to either the unfamiliarity of PCT as an accurate diagnostic marker, or a lack of confidence in the new diagnostic instrument[31].

CONCLUSION

Although no statistically significant reduction in number of patients who received antibiotics was found, the findings in this study suggest that PCT-guided therapy may reduce antibiotics prescriptions in febrile patients from an undifferentiated adult ED population. PCT-guided therapy may be an important tool in antimicrobial stewardship. Larger trials are needed to validate the value of PCT in the ED.

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