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Editorial

Personalized CHF treatment: PCT to guide therapy in heart failure patients

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ABSTRACT

Sorting out the etiology of dyspnea in patients with a history of heart failure is not always straightforward. Although an acute heart failure exacerbation would seem to be easy to distinguish from an acute respiratory illness, data from objective clinical studies has shown otherwise. Procalcitonin (PCT), a biomarker that rises in the setting of bacterial infection, carries great potential for guiding the diagnosis and treatment of heart failure patients with possible acute respiratory infection. In this issue of the International Journal of Cardiology, Kutz et al. demonstrated that patients with a history of heart failure and suspected lower respiratory tract infection experienced reduced antibiotic duration and superior outcomes with PCT-guided therapy. The results in this subset of heart failure patients from the ProHOSP study were consistent with the results seen in the overall study population. This study points to the need for a randomized controlled trial in a broader population of heart failure patients with acute dyspnea, to further define the prominent role that PCT can play in more personalized medical treatments that can improve patient outcomes.

In 1993, The Lancet published a prospective study by Assicot et al. describing a new finding of high concentrations of a 116 amino acid-containing prohormone in bacterial sepsis and prompt reduction of its level with antibiotics [1]. Just over two decades later, this polypeptide – procalcitonin (PCT) – is proving to be an exciting biomarker with potential not only to guide therapy in a variety of patients and clinical settings but also to improve treatment efficiency and accuracy. One important application of PCT under investigation is in evaluating dyspnea. This nonspecific chief complaint frequently poses a significant diagnostic and therapeutic dilemma in patients with preexisting comorbidities, such as a history of heart failure and/or lung disease. Due to similar elements in the history, physical exam, and imaging, superimposed lower respiratory tract infection (LRTI) can be difficult to exclude. Viral versus bacterial etiologies for infection are often not clarified with this information either.

Triggered as a response to bacterial toxins, PCT holds promise in helping clinicians to elucidate these ambiguous cases. The Biomarkers in Acute Heart Failure (BACH) trial was a large international prospective study of 1641 patients presenting to the ED with dyspnea [2]. From the BACH trial came the first findings suggesting that PCT may enhance physician ability to identify pneumonia in patients with acute dyspnea, including the challenging cases of pneumonia superimposed upon acute heart failure (AHF) [3].

Relationships between PCT level, antibiotic initiation, and outcome were also evaluated in the subset of 568 patients from the BACH trial with AHF [3]. Key opportunities for improvement were evident at each end of the treatment spectrum: antibiotics were administered to 20% of AHF patients, but only 5% were actually diagnosed with pneumonia; on the other hand, antibiotics were not administered to 32% of the patients with high PCT values indicative of bacterial infection, half of whom had AHF. These decisions proved consequential. Patients with AHF and low PCT levels (≤0.05 ng/mL) had increased mortality when given antibiotics ($p = 0.049$); conversely, patients with AHF and high PCT levels (>0.21 ng/mL) had increased mortality when not given antibiotics ($p = 0.046$). Extrapolation of these results is greatly limited by the observational rather than randomized controlled study design, as well as the fact that this was a post-hoc analysis. Still, the BACH trial established a strong framework for further PCT studies.

The BACH trial suggested that PCT could lead to more judicious use of antibiotics in patients with AHF. Several characteristics of PCT make it an advantageous sepsis marker compared to the more commonly used C-reactive protein (CRP). PCT rises steeply within 4 h of a bacterial insult (sooner than the rise in CRP) but generally remains low in viral or noninfectious inflammatory states [4]. Spurred by these unique kinetics, PCT-guided algorithms for initiating or discontinuing antibiotics have been tested in several randomized controlled trials, such as ProHOSP. This large multicenter study of 1359 patients with suspected acute LRTI evaluated in the emergency department (ED) found that PCT algorithms significantly reduced antibiotic exposure without increasing adverse outcomes [5]. These findings were substantiated in the ProREAL

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survey, which intentionally tested the PCT algorithms outside of rigorous study settings in 3 countries with distinct antibiotic-prescribing practices [6].

In this issue of the International Journal of Cardiology, Kutz et al. present the first randomized trial to investigate the application of PCT-guided antibiotic therapy in patients with prior heart failure. In their secondary analysis of the subset of 233 ProHOSP patients with a history of heart failure, investigators found that PCT, used to guide initiation and subsequently discontinuation of antibiotics, was associated with significantly decreased antibiotic exposure regardless of low or high initial PCT values ($p < 0.01$ and $p = 0.02$, respectively). These results were consistent with the findings from the overall ProHOSP patient population [5]. The investigators also found that, in accordance with the BACH trial, antibiotics may be detrimental in patients with heart failure who do not have a bacterial infection: the low PCT group randomized to PCT-guided therapy had fewer 30-day adverse outcomes than those randomized to standard treatment ($p = 0.01$). Although not examined in this study, the reason for worse outcomes in this standard therapy group could be due to misdiagnosis leading to both delays in appropriate treatment as well as the initiation of inappropriate treatment (i.e. antibiotics).

This ProHOSP substudy further extends the notion that PCT is a useful biomarker for guiding treatment in patients with a history of heart failure. Unlike the BACH study, the ProHOSP study did not specifically evaluate for the presence of acute heart failure, and the degree to which decompensated heart failure played a role in the study population is undefined. In addition, natriuretic peptide levels were not reported. Previous studies have suggested that PCT can be used in conjunction with natriuretic peptides to further hone in on accurate diagnoses among patients who have signs and symptoms of both acute heart failure and respiratory infection [3]. Future studies with larger numbers of heart failure patients and more complete characterization of their cardiac status would be useful, to prospectively evaluate the interplay of these various biomarkers, PCT-guided therapy, and outcomes. One such study that will help define the role of PCT in heart failure patients is currently in the early stages. The Improved Management of heart failure with ProcAlCiTonin (IMPACT) trial, will enroll acutely dyspneic patients with suspected heart failure, and will randomize them to either PCT-guided or conventional therapy. Studies such as this one are critical to confirm results of prior substudies (including the ProHOSP study) and to help establish the true utility of PCT in heart failure patients.

Some physicians are resistant to the widespread use and uptake of biomarkers, believing that these laboratory tests should not overrule years of clinical judgment [7]. Biomarkers, however, are physiologic tools that can clearly contribute to optimizing care in difficult patient presentations. Aside from the BACH and ProHOSP substudies, the Epidemiological Study of Acute Dyspnea in Elderly Patients (EPIDASA) underscores the diagnostic challenge that clinicians face with this chief complaint. In this prospective observational study of 514 patients age 65 and older evaluated in the ED for dyspnea and acute respiratory failure, 24% of cardiogenic pulmonary edema was misdiagnosed. Other concerning results included a misdiagnosis rate of 20% overall and inappropriate treatment in 32% of patients, leading to increased mortality ($p < 0.001$) [8]. As clinicians strive to improve patient handoffs, meet early goal-directed therapy targets, and prevent hospital readmissions, increasing diagnostic speed and accuracy is essential. With biomarkers like PCT, these advancements are achievable.

The potential of PCT is broad, from predicting mortality risk [9] to optimizing clinician ability to diagnose LRTI in heart failure patients (and others) and safely guiding antibiotic use and duration [5]. In the future, one can envision a multimarker panel for patients with acute dyspnea and a history of cardiac problems, with PCT playing a prominent role alongside natriuretic peptides, highly sensitive troponin, and possibly other markers, to help clinicians sharpen diagnoses, develop treatment plans, and monitor clinical response. However, using multimarker panels in this way to personalize medical care for acutely ill cardiac patients is still a vision on the horizon in need of future studies and better definition. In contrast, the use of PCT to guide therapy seems to be a tangible and realistic target — if not for the present, then certainly for the very near future.

Conflicts of interest

NSL reports no relationships that could be construed as a conflict of interest. LBD has received consulting fees from Alere and diaDexus, has received speaking fees from Critical Diagnostics and Roche, has served on an Advisory Board for Singulex and Critical Diagnostics, and has received research supplies from Critical Diagnostics and BG Medicine.

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Excluding infection through procalcitonin testing improves outcomes of congestive heart failure patients presenting with acute respiratory symptoms: Results from the randomized ProHOSP trial

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ABSTRACT

Background/objectives: We sought to determine whether exclusion of infection and antibiotic stewardship with the infection biomarker procalcitonin improves outcomes in congestive heart failure (CHF) patients presenting to emergency departments with respiratory symptoms and suspicion of respiratory infection.
Methods: We performed a secondary analysis of patients with a past medical history of CHF formerly included in a Swiss multicenter randomized-controlled trial. The trial compared antibiotic stewardship according to a procalcitonin algorithm or state-of-the-art guidelines (controls). The primary endpoint was a 30-day adverse outcome (death, intensive care unit admission); the secondary endpoints included a 30-day antibiotic exposure.
Results: In the 110/233 analyzed patients (47.2%) with low initial procalcitonin (<0.25 μg/L), suggesting the absence of systemic bacterial infection, those randomized to procalcitonin guidance (n = 50) had a significantly lower adverse outcome rate compared to controls (n = 60): 4% vs. 20% (absolute difference −16.0%, 95% confidence interval (CI) −28.4% to −3.6%, P = 0.01), and significantly reduced antibiotic exposure [days] (mean 3.7 ± 4.0 vs. 6.5 ± 4.4, difference −2.8 [95% CI, −4.4 to −1.2], P < 0.01). When initial procalcitonin was ≥0.25 μg/L, procalcitonin-guided patients had significantly reduced antibiotic exposure due to early stop of therapy without any difference in adverse outcomes (25.8% vs. 24.6%, difference [95% CI] 1.2% [−14.5% to 16.9%, P = 0.88]).
Conclusions: CHF patients presenting to the emergency department with respiratory symptoms and suspicion for respiratory infection had decreased antibiotic exposure and improved outcomes when procalcitonin measurement was used to exclude bacterial infection and guide antibiotic treatment. These data provide further evidence for the potential harmful effects of antibiotic / fluid treatment when used instead of diuretics and heart failure medication in clinically symptomatic CHF patients without underlying infection.

1. Introduction

Respiratory symptoms such as cough, sputum production, dyspnea, tachypnea or pleuritic pain are among the most frequent complaints in patients presenting to emergency departments (EDs) [1], but are non-specific to the underlying medical condition. In patients with such symptoms, particularly those with a history of congestive heart failure (CHF), differentiating acute heart failure (AHF) from lower respiratory tract infection (LRTI) is challenging, due to the overlapping clinical picture and radiological findings [2]. Yet, rapid, accurate differential diagnosis is of utmost importance, as delayed targeted therapy [3] or inadequate therapy [4] increase the risk for adverse patient outcome. LRTI is found in only an appreciable minority of patients presenting to hospital with worsening CHF. Importantly, however, such infection significantly increases mortality risk in these patients: in one very large (n = 48,612) population-based study [5], LRTI had a

Abbreviations: AHF, acute heart failure; BACH, Biomarkers in Acute Heart Failure trial; CHF, congestive heart failure; CI, confidence interval; ED, emergency room; ICU, intensive care unit; LRTI, lower respiratory infection; OR, odds ratio; PCT, procalcitonin; SD, standard deviation.

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15.3% prevalence in CHF patients and an odds ratio (OR) of 1.60 (95% confidence interval [CI], 1.38 to 1.85, P < 0.001) for in-hospital death.

A novel approach to identify probable systemic bacterial infection in need of antibiotic therapy is the measurement of circulating serum procalcitonin (PCT) levels [6,7]. This biomarker is up-regulated in response to microbial toxins and certain bacterial-specific proinflammatory mediators, e.g., interleukin-1b, tumor necrosis factor-α and interleukin-6 [8]. In contrast, PCT expression is attenuated by the cytokines typically released in viral infections, e.g., interferon-γ [9,10]. Therefore PCT measurements both flag the presence and track the status of systemic bacterial infection, helping the clinician determine the necessity and optimal duration of antibiotic therapy in patients with respiratory symptoms [8–12]. Several studies have documented the benefits of PCT testing in emergency department patients presenting with fever [13] and respiratory symptoms [7,14,15] among others with regard to faster infection diagnosis, more accurate risk stratification, and optimization of the treatment.

Interestingly, the large, multinational, multicenter Biomarkers in Acute Heart Failure (BACH) trial of 1641 patients presenting to the ED with dyspnea [4] found significantly higher adjusted 90-day all-cause mortality rates in patients with a primary diagnosis of AHF (n = 568) who were not given antibiotics despite PCT elevation (>0.21 μg/L) than in patients with PCT elevation who were given these drugs (P = 0.046). Conversely, patients with PCT within the healthy general population reference range (≤0.05 μg/L, 97.5th percentile) [16], but who nonetheless were given antibiotics, had significantly higher adjusted 90-day all-cause mortality rates than did their untreated counterparts with low PCT (P = 0.049). Although BACH was an observational study, which does not allow inference of causality, these results nonetheless prompt speculation that inadequate therapy, including inappropriate use or inappropriate withholding of antibiotics, may affect mortality in heart failure patients.

We therefore performed a secondary analysis investigating the effects of using PCT to help guide antibiotic treatment decisions in patients with a past medical history of CHF and suspicion of respiratory infection. We studied patients who participated in a previously-concluded antibiotic stewardship trial in individuals presenting to the ED with acute respiratory symptoms — ProHOSP [17]. Like BACH, ProHOSP was a large (n = 1359), prospective, multicenter study. Unlike BACH, however, ProHOSP had a randomized, controlled, interventional design, which allows clearer connections to be drawn between PCT monitoring and the outcome of CHF patients with acute respiratory symptoms.

2. Methods

2.1. ProHOSP

Details of ProHOSP's design have been published elsewhere [18]. Briefly, we consecutively recruited adults (age ≥18 years) with presumed LRTI of <28 days' duration who presented to EDs at any of six Swiss secondary or tertiary care, academic or non-academic hospitals from October 2006 to March 2008. Patients had to have come from the community or a nursing home with one or more of cough, sputum production, dyspnea, tachypnea, or pleuritic pain, plus at least one finding during auscultation (rales, crepitation) or one sign of infection (core body temperature >38.0 °C, shivering, leukocyte count >10 or <4 cells × 10^9/L). Patients were excluded for active intravenous drug abuse, severe immunosuppression other than corticosteroids, potentially imminently life-threatening medical comorbidity, or hospital-acquired pneumonia, defined as a new chest radiographic infiltrate occurring ≥48 h after hospital admission or after prior hospitalization within 14 days before enrollment. Ongoing chronic antibiotic treatment at presentation also was a ground for exclusion, but short-term antibiotic pretreatment did not affect eligibility.

Patients were stratified by study center and presumed type of LRTI, and randomized 1:1 to antibiotic administration according to either i) state-of-the-art evidence-based guidelines tailored to the patient's putative type of LRTI (control group) [19–22] or ii) a previously validated algorithm [23,24] recommending antibiotics only if PCT levels were elevated (PCT group) [18]. Specifically, the PCT algorithm discouraged initiation of antibiotics when PCT was <0.25 μg/L, strongly so when the level was <0.1 μg/L. Conversely, the algorithm encouraged this intervention when PCT was ≥0.25 μg/L, strongly so when the level was >0.5 μg/L. During follow-up, all patients in the PCT group had repeated PCT testing, and the algorithm recommended an early stop of antibiotics when PCT dropped to <0.25 μg/L. For patients with initial PCT >10 μg/L, the algorithm recommended halting antibiotics when PCT concentration had decreased to ≥80%, strongly so when the decrease was ≥90%. The algorithm could be overruled by the treating physician for predefined clinical reasons [18]. Throughout the course of care, the choice of antibiotic regimen for PCT or control patients was at their treating physician's discretion.

PCT was measured in all patients in both randomization arms, but results were communicated only to the treating physicians of patients in the PCT group, via website and together with an antibiotic treatment recommendation based on the algorithm. PCT determinations were scheduled to take place in samples drawn at presentation in the entire study cohort. In inpatients not started on antibiotics, follow-up PCT measurements were made in samples obtained 6–24 h post-admission, while in those on antibiotics, PCT was assessed in samples taken on hospitalization days 3, 5 and 7, so long as antibiotic therapy was ongoing. Outpatients were to have follow-up measurements only if no clinical improvement occurred, in which case PCT was to be determined in samples obtained 24–72 h post-ED presentation.

PCT results were routinely available around the clock within 1–2 h of blood sampling. Measurements were performed at each study center's accredited laboratory by staff blinded to any non-laboratory patient data; an automated rapid sensitive assay (Kryptor PCT; Thermo Fisher Scientific [formerly B·R·A·H·M·S AG], Hennigsdorf, Germany) with a 0.02 μg/L detection limit, 0.06 μg/L functional assay sensitivity, and <20 min incubation time was used.

Upon each patient's presentation, data regarding baseline characteristics, comorbidities, laboratory and vital parameters, radiological results, and current medication were assembled. Comorbidities were identified through patient report and medical chart review.

2.2. Analyzed patients and endpoints

This analysis included all patients enrolled in ProHOSP with a history of CHF (based on patient report and medical chart review, or both) and available initial PCT measurements. The primary endpoint was "adverse outcome", a composite comprising ICU admission, all-cause mortality, or both, within 30 days after study inclusion. Secondary endpoints, all within the same time frame, were 1) total duration of antibiotic exposure (via any administration route); 2) antibiotic-related side effects including diarrhea, nausea, vomiting, and allergic reactions, as judged by the treating physician; and 3) aggregate hospital length-of-stay (ward, ICU or both). Outcomes were assessed during the hospital stay by study physicians not blinded to the patient's group, and through structured phone interviews at day 30 by medical students blinded to the randomization arm.

An independent committee monitored safety and adverse events during the trial. ProHOSP's protocol was approved by participating centers' ethics committees; patients provided written informed consent, including allowing the use of their data in anonymized secondary analyses such as this one. ProHOSP was registered in the "Current Controlled Trials Database" (identifier ISRCTN 95122877; http://www.controlled-trials.com/ISRCTN95122877).

2.3. Statistics

Our primary hypothesis was, based on results of the observational BACH trial [4], that in patients with a history of CHF presenting to the ED with acute respiratory symptoms, PCT-aided antibiotic stewardship would improve clinical outcomes, namely, reduce ICU admissions and mortality, by enhancing diagnostic assessment and decision-making regarding starting or continuing antibiotics. To explore relationships among PCT levels, antibiotic treatment or lack thereof, and outcomes, patients were prospectively divided into two groups: those with initial PCT <0.25 μg/L ("low", indicating minimal likelihood of systemic bacterial infection) versus ≥0.25 μg/L ("elevated", indicating a high probability of systemic bacterial infection). This cut-off was based on ProHOSP's PCT threshold for recommended antibiotic therapy [23]. Within each of these two cut-off groups, we compared patients randomized to the PCT arm or the control arm of ProHOSP. To study differences in primary and secondary endpoints between randomization groups within the low or elevated PCT groups, we used chi-square tests for categorical variables and Student t-test for continuous variables. We calculated 95% CIs for the absolute differences between groups. We also calculated ORs and their 95% CIs through logistic regression analysis. Additionally, for illustration, we present Kaplan–Meier plots of times to adverse outcome.

Discrete variables are expressed as counts (percentages) or vice versa, continuous variables, as means and standard deviations (SDs). All reported CIs are two-sided; tests were carried out at the two-sided 5% significance level. Analyses were performed with STATA 9.2 (Stata Corp, College Station, Texas, USA).

3. Results

3.1. Analyzed patients

Of 1359 patients enrolled in ProHOSP, 233 (17.1%) were identified as having a history of CHF and were thus included in this analysis. The presumed respiratory diagnoses included pneumonia (68%), COPD exacerbation (14%), bronchitis (10%) and other respiratory infections (8%). Besides CHF, these patients had a high prevalence of other cardiovascular disease and risk factors, and were virtually all treated as inpatients (Table 1). Members of the PCT-guided group (n = 116) or the control

Table 1
Patient characteristics in the overall study sample and by ProHOSP randomization group.

Characteristics	All patients (n = 233)	PCT group (n = 116)	Control group (n = 117)	P
Demographic characteristics				
Age, median (IQR), years	81.0 (14.0)	80.5 (14.5)	81.0 (13.0)	0.70
Male, % (n)	61.8% (144)	65.5% (76)	58.1% (68)	0.25
Coexisting illnesses, % (n)[a]				
Coronary heart disease	41.6% (97)	42.2% (49)	41.0% (48)	0.85
Cerebrovascular disease	10.3% (24)	11.2% (13)	9.4% (11)	0.65
Peripheral artery disease	12.0% (28)	8.6% (10)	15.4% (18)	0.11
Chronic renal failure	32.6% (76)	33.6% (39)	31.6% (37)	0.75
Diabetes mellitus	22.7% (53)	24.1% (28)	21.4% (25)	0.64
Chronic obstructive pulmonary disease	50.2% (117)	43.1% (50)	57.3% (67)	0.03
Cardiovascular risk factors				
Current or former tobacco user, % (n)	20.5% (46)	23.3% (27)	16.2% (19)	0.16
Pack years, median (IQR)	40.0 (25.0)	40.0 (30.0)	40.0 (25.0)	0.53
Body mass index > 25 kg/m^2, % (n)	67.8% (158)	63.8% (74)	71.8% (84)	0.19
Clinical history, % (n)				
Antibiotic pretreatment on presentation	24.8% (57)	21.7% (25)	27.8% (32)	0.29
Cough	84.5% (197)	84.5% (98)	84.6% (99)	0.84
Dyspnea	84.1% (196)	81.9% (95)	86.3% (101)	0.40
New York Heart Association class				
I	7.3% (17)	6.9% (8)	7.7% (9)	0.82
II	19.3% (45)	22.4% (26)	16.2% (19)	0.23
III	37.3% (87)	32.8% (38)	41.9% (49)	0.15
IV	20.2% (47)	19.8% (23)	20.5% (24)	0.90
Fever or chills	48.1% (112)	49.1% (57)	47.0% (55)	0.75
Clinical findings				
Confusion, % (n)	6.0% (14)	7.8% (9)	4.3% (5)	0.31
Respiratory rate, median (IQR), breaths/min	20 (11)	22 (10)	20 (10)	0.89
Systolic blood pressure, median (IQR), mm Hg	130 (33)	130 (32)	130 (34)	0.77
Diastolic blood pressure, median (IQR), mm Hg	74 (21)	74 (24)	74 (16)	0.81
Heart rate, median (IQR), beats/min	92 (27)	91 (29)	93 (30)	0.34
Rales during auscultation, % (n)	77.3% (180)	78.4% (91)	76.1% (89)	0.95
Body temperature, median (IQR), °C	37.8 (1.7)	37.8 (1.8)	37.8 (1.5)	0.56
Initial laboratory findings, median (IQR) unless indicated otherwise				
PCT, μg/L	0.27 (0.92)	0.30 (1.14)	0.24 (0.52)	0.25
PCT ≥0.25 μg/L, % (n)	52.8% (123)	56.9% (66)	48.7% (57)	0.21
Pro-atrial natriuretic peptide, pmol/L	331.0 (301.0)	355.0 (315.5)	317.0 (229.0)	0.25
White blood cell count, cells × 10^9/L	11.1 (7.2)	11.4 (7.5)	11.1 (6.9)	0.27
C-reactive protein, mg/L	104.3 (150.0)	109.0 (156.0)	99.3 (143.5)	0.54
Treatment site, % (n)				
Inpatient	97.9% (228)	98.3% (114)	97.4% (114)	0.66

PCT, procalcitonin; and IQR, interquartile range.
[a] All cormorbidity data were based on patient report and medical chart review. Due to inclusion criteria for the present analysis, all patients had a history of CHF.

group (n = 117) in ProHOSP were well-balanced (P ≥ 0.11) regarding all tested demographic, anamnestic, clinical, and laboratory variables, site-of-care, or prevalence of LRTI or AHF as the final diagnosis, except that the control group had a significantly higher prevalence of chronic obstructive pulmonary disease (Table 1). The groups also were similar regarding the proportions presenting at each study site (data not shown). Blood culture, sputum culture and urine antigen testing showed evidence of typical respiratory pathogens (mainly *Streptococcus pneumonia*) in 28 patients (12.0%).

Median PCT levels (μg/L) in the low PCT group were 0.14, 0.13, 0.10 and 0.10 without any difference between randomization arms (P > 0.05 for all comparisons). In the high PCT group, median PCT levels were 0.99, 0.63, 0.31 and 0.19; again without any difference between randomization groups (P > 0.05 for all comparisons).

3.2. Outcomes: All analyzed patients

Of the 233 analyzed patients, 45 (19.3%) in total reached the primary endpoint of adverse outcome within 30 days of ED presentation, including all-cause mortality in 22 (9.4%) (occurring in the hospital in 20 [8.6%]) and ICU admission in 27 (11.6%). Four of these patients (1.7%) reached both outcomes.

Overall, mortality or ICU admission combined was non-significantly lower in the PCT group than in controls: 16.4% (19/116) versus 22.2% (26/117), P = 0.26, −5.8% absolute difference (95% CI −16.0% to 4.4%). On average, antibiotic exposure (by any administration route) was significantly shorter in PCT-guided patients versus controls: 6.2 versus 8.4 days, absolute difference −2.1 days (95% CI −3.5 to −0.8 days, P < 0.01). Antibiotic side effect incidence was 18.1% in the PCT group compared to 34.2% among the controls (P < 0.01) (absolute difference −16.1% [−27.3% to −4.9%]). Mean total hospital length-of-stay in survivors was similar, 13.4 [±0.8] days versus 12.5 [±0.8] days (absolute difference of 0.9 days, 95% CI −1.3 to 3.1 days, P = 0.25).

3.3. Patients with initial PCT <0.25 μg/L

The 110 patients (47.2%) with low initial PCT, indicating a probable absence of systemic bacterial infection, were well balanced between the PCT group and the control group (Table 2). As seen in Table 3 and Fig. 1, the PCT-guided group had a significantly lower adverse outcome rate and significantly shorter antibiotic exposure than did controls. The PCT-guided group also had lower 30-day all-cause mortality and antibiotic side effect incidence and duration, but these differences did not reach significance. The groups had similar hospital length-of-stay. Additionally, result of a time to event analysis was similar where the time to the first adverse outcome was significantly longer in the PCT-guided group (Fig. 2).

This significant finding was also confirmed in logistic regression analysis where PCT testing had an odds ratio (OR) of 0.17 (95% CI 0.04, 0.79, P = 0.02) for adverse outcome. This was also true when adjusting

Table 2
Patient characteristics by ProHOSP randomization group in patients with low PCT values (<0.25 μg/L) (n = 110).

Characteristics	PCT group (n = 50)	Control group (n = 60)	P
Demographic characteristics			
Age, median (IQR), years	79.0 (20.0)	77.5 (14.0)	0.78
Male, % (n)	66.0% (33)	50.0% (30)	0.09
Coexisting illnesses, % (n)[a]			
Coronary heart disease	44.0% (22)	43.3% (26)	0.94
Cerebrovascular disease	12.0% (6)	5.0% (3)	0.18
Peripheral artery disease	6.0% (3)	21.7% (13)	0.20
Chronic renal failure	16.0% (8)	25.0% (15)	0.25
Diabetes mellitus	30.0% (15)	20.0% (12)	0.23
Chronic obstructive pulmonary disease	44.0% (22)	60.0% (36)	0.09
Cardiovascular risk factors			
Current or former tobacco user, % (n)	18.0% (9)	18.3% (11)	0.97
Pack years, median (IQR)	40.0 (40.0)	40.0 (20.0)	0.83
Body mass index > 25 kg/m^2, % (n)	74.0% (37)	70.0% (42)	0.64
Clinical history, % (n)			
Antibiotic pretreatment on presentation	20.0% (10)	25.0% (15)	0.53
Cough	88.0% (44)	91.7% (55)	0.51
Dyspnea	80.0% (40)	88.3% (53)	0.32
New York Heart Association class			
I	6% (3)	6.7% (4)	0.89
II	20% (10)	20.0% (12)	1.00
III	40% (20)	38.3% (23)	0.86
IV	14.0% (7)	23.3% (14)	0.22
Fever or chills	40.0% (20)	36.7% (22)	0.73
Clinical findings			
Confusion, % (n)	4.0% (2)	3.6% (2)	0.86
Respiratory rate, median (IQR), breaths/min	20 (9)	20 (12)	0.87
Systolic blood pressure, median (IQR), mm Hg	130 (28)	135 (33)	0.31
Diastolic blood pressure, median (IQR), mm Hg	75 (19)	78 (16)	0.46
Heart rate, median (IQR), beats/min	83 (24)	90 (30)	0.20
Rales during auscultation, % (n)	68.0% (34)	70.0% (42)	0.55
Body temperature, median (IQR), °C	37.5 (1.8)	37.4 (1.6)	0.51
Initial laboratory findings, median (IQR) unless indicated otherwise			
PCT, μg/L	0.13 (0.09)	0.14 (0.09)	0.75
Pro-atrial natriuretic peptide, pmol/L	372.0 (398.0)	298.0 (226.0)	0.13
White blood cell count, cells × 10^9/L	10.5 (4.6)	10.1 (5.8)	0.24
C-reactive protein, mg/L	72.2 (94.0)	83.0 (88.0)	0.87
Treatment site, % (n)			
Inpatient	98% (49)	100% (60)	0.27

PCT, procalcitonin; and IQR, interquartile range.
[a] All cormorbidity data were based on patient report and medical chart review. Due to inclusion criteria for the present analysis, all patients had a history of CHF.

the analysis for type of infection (i.e., COPD) (OR 0.19 [95% CI 0.04, 0.91, P = 0.037]).

In addition, we also investigated the effects of PCT testing in different subgroups representing different probabilities for bacterial infections. As demonstrated in Fig. 3, in patients with normal WBC (≤10 G/L), normal body temperature (<38 °C) and no history of fever the effect of PCT testing on outcome was more favorable compared to patients with higher WBC, higher temperature and fever. Only in patients with low PCT, however, were these effects significant.

3.4. Patients with initial PCT ≥ 0.25 μg/L

Among patients with elevated initial PCT, indicating probable systemic infection, the group randomized to PCT guidance or the control group was well-balanced, except that larger proportions of the controls were overweight/obese and had New York Heart Association class III dyspnea (Table 4). The PCT-guided group had significantly shorter antibiotic courses and overall lower antibiotic side effect incidence as compared to control patients. There was no difference in clinical outcomes of patients between the randomization groups (Table 5, Fig. 1).

4. Discussion

Discriminating acute LRTI from AHF in patients with past medical history of CHF presenting to the ED with respiratory symptoms and suspicion of infection is difficult because of overlapping and non-specific physical exam and chest radiological abnormalities. Incorrect differentiation may have dramatic consequences because patients with LRTIs are potentially volume-depleted and thus require fluids along with antibiotic therapy, whereas AHF patients have fluid overload and require diuretics, among other medications.

The present analysis may help address this diagnostic difficulty in emergency care through its main finding, that in patients with CHF and low initial PCT values (≤0.25 μg/L), antibiotic stewardship aided by measuring that blood biomarker was associated with significantly less frequent adverse outcome, defined as death or ICU admission. Specifically, PCT guidance was associated with a reduction in adverse outcome incidence from 20% to 4% in PCT-guided patients relative to controls. These groups were similar in all tested characteristics, but differed significantly regarding antibiotic exposure — which was lower in the PCT-guided patients. These observations suggest that ruling out LRTI, and hence, avoiding misuse of antibiotic therapy, through PCT measurement may be associated with improved clinical outcomes of CHF patients presenting to the ED with respiratory symptoms. Interestingly, a subgroup analysis found the most effects of PCT testing in patients with low probability for bacterial infection, i.e. patients with low PCT levels, low WBC levels, low body temperature and no history of fever. In these patients a biomarker such as PCT may help to rule out bacterial pneumonia and thus improve the therapeutic management.

4.1. Context

These results accord with observations in BACH [4] that patients with past medical history of CHF presenting to the ED with

Table 3
Primary and secondary endpoints by initial PCT value and ProHOSP treatment group assignment: Patients with low initial PCT (<0.25 μg/L) (n = 110). Bold value indicate significance at p < 0.05.

Outcomes	PCT group (n = 50)	Control group (n = 60)	Absolute difference, PCT group vs. control group (95% CI)	P
Primary endpoint				
30-Day adverse outcome (all-cause mortality, ICU admission or both), % (n)	4.0% (2)	20.0% (12)	−16.0% (−28.4% to −3.6%)	**0.01**
Secondary endpoints				
30-Day all-cause mortality, % (n)	4.0% (2)	11.7% (7)	−7.7% (−18.1% to 2.7%)	0.14
30-Day antibiotic exposure (days), mean ± SD	3.7 ± 4.0	6.5 ± 4.4	−2.8 (−4.4 to −1.2) days	**<0.01**
30-Day reported antibiotic-related side effects[a]				
Incidence of reported side effects, % (n)	14.0% (7)	28.3% (17)	−14.3% (−29.9% to 1.2%)	0.07
Duration of reported side effects (days), mean ± SD	3.0 ± 1.4	4.0 ± 3.2	−1.0 (−6.0 to 4.0) days	0.68
Hospital length-of-stay (hospital survivors only) (days), mean ± SD	(n = 48) 12.7 ± 8.3	(n = 53) 10.9 ± 7.1	1.9 (−1.2 to 4.9) days	0.23

CI, confidence interval; ICU, intensive care unit; and SD, standard deviation. Numbers may not add exactly due to rounding.
[a] As assessed by the attending physicians.

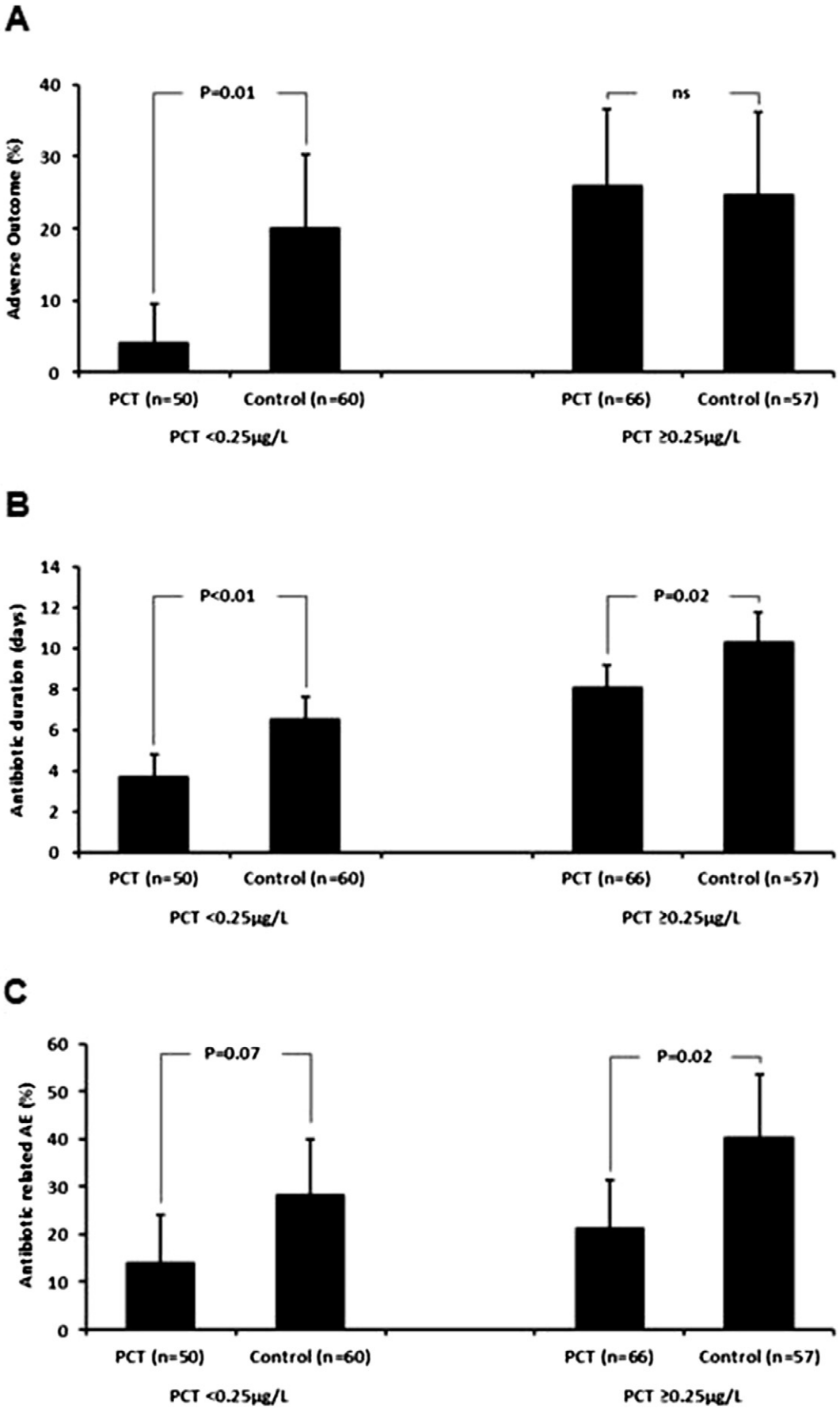

Fig. 1. Endpoints by randomization group in patients with low (<0.25 µg/L) or high (≥0.25 µg/L) initial PCT levels. Panel A, primary endpoints. Panels B and C, selected secondary endpoints. PCT, procalcitonin.

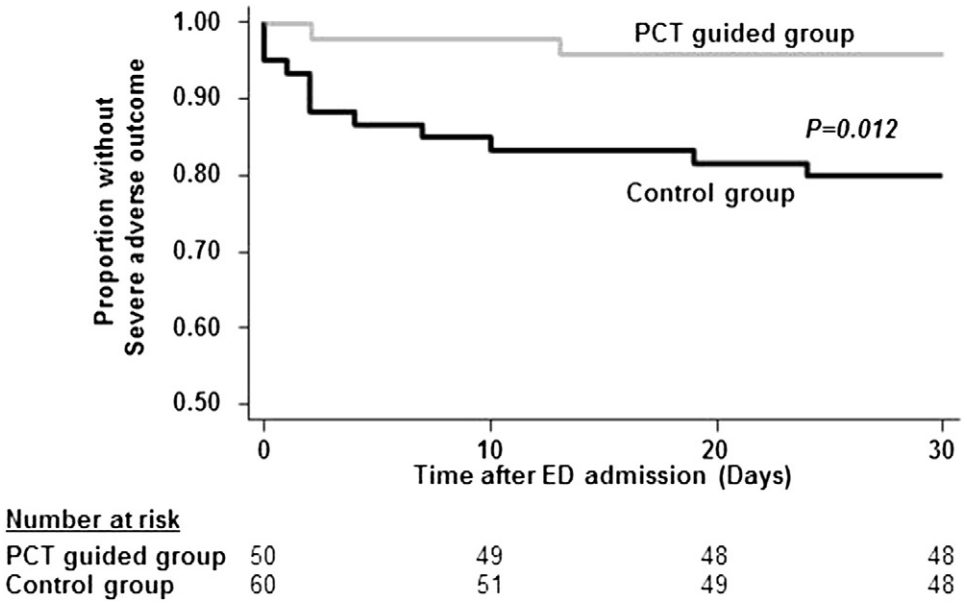

Fig. 2. Time to the first adverse outcome by randomization group in patients with low initial PCT levels (<0.25 μg/L). Adverse outcome included all-cause mortality or ICU admission. Difference between groups, P = 0.012, log rank test. ED, emergency department; ICU, intensive care unit; and PCT, procalcitonin.

respiratory symptoms and PCT values within the healthy population reference range (<0.05 μg/L) had better outcomes if they did not receive antibiotics. Yet, as acknowledged by the BACH investigators, due to their study's lack of randomization, causal inferences could not be drawn. For example, the observed difference in death rates may have been attributable to sicker patients more often receiving antibiotics. Our data from a subgroup of patients from randomized, controlled, interventional trial therefore strengthen support for the hypothesis that the initial PCT concentration effectively identifies CHF patients whose respiratory symptoms are unlikely to be due to systemic bacterial infection, and in whom antibiotic therapy may therefore be counterproductive. Whether these results are also true in CHF patients with dyspnea due to acute heart failure needs verification in a prospective trial.

Our results are also in line with previous ED studies including patients with fever, where PCT was found to have several advantages, such as faster diagnosis, more accurate risk stratification, and optimization of the treatment, with consequent benefit to the patient and considerably reduced costs [13,25]. Our results also correspond to the main randomized ProHOSP trial [17] where PCT testing resulted in a safe and marked reduction in antibiotic use of 34.8% (95% CI, −40.3% to −28.7%) in patients with different severities of respiratory infections without negatively impacting on clinical outcomes (non-inferiority) and with significantly reducing antibiotic-associated side effects.

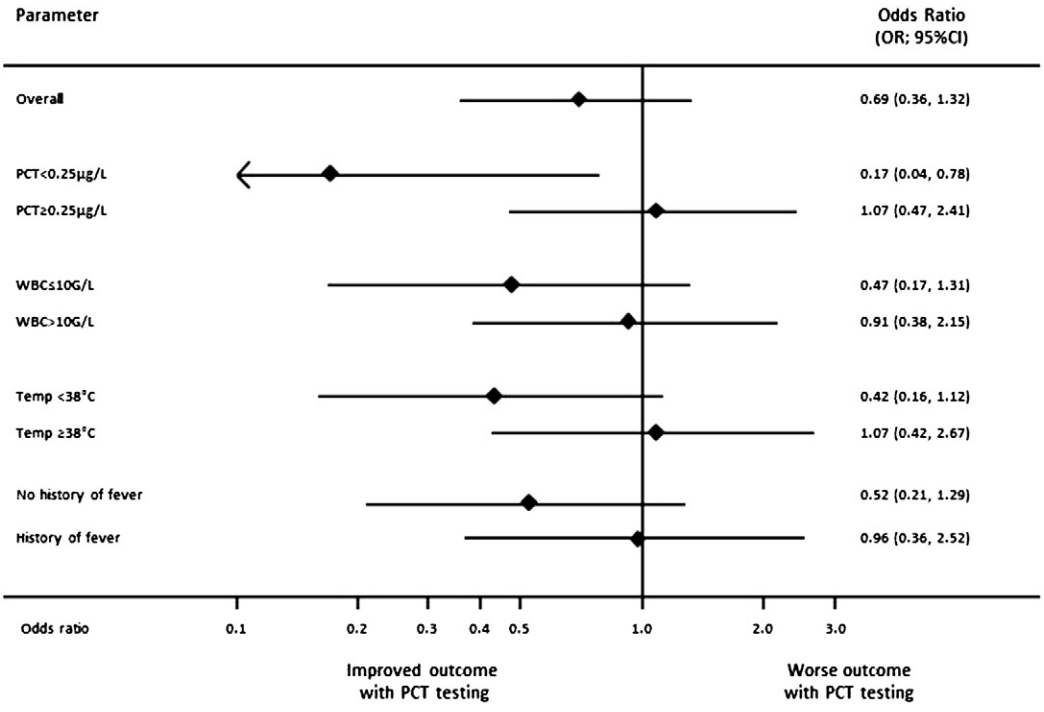

Fig. 3. Sensitivity analysis about the effect of PCT testing within different subgroups. PCT, procalcitonin; WBC, white blood cells count; and Temp, temperature.

Table 4
Patient characteristics by ProHOSP randomization group in patients with elevated PCT values (≥0.25 μg/L) (n = 123). Bold value indicate significance at p < 0.05.

Characteristics	PCT group (n = 66)	Control group (n = 57)	P
Demographic characteristics			
Age, median (IQR), years	82.5 (11.0)	82.0 (11.0)	0.69
Male, % (n)	65.2% (43)	66.7% (38)	0.86
Coexisting illnesses, % (n)[a]			
Coronary heart disease	40.9% (27)	38.6% (22)	0.79
Cerebrovascular disease	10.6% (7)	14.0% (8)	0.56
Peripheral artery disease	10.6% (7)	8.8% (5)	0.73
Chronic renal failure	47.0% (31)	38.6% (22)	0.35
Diabetes mellitus	19.7% (13)	22.8% (13)	0.67
Chronic obstructive pulmonary disease	42.4% (28)	54.4% (31)	0.19
Cardiovascular risk factors			
Current or former tobacco user, % (n)	27.3% (18)	14.0% (8)	0.07
Pack years, median (IQR)	40.0 (30.0)	55.0 (37.5)	0.22
Body mass index >25 kg/m^2, % (n)	56.1% (37)	73.7% (42)	**0.04**
Clinical history, % (n)			
Antibiotic pretreatment on presentation	22.7% (15)	29.8% (17)	0.33
Cough	81.1% (54)	77.2% (44)	0.66
Dyspnea	83.3% (55)	84.2% (48)	0.83
New York Heart Association class			
I	7.6% (5)	8.8% (5)	0.81
II	24.2% (16)	12.3% (7)	0.09
III	27.3% (18)	45.6% (26)	**0.03**
IV	24.2% (16)	17.5% (10)	0.36
Fever or chills	56.1% (37)	57.9% (33)	0.84
Clinical findings			
Confusion, % (n)	10.6% (7)	5.3% (3)	0.36
Respiratory rate, median (IQR), breaths/min	22 (13)	20 (7)	0.65
Systolic blood pressure, median (IQR), mm Hg	131 (30)	128 (35)	0.40
Diastolic blood pressure, median (IQR), mm Hg	73 (25)	70 (19)	0.64
Heart rate, median (IQR), beats/min	94.5 (38)	95 (27)	0.75
Rales during auscultation, % (n)	86.4% (57)	82.5% (47)	0.76
Body temperature, median (IQR), °C	38.1 (1.7)	38.1 (1.5)	0.90
Initial laboratory findings, median (IQR) unless indicated otherwise			
PCT, μg/L	0.99 (2.20)	0.81 (2.99)	0.65
Pro-atrial natriuretic peptide, pmol/L	339.0 (288.0)	336.0 (318.0)	0.95
White blood cell count, cells × 10^9/L	12.8 (8.0)	13.1 (8.3)	1.00
C-reactive protein, mg/L	152.0 (170.0)	154.0 (150.0)	0.94
Treatment site, % (n)			
Inpatient	98.5% (65)	94.7% (54)	0.24

PCT, procalcitonin; and IQR, interquartile range.
[a] All cormorbidity data were based on patient report and medical chart review. Due to inclusion criteria for the present analysis, all patients had a history of CHF.

Our results in "low initial PCT" patients are also in line with findings in a recent meta-analysis [26]. This meta-analysis incorporated individual data from 4211 patients with respiratory infections from fourteen previous randomized, controlled trials comparing antibiotic administration based on a PCT algorithm versus usual care. Among outcomes examined was "treatment failure", a composite defined differently according to the setting (primary care, ED, ICU), but always including short-term death, and frequently, respiratory tract infection worsening, complications or recurrence. Interestingly, PCT guidance was associated with a significantly lower risk for treatment failure (OR 0.82, 95% CI 0.71–0.97, P = 0.02). In group analysis, this effect was robust for patients presenting to the ED (OR 0.76, 95% CI 0.61–0.95, P = 0.014). It remains somewhat unclear why PCT monitoring resulted in improvement in this outcome. Possible explanations include (a) PCT may provide additional useful information which can influence decision-making in areas such as safe and early discharge; (b) in controls, treatment failures may relate to prolonged and unjustified antibiotic exposure; and (c) in line with the current report, PCT may improve individualized treatment decisions regarding initial medication in polymorbid patients with different possible etiologies for their respiratory symptoms.

Patients with initial high PCT were found to have lower antibiotic exposure — mainly due to earlier stop of antibiotic therapy (when PCT levels dropped below 0.25 μg/L or by at least 80% of the maximum level) without affecting the outcome of patients. However, this analysis was underpowered to find differences in patient outcomes associated with antibiotic exposure such as side effects or emergence of multi resistant bacteria. Nevertheless, previous trials focusing on these issues found benefits of early stop of therapy in patients with high PCT [27–29].

4.2. Limitations

Nonetheless, several limitations should be considered when interpreting our results. Firstly, this was a secondary analysis of a trial designed and powered to answer a different question, i.e., whether in a broader patient population, PCT-aided antibiotic stewardship could reduce antibiotic exposure and side effects without compromising patient outcomes. Clinical information about CHF and its treatment therefore was not systematically collected during ProHOSP and may not always have been complete, a situation that only partly could be mitigated by retrospective chart review. It is thus possible that CHF in patients was under-diagnosed or over-diagnosed. Secondly, this analysis involved a relatively small part of the ProHOSP cohort (n = 233/1359), and our finding of improved outcomes with PCT guidance was seen in an even smaller group, patients with low initial PCT (n = 110). Thirdly, unlike in the BACH trial where patients with dyspnea were included, the ProHOSP population had a strong suspicion of LRTI and it remains unclear whether results are generalizable to patients with a lower pretest probability of such infection or of AHF. Forth, it is not possible to see whether in an individual patient with suspicion of respiratory infection antibiotics were necessary or not given the absence of a true infection gold standard (i.e., only 12% of our sample had positive proof of infection). The finding of this analysis that PCT testing resulted in lower antibiotic exposure and thereby improved patient outcomes provides, however, indirect proof that PCT improves infection diagnosis and management. Fifth, no measurement of natriuretic peptides was routinely performed in this study

Table 5
Primary and secondary endpoints by initial PCT value and ProHOSP treatment group assignment: Patients with elevated initial PCT (≥0.25 μg/L) (n = 123). Bold value indicate significance at p < 0.05.

	PCT group (n = 66)	Control group (n = 57)	Absolute difference, PCT group vs. control group (95% CI)	P
Primary endpoint				
30-Day adverse outcome (all-cause mortality, ICU admission or both), % (n)	25.8% (17)	24.6% (14)	1.2% (−14.5% to 16.9%)	0.88
Secondary endpoints				
30-Day all-cause mortality, % (n)	10.6% (7)	10.5% (6)	0.1% (−11.0% to 11.2%)	0.99
30-Day antibiotic exposure (days), mean ± SD	8.1 ± 4.6	10.3 ± 5.6	−2.2 (−4.0 to −0.3)	**0.02**
30-Day reported antibiotic-related side effects[a]				
Incidence of reported side effects, % (n)	21.2% (14)	40.4% (23)	−19.1% (−35.3% to −2.9%)	**0.02**
Duration of side effects (days), mean ± SD	2.8 ± 2.4	4.0 ± 3.7	−1.2 (−3.7 to 1.4)	0.35
Hospital length-of-stay (survivors only) (days), mean ± SD	(n = 59) 13.9 ± 7.6	(n = 51) 14.2 ± 9.2	−0.3 (−3.5 to 2.9)	0.84

CI, confidence interval; ICU, intensive care unit; and SD, standard deviation. Numbers may not add exactly due to rounding.
[a] As assessed by the attending physicians.

which would help in the better characterization of our cohort. Finally, we did not blind physicians with regard to allocation to control or intervention group, and also outcome assessment was only partly blinded, which may have introduced some bias.

4.3. Future directions

Given these limitations, and the different PCT cut-offs used in BACH [4] and in our analysis, a large, randomized interventional trial is urgently needed to definitively validate in the CHF patient population with acute respiratory symptoms and possible bacterial LRTI the potential benefits of PCT testing, including allowing earlier adequate treatment of the underlying condition. Maisel and colleagues have announced plans for such a trial (presentation by Alan Maisel, MD, International Symposium on Intensive Care and Emergency Medicine, Brussels, Belgium, March 21, 2013).

Additionally, it appears that outcome advantages associated with PCT monitoring will be assessed in a broader spectrum of cardiovascular patients. Based on a four-trial meta-analysis showing such advantages from preventing post-stroke infections through antibiotic therapy [30], Ulm et al. plan to investigate in the STRAWINSKI study whether PCT-based early identification and treatment of mainly respiratory bacterial infections improve functional outcome after severe ischemic stroke [31]. If this latter hypothesis also proves to be correct, PCT may be a promising diagnostic biomarker in the field of cardiovascular diseases.

5. Conclusions

Patients with a medical history of CHF presenting to the emergency department with respiratory symptoms and suspicion for respiratory infection had decreased antibiotic exposure and improved outcomes when PCT measurement was used to exclude bacterial infection and guide antibiotic treatment. These data provide further evidence for the potential harmful effects of antibiotics when used indiscriminately in clinically symptomatic CHF patients without underlying infection. Whether timelier, more appropriate treatment of AHF explains that our results need verification in a well-powered randomized trial.

Conflict of interest

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