Use of procalcitonin for the diagnosis of pneumonia in patients presenting with a chief complaint of dyspnoea: results from the BACH (Biomarkers in Acute Heart Failure) trial

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Aims
Biomarkers have proven their ability in the evaluation of cardiopulmonary diseases. We investigated the utility of concentrations of the biomarker procalcitonin (PCT) alone and with clinical variables for the diagnosis of pneumonia in patients presenting to emergency departments (EDs) with a chief complaint of shortness of breath.

Methods and results
The BACH trial was a prospective, international, study of 1641 patients presenting to EDs with dyspnoea. Blood samples were analysed for PCT and other biomarkers. Relevant clinical data were also captured. Patient outcomes were assessed at 90 days. The diagnosis of pneumonia was made using strictly validated guidelines. A model using PCT was more accurate [area under the curve (AUC) 72.3%] than any other individual clinical variable for the diagnosis of pneumonia in all patients, in those with obstructive lung disease, and in those with acute heart failure (AHF). Combining physician estimates of the probability of pneumonia with PCT values increased the accuracy to 86% for the diagnosis of pneumonia in all patients. Patients with a diagnosis of AHF and an elevated PCT concentration (>0.21 ng/mL) had a worse outcome if not treated with antibiotics (P = 0.046), while patients with low PCT values (<0.05 ng/mL) had a better outcome if they did not receive antibiotic therapy (P = 0.049).

Conclusion
Procalcitonin may aid in the diagnosis of pneumonia, particularly in cases with high diagnostic uncertainty. Importantly, PCT may aid in the decision to administer antibiotic therapy to patients presenting with AHF in which clinical uncertainty exists regarding a superimposed bacterial infection.

Trial registration: NCT00537628

Keywords
Acute heart failure • Procalcitonin • Pneumonia • Survival • Diagnosis

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Introduction

The chief complaint of shortness of breath in patients presenting with suspected pneumonia requires a rapid accurate assessment so that early antibiotic therapy can be initiated and appropriate additional management implemented.\(^1,2\) The diagnosis of pneumonia can be difficult in patients with pre-existing parenchymal lung disease because of baseline abnormal chest imaging, or in those presenting with an acute exacerbation of obstructive lung disease (AECOPD), bronchitis, or viral syndrome, because of overlapping symptoms. Detecting superimposed pneumonia in patients presenting with acute heart failure (AHF) is additionally difficult because of the non-specific nature of chest X-ray abnormalities in the setting of cardiogenic pulmonary oedema. Unfortunately, misdiagnoses may result in delayed or erroneous treatment potentially increasing adverse outcomes.\(^3,4\) Procalcitonin (PCT) expression in parenchymal tissue is induced by bacterial infection. PCT is a diagnostic marker of severe bacterial infections. While PCT release is not organ specific, concentrations have been successfully used to diagnose and guide antibiotic therapy (initiation and cessation) in lower respiratory tract infections, pneumonia, and sepsis.\(^5,6\) However, PCT has never been extensively studied for its ability to identify pneumonia or bacterial infection in the setting of AHF. We hypothesized that in patients presenting with a chief complaint of shortness of breath, PCT can significantly enhance the clinician's ability to diagnose pneumonia, whether occurring in isolation, or in the setting of AHF or of AECOPD. We also evaluated the association between PCT concentration, antibiotic treatment, and outcome in patients with a primary diagnosis of AHF, reasoning that overlapping symptoms of cough, shortness of breath, and abnormal chest imaging make this group uniquely challenging for clinicians with regards to the diagnosis of superimposed pneumonia, possibly leading to inappropriate antibiotic utilization.

Methods

The BACH (Biomarkers in Acute Heart Failure) trial was a prospective, 15-centre international study of 1641 patients presenting to the emergency department (ED) with a chief complaint of dyspnoea. All sites received local Institutional Review Board approval. The primary results have been reported elsewhere.\(^7\)

Study population

A total of 1641 patients reporting shortness of breath upon presentation to the ED were enrolled from March 2007 to February 2008. Patients were excluded if they were under 18 years of age, unable to provide consent, had an acute ST-elevation myocardial infarction, were receiving haemodialysis, or had renal failure. The emergency physicians (EPs), blinded to the results of the investigational markers, assessed the patients enrolled in the study for the diagnosis of AHF or pneumonia using two separate visual analogue scales (VASs) and assigned a value of 0–100% clinical diagnostic certainty.

Confirmation of diagnosis

The gold standards for the diagnoses were determined by two cardiologists who independently reviewed all medical records and classified the likely diagnosis as heart failure (HF), pneumonia, a combination of both, or another diagnosis. Both were blinded to the other's assessments, investigational markers, and the EP's diagnosis. In the event of disagreement that could not be settled, a third adjudicator was used. In cases of suspected pneumonia, diagnosed using modified criteria from Fine et al. and Leroy et al.,\(^8,9\) a single pulmonologist, blinded only to biomarker values, reviewed each case. All cases of pneumonia were required to have a new infiltrate on chest imaging in combination with microbiological proof of infection, or more than one of the major criteria. In cases of equivocal chest imaging (interstitial pattern, effusions), at least two major criteria were necessary. Community-acquired and healthcare-associated pneumonias were both recorded as pneumonia.

Biomarker assessment

Procalcitonin and other biomarkers were quantified with an automated sandwich immunoassay using TRACE technology described previously.\(^7\) The PCT-sensitive KRYPTOR assay has a detection limit of 0.02 ng/mL and a functional assay sensitivity of 0.06 ng/mL. The inter-assay coefficient of variation for concentrations >0.3 ng/mL is <6%. Samples were processed by personnel blinded from any patient data. White blood cell count (WBC) and C-reactive protein, if measured as part of the clinician's usual diagnostic workup, were potentially known to the clinician at the time of VAS determination.

Statistical analysis

Values are expressed as means and standard deviations, medians and interquartile ranges (IQR), or counts and percentages, as appropriate. Patients with and without pneumonia were compared with independent samples t-tests or Fisher's exact tests, as appropriate. Variables were log-transformed if appropriate.

Logistic regression was used to evaluate PCT for the diagnosis of pneumonia, for both uni- and multivariable analysis. To demonstrate independence from clinical variables, the added value of PCT on top of (i) a multivariable model with the seven most significant univariate variables and (ii) the physician-estimated probability of pneumonia was evaluated based on the likelihood ratio \(\chi^2\) test for nested models. The concordance index [C index or area under the curve (AUC)] is given as an effect measure for uni- and multivariable models. For multivariable models, a bootstrap-corrected version of the C index/AUC is given. For continuous variables, odds ratios (ORs) were standardized to describe the OR for a change of one IQR. The 95% confidence intervals (CIs) for risk factors and significance levels for \(\chi^2\) are given.\(^10\) Net reclassification improvements (NRI) were calculated for adding PCT based on categories which represent approximately the 15th and 85th percentile of the predicted probability for the model excluding PCT.\(^11\) Receiver operating characteristic (ROC) curves were constructed to assess the sensitivity and specificity of PCT and multivariable models to compare their ability to predict pneumonia.

Cox proportional hazards regression was used to analyse the association of risk factors with survival in uni- and multivariable analyses. The C index is given as an effect measure. Survival curves plotted by the Kaplan–Meier method were used for illustration. For categorical variables, log-rank test \(P\)-values are given. To account for systematic differences between patients with and without antibiotic treatment, survival rates were adjusted for covariates.\(^12\)

All analyses utilized a two-sided \(P\)-value of 0.05 for significance. All statistical analyses were performed using R version 2.5.1 (http://www.r-project.org) and Statistical Package for the Social Sciences (SPSS) version 16.0 (SPSS Chicago, IL, USA).
Results

A total of 1641 patients were evaluated in the ED for shortness of breath, of which 6.8% (112) received a primary diagnosis of pneumonia, 34.6% (568) AHF, 12.2% (201) chronic obstructive pulmonary disease (COPD) exacerbation, 7.0% (130) asthma exacerbation, 6.5% (106) chest pain, 3.7% (61) bronchitis, 3.4% (55) arrhythmia, 2.4% (39) acute coronary syndrome, 2.3% (38) pulmonary embolism, 1.6% (27) influenza, and 18.5% (304) other diseases. A total of 155 patients (9.4%) with a primary or secondary diagnosis of pneumonia (112 as primary, and 43 as secondary) were combined. There were 407 patients (24.8%) diagnosed with an AECOPD (271 with COPD and 136 with asthma).

Patient characteristics in the pneumonia group and the non-pneumonia group are shown in Table 1. Patients with pneumonia were significantly more likely to have a past medical history of COPD and pneumonia, and a recent history of cough and night sweats. A past medical history of HF, coronary artery disease, myocardial infarction, and angioplasty was significantly more common in patients with pneumonia than in patients without pneumonia. PCT levels were obtained for 99.4% of all patients. PCT ranged from 0.02 to 349 ng/mL, with a median of 0.07 ng/mL and an IQR from 0.05 to 0.13 ng/mL. In healthy subjects, PCT plasma concentrations are typically <0.05 ng/mL.12

Procalcitonin for the diagnosis of pneumonia

Overall, 155 (9.4%) patients had a primary or secondary diagnosis of pneumonia. Twenty-nine of these had concurrent AHF and 17 had a concurrent AECOPD (13), asthma (2), or bronchitis (2). For patients with pneumonia, median PCT concentration was 0.18 ng/mL (IQR 0.07–0.58), and for patients without pneumonia PCT was 0.07 ng/mL (IQR 0.05–0.12). In total, 203 patients were on antibiotics upon entry. Their median PCT concentration was 0.08 ng/mL (IQR 0.05–0.20). A univariate logistic regression model for predicting the diagnosis of pneumonia was highly significant when the chest X-ray is included in the multivariable model (AUC 0.863, df = 1, P < 0.0001). The bootstrap-corrected AUC for the combined model including PCT was 0.863 (P < 0.0001), with an NRI of 5.0% (95% CI 4.0–6.2%). The model including PCT moved 2.1% of pneumonia into a higher probability category, and 5.3% of non-pneumonia into a lower probability category.

Similarly, in a model incorporating both log-transformed PCT and physician-estimated probability, both variables contributed significantly to the prediction of pneumonia (P < 0.0001). PCT increased the AUC from 0.850 to 0.864 (χ² for adding PCT to the model 37.5, df = 1, P < 0.0001). The bootstrap-corrected AUC for the combined model including PCT was 0.863 (P < 0.0001), with an NRI of 5.0% (95% CI 4.0–6.2%). The model including PCT moved 2.1% of pneumonia into a higher probability category, and 5.3% of non-pneumonia into a lower probability category.

Decreasing clinical uncertainty in difficult to diagnose pneumonia cases

At presentation, doctors were uncertain (defined as probability estimates between 21% and 80%) about the presence of pneumonia in 30% of patients (n = 499). In the 208 patients who presented with a PCT value >0.25 ng/mL, a concentration that predicts bacterial infection,13 the EP-estimated probability of pneumonia was high (>80%) in only 15% of cases. The distributions of the physician probability estimates are illustrated in Figure 2. This figure also demonstrates how the uncertain category (labelled ‘Medium’) would be reduced by 82% if physician estimates were combined with a model ruling out pneumonia when PCT values were >0.25 ng/mL.

Procalcitonin and the decision to give antibiotics to patients presenting with acute heart failure

PCT was significantly associated with 90-day all-cause mortality for patients diagnosed with AHF (P = 0.0024). Figure 3 illustrates this relationship in a Kaplan–Meier plot of PCT quintiles. Patients in the first quintile (PCT < 0.05 ng/mL) had a 90-day survival rate of 92.0%, which fell to 80.5% (hazard ratio 2.6) for patients in the fifth quintile (PCT > 0.21 ng/mL). One-fifth (20.8%) of these patients diagnosed with AHF were also
Table 1: Patient characteristics grouped by the presence or absence of pneumonia

| Variables                          | N    | Non-pneumonia (n = 1486) | Pneumonia (n = 155) | P-value |
|------------------------------------|------|--------------------------|---------------------|---------|
| **Demographics**                   |      |                          |                     |         |
| Age (years)                        | 1641 | 63.5 ± 17.0              | 66.3 ± 15.8         | 0.0517  |
| Male gender                        | 1641 | 770 (51.8)               | 89 (57.4)           | 0.2049  |
| Race                               | 1626 |                          |                     | 0.0005  |
| White                              |       | 966 (65.6)               | 124 (80.5)          |         |
| Black                              |       | 451 (30.6)               | 25 (16.2)           |         |
| Other                              |       | 55 (3.7)                 | 5 (3.2)             |         |
| **Recent history**                 |      |                          |                     |         |
| Smoking                            | 1593 | 420 (29.1)               | 49 (32.9)           | 0.3456  |
| Wheezing                           | 1543 | 430 (30.6)               | 38 (27.3)           | 0.4409  |
| Cough                              | 1603 | 811 (54.6)               | 137 (88.4)          | <0.0001 |
| Weight gain                        | 1438 | 235 (17.9)               | 14 (10.9)           | 0.0497  |
| Night sweats                       | 1495 | 284 (20.9)               | 40 (29.2)           | 0.0294  |
| Orthopnoea                         | 1536 | 625 (44.8)               | 64 (45.7)           | 0.8587  |
| Dyspnoea at rest                   | 1605 | 719 (49.6)               | 76 (49.4)           | 1.0000  |
| **Exam variables**                 |      |                          |                     |         |
| Heart rate (b.p.m.)                | 1641 | 89.8 ± 23.6              | 101.6 ± 22.8        | <0.0001 |
| Systolic BP (mmHg)                 | 1641 | 140.6 ± 30.4             | 133.5 ± 31.3        | 0.0055  |
| Diastolic BP (mmHg)                | 1641 | 80.8 ± 18.2              | 74.9 ± 19.9         | 0.0002  |
| BMI (kg/m²)                        | 1399 | 29.4 ± 8.9               | 27.0 ± 7.6          | 0.0034  |
| Temperature (°C)                   | 1576 | 36.7 ± 0.63              | 37.4 ± 1.00         | <0.0001 |
| Pulse oximetry (%)                 | 1609 | 95.3 ± 5.3               | 93.2 ± 5.3          | <0.0001 |
| Rales                              | 1624 | 452 (30.8)               | 72 (46.5)           | 0.0001  |
| S3                                 | 1580 | 43 (3)                   | 1 (0.7)             | 0.1175  |
| Murmur                             | 1604 | 226 (15.5)               | 28 (18.7)           | 0.3467  |
| Elevated JVP                       | 1539 | 256 (18.4)               | 15 (10.1)           | 0.0121  |
| Oedema                             | 1615 | 548 (37.5)               | 40 (26.1)           | 0.0060  |
| Ascites                            | 1579 | 38 (2.7)                 | 3 (2)               | 0.7917  |
| Wheezing                           | 1619 | 397 (27.1)               | 55 (35.5)           | 0.0304  |
| **History variables**              |      |                          |                     |         |
| Arrhythmia                         | 1555 | 365 (25.9)               | 40 (27.2)           | 0.7671  |
| Asthma                             | 1594 | 289 (20.0)               | 29 (19.2)           | 0.9148  |
| CRI                                | 1584 | 222 (15.5)               | 24 (16.2)           | 0.8117  |
| HF                                 | 1597 | 531 (36.7)               | 38 (25.5)           | 0.0069  |
| CAD                                | 1587 | 469 (32.6)               | 34 (23)             | 0.0159  |
| COPD                               | 1594 | 409 (28.4)               | 62 (40.8)           | 0.002   |
| DM                                 | 1621 | 427 (29.1)               | 35 (22.7)           | 0.1104  |
| Hyperlipidaemia                    | 1549 | 529 (37.5)               | 41 (29.5)           | 0.0654  |
| Hypertension                       | 1614 | 987 (67.5)               | 93 (61.6)           | 0.1470  |
| MI                                 | 1584 | 282 (19.7)               | 18 (11.9)           | 0.0214  |
| Pneumonia                          | 1536 | 196 (13.2)               | 64 (41.3)           | 0.0005  |
| Pulmonary embolism                 | 1604 | 75 (5.2)                 | 10 (6.5)            | 0.4482  |
| CABG                               | 1615 | 141 (9.7)                | 17 (11.0)           | 0.5687  |
| Angioplasty/stent                  | 1602 | 194 (13.4)               | 10 (6.6)            | 0.0147  |
| Stroke/CVA                         | 1608 | 151 (10.4)               | 14 (9.0)            | 0.6774  |
| Pacemaker/ICD                      | 1616 | 144 (9.9)                | 18 (11.6)           | 0.4820  |
| Prosthetic valve                   | 1612 | 37 (2.5)                 | 6 (3.9)             | 0.2935  |
| **Outpatient medications (known)** |      |                          |                     |         |
| Aspirin                            | 1616 | 526 (36.0)               | 48 (31.4)           | 0.2870  |
| Clopidogrel                        | 1617 | 124 (8.5)                | 7 (4.6)             | 0.1175  |
| Warfarin                           | 1615 | 232 (15.9)               | 25 (16.3)           | 0.9075  |

Continued
treated with antibiotics (excluding those already on antibiotics at the time of presentation), while only 5.1% (29) of those were ultimately diagnosed with pneumonia, suggesting the possibility of unnecessary antibiotic therapy. Additionally, in patients not treated with antibiotics on presentation, PCT predicted the possible need for antibiotic therapy during follow-up, representing a potential missed opportunity to treat: 33.0% of patients with PCT<0.5 ng/mL (P=0.01). Notably, of the 117 patients with PCT concentrations suggesting significant bacterial infection (>0.5 ng/mL), 38 (32%) did not receive antibiotic therapy. In this group, half were diagnosed with AHF, highlighting the difficulty of diagnosing superimposed bacterial infection in patients presenting with AHF.

| Table 1 Continued |
|-------------------|
| **Variables**     | **N** | **Non-pneumonia (n = 1486)** | **Pneumonia (n = 155)** | **P-value** |
| Beta-blockers     | 1613  | 580 (39.7)                     | 47 (31.1)               | 0.0436      |
| ACE inhibitors or ARBs | 1616  | 622 (42.5)                     | 58 (37.9)               | 0.3019      |
| Statins           | 1617  | 329 (22.5)                     | 40 (26.1)               | 0.3124      |
| Calcium channel blockers | 1614  | 485 (33.1)                     | 32 (20.9)               | 0.0019      |
| Diuretics         | 1618  | 713 (48.7)                     | 61 (39.9)               | 0.0412      |
| Digoxin           | 1617  | 111 (7.6)                      | 9 (5.9)                 | 0.5196      |
| Aldosterone inhibitor | 1615  | 139 (9.5)                      | 10 (6.6)                | 0.3016      |
| Anti-arrhythmics  | 1616  | 84 (5.7)                       | 8 (5.3)                 | 1.000       |
| Nebulizer/inhaler | 1613  | 497 (34.0)                     | 64 (42.1)               | 0.0492      |
| Steroids          | 1582  | 341 (23.8)                     | 50 (33.3)               | 0.0127      |
| Antibiotics       | 1614  | 161 (11.0)                     | 42 (27.6)               | <0.0001     |
| Smoking cessation therapy | 1577  | 27 (1.9)                       | 1 (0.7)                 | 0.5111      |
| Other             | 1593  | 941 (65.2)                     | 89 (59.3)               | 0.1523      |

Values are mean ± SD or n (%) and compared with independent samples t-test or Fisher exact tests, respectively.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass grafting; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRI, chronic renal insufficiency; CVA, cerebral vascular accident; DM, diabetes mellitus; HF, heart failure; ICD, implantable cardiac defibrillator; JVP, jugular venous pressure; MI, myocardial infarction.

| Table 2 Prediction of pneumonia diagnoses (n = 155 events) from signs, physician-estimated probability of pneumonia (visual analogue scale), and procalcitonin concentration |
|-------------------|
| **Predictor**     | **Univariable model results** | **Multivariable model results** |
|                   | OR 95% CI | χ²  P-value | AUC | OR 95% CI | χ²  P-value | AUC |
| Model with individual variables |
| Temperature (°C)  | 2.2 1.9–2.5 | 124.1 <0.0001 | 0.709 | 1.8 | 1.5–2.1 | 45.5 <0.0001 |
| PCT (log, ng/mL) | 1.9 1.7–2.1 | 106.8 <0.0001 | 0.723 | 1.6 | 1.4–1.9 | 38.7 <0.0001 |
| Cough (yes)      | 6.7 4.0–11.4 | 76.2 <0.0001 | 0.668 | 4.7 | 2.6–8.5 | 25.5 <0.0001 |
| Past pneumonia (yes) | 4.7 3.3–6.7 | 65.0 <0.0001 | 0.647 | 3.7 | 2.4–5.7 | 34.5 <0.0001 |
| Heart rate (b.p.m.) | 1.7 1.4–2.1 | 31.4 <0.0001 | 0.651 | 1.6 | 1.2–2.1 | 12.8 0.0004 |
| Rales (yes)      | 1.9 1.4–2.7 | 15.0 0.0001 | 0.578 | 1.5 | 1.0–2.3 | 3.3 0.0696 |
| Pulse oximetry (log, %) | 0.9 0.8–0.9 | 12.2 0.0005 | 0.659 | 1.0 | 0.9–1.1 | 0.6 0.4397 |
| Diastolic BP (mmHg) | 0.7 0.6–0.9 | 11.2 0.0008 | 0.580 | 0.7 | 0.5–0.9 | 7.2 0.0073 |
| Model with summary variable |
| VAS pneumonia (%) | 5.5 4.4–6.9 | 265.5 <0.0001 | 0.850 | 4.7 | 3.7–6.0 | 163.0 <0.0001 |
| PCT (log, ng/mL) | 1.9 1.7–2.1 | 106.8 <0.0001 | 0.723 | 1.4 | 1.3–1.7 | 27.2 <0.0001 |

Area under the curve (AUC) is bootstrap corrected for multivariable models. BP, blood pressure; CI, confidence interval; OR, odds ratio; PCT, procalcitonin; VAS, visual analogue scale.
Procalcitonin, antibiotic administration, and survival in patients presenting with acute heart failure

Unadjusted data showed that patients treated with antibiotics had higher 90-day all-cause mortality than patients not treated ($P = 0.032$). After adjustment of covariates to control for group differences with respect to expected outcome, overall survival rates for AHF patients were not different whether or not they were treated with antibiotics ($P = 0.583$, Figure 4A). However, dividing the AHF patients into subgroups based on PCT concentration revealed survival differences between those treated or not treated with antibiotics. Patients with a PCT concentration $>0.21$ ng/mL had significantly worse survival if not treated with antibiotics ($P = 0.046$, Figure 4B). For AHF patients with PCT concentrations between 0.05 and 0.21 ng/mL, antibiotic treatment did not affect survival ($P = 0.36$, Figure 4C). AHF patients with low PCT values ($<0.05$ ng/mL, Figure 4D) had an increased mortality if they were treated with antibiotics ($P = 0.049$).

The utility of procalcitonin combined with mid-regional pro atrial natriuretic peptide in the differential diagnosis of dyspnoea

Figure 5 illustrates schematically how the combination of mid-regional pro atrial natriuretic peptide (MR-proANP) [or brain natriuretic peptide (BNP)] and PCT can be used to diagnose acutely dyspnoic patients with AHF and/or pneumonia: a PCT $>0.1$ ng/mL together with an MR-proANP $>350$ pmol/L defined community-acquired pneumonia occurring with concomitant AHF; a PCT $>0.1$ ng/mL with an MR-proANP $<100$ pmol/L defined community-acquired pneumonia alone, while an MR-proANP $>350$ pmol/L and a PCT $<0.1$ ng/mL defined HF alone. A similar algorithm can be deduced for BNP. The median and IQR for PCT and MR-proANP values in the four subgroups are listed in the legend of Figure 5.

Discussion

Differentiating the diagnosis of pneumonia from that of HF can be difficult, and disastrous consequences may occur from a mistake.$^3$ Moreover, detecting superimposed pneumonia in patients...
presenting with AHF is additionally difficult because of the similar and therefore non-specific physical exam and chest X-ray abnormalities. This can also lead to great morbidity and mortality.\textsuperscript{3,4} This study serves to highlight the difficulty clinicians face in diagnosing pneumonia in patients presenting with AHF.

In HF patients it is obviously important to identify those with the highest risk in order to improve outcome. Superimposed pulmonary disease has been shown to lead to increased morbidity and mortality in HF patients. Iverson and colleagues\textsuperscript{14} have shown a clear link between lung function and outcome in HF patients by demonstrating the prognostic importance of spirometric variables, in addition to known risk factors, including self-reported COPD. These authors posit the knowledge that patients who have COPD may reduce the risk of overdosing diuretics due to misinterpretation of the primary underlying cause of dyspnoea. A similar argument can be made for those with pneumonia in our study.

Our results suggest that PCT provides additive diagnostic information in patients presenting with shortness of breath; models using PCT were robust when clinical uncertainty existed. Furthermore, our data speak to the potential utility of PCT in predicting clinical benefit from antibiotic treatment. Patients with a PCT concentration $>0.21$ ng/mL had significantly worse survival if not treated with antibiotics, and those with PCT values $<0.05$ ng/mL had an increased mortality if they were treated with antibiotics, suggesting that the risks of antibiotic administration may outweigh the benefits in this group. Taken together, these data suggest that the incorporation of PCT into the decision

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**Figure 4** Kaplan–Meier plot for antibiotic treatment and all-cause mortality within 90 days for patients with acute heart failure (A; all AHF patients) and subgrouped by procalcitonin (PCT) quintiles: PCT $>0.21$ ng/mL (B; highest quintile, $P = 0.049$), between 0.05 and 0.21 (C; $P = 0.36$, summarizing quintiles 2–4), and $<0.05$ ng/mL (D; lowest quintile, $P = 0.046$). Survival rate is adjusted for covariates; see Methods.

**Figure 5** Median procalcitonin (PCT) and mid-regional pro atrial natriuretic peptide (MR-proANP) concentrations (left), as well as median PCT and brain natriuretic peptide (BNP) concentrations (right) for patients with acute heart failure (AHF) alone, pneumonia alone, AHF and pneumonia, and those without either condition. The median and interquartile range (IQR) for PCT (in ng/mL) in the four subgroups were as follows: no AHF, no pneumonia 0.06 (0.04–0.09); pneumonia, no AHF 0.23 (0.07–0.92); AHF, no pneumonia 0.09 (0.06–0.16); and AHF and pneumonia 0.14 (0.09–0.26). For MR-proANP (in pmol/L): no AHF, no pneumonia 84 (47–183); AHF, no pneumonia 141 (62–240); AHF, no pneumonia 417 (277–620); and AHF and pneumonia 398 (279–635). For BNP (in ng/mL): no AHF, no pneumonia 50 (20–166); pneumonia, no AHF 122 (37–292); AHF, no pneumonia 766 (409–1461); and AHF and pneumonia 400 (210–857).
to administer antibiotic therapy to patients presenting with AHF may impact survival.

Our data also demonstrate that combining PCT with MR-proANP, which was reported in this population to aid in the diagnosis of AHF, holds promise for the categorization of acutely dyspneic patients into three groups mandating early therapy, specifically those with either HF alone, pneumonia alone, or both in combination. Figure 5 shows the median PCT and MR-proANP/BNP concentrations in all patients, grouped by the presence or absence of pneumonia and AHF, and underscores how multiple biomarkers may be combined to assist in the diagnosis of clinically challenging overlapping disease states. Gheorghiade et al. and colleagues have previously proposed that a wide range of clinical and laboratory markers be used in combination to assess and grade congestion in acute HF more optimally in order to better direct management. It could be argued that improved grading strategies, making optimal use of serum biomarkers, would be equally if not more important in the acute management of the undifferentiated dyspnea that presents to EDs.

Limitations

There are several limitations of our study. Antibiotic treatment was neither randomized nor standardized in terms of type and dosage, and the analysis was post-hoc and not pre-specified. C-reactive protein measurements, which are frequently used in the differential diagnosis of HF vs. pneumonia, were not included in the analysis. Due to the lack of randomization, it is probable that sicker patients were also more likely to receive antibiotics, which probably explains the observed difference in risk of death. The number of patients ultimately diagnosed with both pneumonia and AHF was low, possibly reflecting our broad inclusion criteria of undifferentiated dyspnea, consistent with the primary endpoint of the trial. This might also reflect a pre-selection bias of the on-site cardiologist responsible for making the initial assessment and therefore some cases of pneumonia might have escaped detection. This may also explain the slightly worse diagnostic performance in patients with concurrent AHF.

Hence our conclusions are exploratory and need validation in a randomized controlled trial. The rationale for carrying out this analysis in the large BACH dyspnea trial was to evaluate whether PCT could aid in the decision to initiate antibiotics in patients with a primary diagnosis of AHF, where pneumonia occurs as a relevant but possibly less apparent co-morbidity. If this is proven, a logical next phase might then be a study treating according to biomarker stratification.

Another potential limitation is that the confirmation of diagnosis was performed by two independent cardiologists who made the final diagnosis. This method of diagnosis has the potential for bias of underreporting when two specialists from the same discipline are making the final diagnosis.

Clinical implications

This study extends the knowledge from previous work evaluating the clinical utility of PCT in the diagnosis and management of patients with suspected community-acquired pneumonia in the setting where AHF is also a possibility. There is a strong likelihood that PCT levels will help guide diagnostic therapeutic decisions with antibiotics. This needs to be tested in a large randomized interventional trial.

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