

Serial Procalcitonin Levels and Bacterial Etiology in Hospitalized Patients with Community-Acquired Pneumonia

Pierre Ankomah

Massachusetts General Hospital

Suzanne M McCluskey

Massachusetts General Hospital

Michael Abers

Massachusetts General Hospital

Benjamin Bearnot

Massachusetts General Hospital

Phillip Schuetz

University of Basel, Kantonsspital Aarau

Victor Chiappa

Massachusetts General Hospital

Jatin M Vyas

Massachusetts General Hospital

Michael K. Mansour (✉ mkmansour@mgh.harvard.edu)

Massachusetts General Hospital

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Abstract

Background: Accurate determination of the microbial etiology of pneumonia has important consequences for appropriate administration of antimicrobials and antimicrobial stewardship. Procalcitonin (PCT) is a biomarker that is finding increasing diagnostic and prognostic utility in lower respiratory infections, however, it remains unclear whether it can be helpful in predicting the bacterial etiology of pneumonia. In this study, we examined the relationship between serial PCT measurements and bacterial etiology in hospitalized patients with community-acquired pneumonia, including those at high risk for infections due to multi-drug resistant organisms (MDRO), to determine whether PCT at admission and its trajectory early in the hospital course of patients provides distinguishing information between different bacterial causes of pneumonia.

Methods: We analyzed data collected from a prospective cohort study of 505 patients admitted to a tertiary care center with a clinical syndrome consistent with pneumonia. Bacterial etiology of pneumonia was determined from high quality respiratory samples, blood cultures and other relevant diagnostic tests according to standard protocols in conjunction with clinical review. Daily plasma procalcitonin levels were measured for these patients serially during the first four days of hospitalization. We compared procalcitonin levels associated with different bacterial etiologies of pneumonia over the first four days of admission, using the Mann-Whitney-U test to assess for statistical significance.

Results: Out of 505 patients, the diagnosis of pneumonia was adjudicated in 322, and bacterial etiology determined in 64 cases. The predominant pathogens were *Staphylococcus aureus* (n = 19; 12 Methicillin Resistant (MRSA) and 7 Methicillin Susceptible (MSSA)), *Pseudomonas aeruginosa* (n = 12), *Streptococcus pneumoniae* (n = 6), and *Haemophilus influenzae* (n=5). We found higher procalcitonin values for *S. pneumoniae* relative to other etiologies, a delayed rise for *Pseudomonas* over time, and consistently low PCT values for infections due to multiple bacteria. In addition, our results also suggest that procalcitonin values on the second day of hospitalization, rather than at admission, may have the most utility in distinguishing between bacterial etiologies.

Conclusion: Serial procalcitonin values during the early course of bacterial pneumonia reveal a difference between pneumococcal and other bacterial etiologies, and may have an adjunct role in guiding antibiotic choice and duration.

Background

During management of pneumonia, clinicians consider and investigate potential microbial etiology in order to inform treatment decisions. However, the diagnostic tools remain limited for determination of bacterial etiology of pneumonia (1). The most commonly used diagnostic aid in this endeavor is sputum culture, which is fraught with multiple challenges including specimen quality and difficulties in culturing/isolating organisms (2). Recent advances in nucleic acid detection may offer additional sensitivity, but these methods do not address issues of true invasive disease compared to colonization (3). To differentiate between commensal and invasive pathogens, serum biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT) that may reflect the activation state of the host immune system have been investigated as supplementary diagnostic and prognostic aids in the clinical decision making process (4). PCT has shown promise as a means of distinguishing between viral and bacterial causes of pneumonia, as well as, via serial assessments, assisting in decisions regarding antibiotic course (4,5). This strategy of PCT-guided antibiotic treatment has the potential to reduce antibiotic exposure, though data are conflicting about how this translates into clinical practice (6–8).

While the majority of studies investigating the clinical utility of PCT have been in the context of differentiating between clinical syndromes that require antibiotics and those that do not, a few studies have also assessed the association between PCT levels and bacterial etiologies of pneumonia (9–13). However, the pertinent comparisons in these studies were made between aggregate groups, such as “classic bacterial” versus “atypical” causes of pneumonia (9,13), gram positive versus gram negative organisms (10), and pneumococcal or non-pneumococcal pneumonia (11,12). Accordingly, though two studies (11,12) did report higher PCT levels for pneumococcal compared to non-pneumococcal pneumonia, no granular conclusions were reached regarding PCT values associated with specific bacteria. Another crucial limitation of these studies is that they were generally limited to community-acquired pneumonia (CAP) due to relatively drug-susceptible organisms, with only a small proportion of cases being due to bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) or *Pseudomonas aeruginosa*. In addition, with the exception of the study done by Tamura *et al.*, (11), all the other studies assessed PCT values only during initial evaluation, and Tamura *et al* used the serial data to distinguish between disease severity and mortality risk in pneumococcal versus non-pneumococcal pneumonia.

Here, using data obtained during a prospective observational study to evaluate the utility of procalcitonin in clinical prognostication for patients hospitalized with pneumonia (14), we investigate the relationship between PCT measurements and bacterial etiology of pneumonia. Importantly, the population we examine comprises a large proportion of patients who had been hospitalized in an acute-care hospital within the preceding 90 days, or had received outpatient treatment, including intravenous therapy within the preceding 30 days (14) and thus had putatively elevated risk factors for pneumonia caused by multi-drug resistant organisms (MDRO) (15). We examine initial PCT values associated with different bacterial pathogens on admission, and assess serial daily PCT values to explore differences in trajectory of PCT during treatment/resolution of infections.

Methods

Study Design: We analyzed data from a prospective cohort study of adult patients admitted for at least one night to a tertiary care center in Boston, Massachusetts between March to September 2013, with symptoms and imaging findings concerning for pneumonia (14). Chart review was performed by two independent Internal Medicine physicians to adjudicate the clinical diagnosis of pneumonia, with any discordance reviewed by a committee for a final decision (14). A notable exclusion criterion was for patients with prior hospitalization within the preceding 14 days to eliminate potential complicating impact of lingering radiographic findings from prior pneumonia or effect of previous antibiotic treatment on PCT levels. In addition, patients with cardiogenic shock, trauma, burns and ST-elevation myocardial infarction were excluded from the study as these conditions non-specifically elevated PCT independent of bacterial infection.

Microbiological Diagnostics: Blood, sputum, pleural fluid, bronchoalveolar lavage (BAL) cultures, respiratory viral PCRs and urine antigens for *Streptococcus pneumoniae* and *Legionella pneumophila* were obtained at the discretion of the primary clinical team. Organisms known to cause respiratory infections were classified as the causative agent(s) for pneumonia if at least one of the following criteria were met: (i) concurrent bacteremia, (ii) positive urine antigen test, (iii) organism isolated from appropriate sputum or endotracheal specimens (with <10 epithelial cells/hpf and >25 WBC/hpf), in at least “moderate quantity” (16) and/or (iv) organism isolated from pleural fluid or BAL samples. Infections were classified as having mixed etiology if multiple pathogens met the above criteria.

Assessment of Procalcitonin: The VIDAS BRAHMS PCT (bioMérieux, Inc., Durham, NC), an enzyme-linked fluorescent assay with a detection range of <0.05 ng/mL to >200 ng/mL, was used to measure plasma procalcitonin on hospital days 1-4 (14).

Statistical Analysis: For comparisons of patient demographic and clinical characteristics, the p value for age was calculated using an ANOVA test, and p values for categorical variables were calculated from Fisher’s exact test analyses. Comparisons of the relative proportions of different groups that met a composite severity endpoint of bacteremia, ICU admission or death were undertaken using Fisher’s exact test analyses. Continuous data were summarized using median and interquartile ranges. PCT values of <0.05 ng/mL were coded as 0.05 ng/mL to provide non-zero values to facilitate statistical comparisons. A two-tailed Mann-Whitney-U test was utilized for two-group comparisons for continuous data, with p values less than 0.05 considered to indicate statistical significance. Analyses were undertaken using R version 4.0.2 (The R project for Statistical Computing).

Results

A clinical diagnosis of pneumonia was adjudicated in 322 out of 505 participants in the cohort study following blinded chart review. Bacterial etiology was determined in 64 (19.8%) of those cases, and 5 (1.6%) patients had viral pneumonias. Given the goal of this study, subsequent analyses focused solely on bacterial etiologies of pneumonia. Table 1 shows the bacteria identified, and for each, the number of patients who met a composite severity endpoint of bacteremia, admission to an Intensive Care Unit (ICU), or death.

Table 1. Distribution of the bacterial etiology of pneumonia with number of corresponding cases that met a composite severity endpoint of bacteremia, admission to the ICU or death

Etiology	Total number	Number of cases meeting composite endpoint of bacteremia, ICU admission or death
Methicillin-Resistant <i>Staphylococcus aureus</i>	12	7
Methicillin-Susceptible <i>Staphylococcus aureus</i> (MSSA)	7	3
<i>Pseudomonas aeruginosa</i>	12	4
<i>Streptococcus pneumoniae</i>	6	3
<i>Haemophilus influenza</i>	5	2
<i>Serratia marcescens</i>	3	2
<i>Escherichia coli</i>	3	2
<i>Legionella pneumophila</i>	2	1
<i>Stenotrophomonas maltophilia</i>	1	1
<i>Streptococcus gordonii</i>	1	1
<i>Actinomyces odontolyticus</i>	1	0
Mixed infections	11	8
Total with Bacterial Etiology for Pneumonia Identified	64	34
No Bacterial Etiology for Pneumonia Identified	258	46
Total	322	80

Predominant bacterial pathogens were *Staphylococcus aureus* (n=19; 12 Methicillin Resistant (MRSA) and 7 Methicillin Susceptible (MSSA)), *Pseudomonas aeruginosa* (n = 12), *Streptococcus pneumoniae* (n=6), and *Haemophilus influenza* (n=5). Pneumonias due to *Serratia marcescens* (n=3), *Escherichia coli* (n=3), *Legionella pneumophila* (n=2), *Stenotrophomonas maltophilia* (n=1), *Streptococcus gordonii* (n=1) and *Actinomyces odontolyticus* (n=1) were also identified. Eleven infections were characterized as mixed, with 9 of the combinations involving *S. aureus* (5 MRSA and 4 MSSA) in combination with *Acinetobacter baumannii* (n=2), *P. aeruginosa* (n=2), *E. coli* (n=2), *Klebsiella pneumoniae* (n=1), *H. influenzae* (n=1), and *Streptococcus anginosus* (n=1). Other combinations included *S. pneumoniae* with *Moraxella catarrhalis* and one that involved *E. coli*, *Proteus mirabilis* and *K. pneumoniae*. The relative contribution of different microbiological samples to identifying each bacterial etiology of pneumonia is available in Supplementary Table 1 (Table S1). While there was no statistically significant difference between the rates at which pneumonia due to particular bacterial etiologies met the composite severity endpoint (p=0.79), patients who had specific bacterial etiologies identified as the causative agent of their pneumonia were more likely to meet the severity endpoint than those who did not (p=3.5e-08). Subsequent analyses focused on comparing PCT levels for *S. pneumoniae*, *H. influenzae*, MSSA, MRSA, *P. aeruginosa*, the Enterobacteriaceae (*E. coli* and *S. marcescens*) and mixed infections. This approach was chosen for two reasons: (i) to maximize comparisons between the largest groups, and (ii) to provide comparisons between microbial etiologies that prompt consideration for adjustment in therapy from typical CAP regimens. Demographic information for patients belonging to these groups is shown in Table 2.

Table 2. Demographic and Clinical Characteristics of Patients with different etiologies of pneumonia

Population Characteristics	Microbial Etiology of pneumonia								
	MRSA	MSSA	Pseudomonas aeruginosa	Streptococcus pneumoniae	Haemophilus influenzae	Enterobacteriaceae	Mixed infections	No Bacterial etiology identified	P value
Age	69 (22-89)	64 (49-83)	68 (48-82)	59 (37-77)	52 (23-81)	69 (53-94)	54 (23-87)	68 (22-99)	0.082
Male Gender	8 (66)	5 (71)	7 (58)	4 (67)	2 (40)	4 (67)	8 (73)	153 (59)	0.95
Active smoker	1 (8)	0	2 (17)	3 (50)	2 (40)	1 (17)	4 (36)	61 (24)	0.29
Medical comorbidities									
Diabetes	3 (25)	4 (57)	3 (25)	1 (17)	1 (20)	1 (17)	2 (18)	59 (23)	0.70
Heart Failure	5 (42)	0	2 (17)	1 (17)	1 (20)	1 (17)	2 (18)	54 (21)	0.68
Renal Failure	4 (33)	0	2 (17)	2 (33)	0	0	1 (9)	57 (22)	0.47
Cirrhosis	1 (8)	0	0	0	0	1 (17)	0	12 (5)	0.66
Malignancy	5 (42)	3 (43)	6 (50)	5 (83)	5 (100)	4 (67)	5 (45)	79 (31)	0.0013
Underlying lung disease (Asthma, COPD, Pulmonary Hypertension or Interstitial Lung Disease)	6 (50)	3 (43)	9 (75)	4 (67)	4 (80)	5 (83)	5 (45)	138 (53)	0.50

Data are presented as mean (range) or n (%). Percentages may not total 100 because of rounding.

There were no statistically significant differences in age, gender and smoking status of patients with pneumonia caused by different bacteria or those from whom the causative bacterial etiology was not identified. Similarly, patients with diabetes, renal failure, cirrhosis and underlying chronic lung conditions including asthma, COPD, pulmonary hypertension and interstitial lung disease were equivalently represented in the patient groups. In a notable exception, there was a statistically significant difference in the prevalence of malignancy in the different patient groups ($p=0.0013$), driven by the finding that there was a smaller percentage of patients with malignancy in the group for which a bacterial etiology for pneumonia was not identified.

PCT values were available for all patients on hospital day 1, 91% on day 2, 86% on day 3, and 78% of patients on hospital day 4. We constructed boxplots for all available PCT data showing median and interquartile values for different bacterial etiologies from hospital days 1-4 (Figures 1a – 1d respectively).

Median PCT value the time of admission was highest for *S. pneumoniae* (3.7 ng/mL) and lowest for mixed infections (0.05 ng/mL), with intermediate values for *S. aureus* (0.47 and 0.12 ng/mL for MRSA and MSSA respectively), *H. influenzae* (0.12 ng/mL) and *P. aeruginosa* (0.065 ng/mL). Significant differences were observed between mixed infections compared to *S. pneumoniae* ($p=0.014$) and to MRSA ($p=0.018$).

Day 2 PCT values increased from levels obtained on admission for *S. pneumoniae* (a 71% increase to 6.34 ng/mL), *P. aeruginosa* (a 407% increase to 0.33 ng/mL), and MSSA (doubling to 0.24 ng/mL). PCT values were relatively stable for *H. influenzae* and mixed infections, and decreased for MRSA (by 64%). Pneumococcal pneumonias resulted in significantly higher PCT values when compared to *P. aeruginosa* ($p=0.0043$), *H. influenzae* ($p=0.036$) and mixed infections ($p=0.0016$). Significant differences were observed between median PCT values for mixed infections when compared to *P. aeruginosa* ($p=0.044$), Enterobacteriaceae ($p=0.024$) as well as both MSSA and MRSA ($p=0.018$ and $p=0.031$ respectively),

Median PCT values on hospital day 3 almost tripled for MSSA in comparison to values from day 2, but decreased by 64% for *S. pneumoniae*, and by 57% for Enterobacteriaceae. The PCT values for other pathogens were relatively stable. The significant differences between PCT levels for pneumococcus compared to mixed infections ($p=0.008$) and *P. aeruginosa* ($p=0.032$) persisted into day 3 of assessment, as did the comparison between mixed infections and MSSA ($p=0.039$). PCT values for pneumococcal infections were also higher than those for MRSA ($p=0.043$). Notably, the values for infections due to MRSA and MSSA diverged the most on day 3, but did not reach statistical significance ($p=0.27$).

On hospital day 4, median PCT values for all pathogens fell within a narrow range (0.05 ng/mL to 0.47 ng/mL). Pseudomonal infections had very low PCT values, and were significantly lower than values for *S. pneumoniae* ($p=0.047$) and MSSA ($p=0.017$).

Discussion

In this study, we compared serial PCT measurements in a population of hospitalized patients with community-acquired pneumonia caused by different bacteria. We observed higher values of PCT at the time of admission in pneumococcal infections compared to infections due to *S. aureus* (including MRSA), *P. aeruginosa*, *H. influenzae* and to those involving multiple bacteria. By measuring PCT levels through the first four days of hospitalization, we noted that differences in PCT values were most pronounced on day 2 of the hospitalization, with limited discriminatory utility from data collected at later time points.

Previous studies in patients with community-acquired pneumonia similarly demonstrated higher levels of PCT on admission for *S. pneumoniae* compared to non-pneumococcal causes (11, 12). Our study examined the non-pneumococcal bacteria individually rather than in aggregate, and also included bacteria such as MRSA and *P. aeruginosa* that are more commonly associated with nosocomial pneumonias, yet we still observed similar results. Tamura *et al.* speculate that this effect is potentially because *S. pneumoniae* causes more systemic inflammation than the other etiologies of pneumonia, although further investigation is required to explore this hypothesis (11). Another notable result in our study is that infections with multiple bacterial pathogens identified in individual patients had the lowest PCT values. In fact, median PCT values associated with these mixed infections over the four days of our analysis were consistently less than 0.1 ng/mL, a cutoff value which in isolation would suggest a syndrome unlikely to represent bacterial pneumonia (17). The reason for this result is unclear and warrants further investigation. It does, however, prompt consideration that the inflammatory response to concurrent infection due to different bacteria, as measured by PCT levels, may not be synergistic.

In most clinical practice, admission values of PCT are the sole values used to assist clinical decision-making. It is worth noting, however, that serial PCT evaluations have been utilized in some settings to guide de-escalation of antibiotic therapy based on the expectation that PCT values fall by approximately 50% per day during resolution of infection (8). In our study, for MSSA, *S. pneumoniae*, and prominently for *P. aeruginosa* (for which the median day 1 PCT value was less than the aforementioned cutoff value of 0.1 ng/mL), there was a notable increase in PCT values from day 1 to day 2 of hospitalization. In addition, differences between PCT values associated with different bacteria were altogether greatest on day 2 of hospitalization. This prompts caution regarding the practice of making decisions about antimicrobial therapy solely on the basis of the admission PCT level. Our results suggest that serial measurement of PCT to include day 2 of hospitalization may be more appropriate to gain discriminatory information between different pathogens. We speculate that about 48 hours into a hospitalization may represent a period where inflammatory sequelae of infection are peaking, prior to antibiotic therapy reducing the infectious and inflammatory burden on the host, but this needs further experimental investigation.

Limitations of this study include the small sample number of cases attributable to specific bacterial pathogens and thus a lack of statistical power to allow the derivation of PCT thresholds that discriminate between pathogens. In addition, given that microbial diagnostic samples were obtained at the discretion of the clinical team, there was a lack of testing standardization for all patients, though this is an approach that is more reflective of clinical reality. Also of note, viral infections, which are known to contribute a high proportion to cases of CAP (18), were under-represented in the larger study from which data was collected. While this may have been in part due to enrollment (from March to September) outside of the peak of respiratory viral season, the contribution of non-standardized sampling cannot be discounted.

Despite the aforementioned limitations, this is an exploratory and hypothesis-generating study that adds to the growing literature on the diagnostic utility of PCT values in pneumonia. Unlike previous studies which were limited to patients with CAP secondary to relatively drug-sensitive organisms, our study contains a large proportion of MDRO bacteria. In addition, our serial PCT data suggests the measurement of a single admission PCT provides limited information, and that serial values have more utility for the evaluation of pneumonia.

Conclusions

The identification of a bacterial etiology in pneumonia is often challenging. We examined the relationship between serial PCT measurements and bacterial etiology in patients with community-acquired pneumonia, including many with risk factors for MDRO infections. We found higher procalcitonin values for *Streptococcus pneumoniae* relative to other etiologies, a delayed rise for *Pseudomonas* over time, and consistently low PCT values for infections due to multiple bacteria. We also found that PCT levels obtained on day 2 of hospitalization were the most useful in distinguishing between different bacterial etiologies. The results of our study suggest that serial PCT evaluations may have a role in discriminating among different bacterial causes of pneumonia, and can potentially contribute to the implementation of tailored antibiotic regimens for pneumonia.

List Of Abbreviations

PCT: Procalcitonin

CAP: Community-acquired pneumonia

MDRO: Multi-drug resistant organisms

Declarations

Ethics approval and consent to participate

The study was submitted to and approved by the Massachusetts General Hospital Institutional Review Board (Protocol no. 2012P001590), and the study was granted a waiver of informed consent. All administrative permissions required in order to access and use the data in the study were granted by the Massachusetts General Hospital Institutional Review Board.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

This work was supported by an unrestricted grant from bioMérieux (to M.K.M). P.S has received research grants from bioMérieux. bioMérieux manufactures the VIDAS B.R.A.H.M.S PCT automated test for the determination of procalcitonin (PCT) in human serum or plasma. There are no competing interests for the remaining authors.

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Authors' contributions

P.A analyzed and interpreted the patient data and wrote the manuscript. S.M.M analyzed and interpreted the patient data. M.A analyzed and interpreted the patient data. B.B analyzed and interpreted the patient data. P.S analyzed and interpreted the patient data. V.C analyzed and interpreted the patient data. J.M.V analyzed and interpreted the patient data. M.K.M analyzed and interpreted the patient data and wrote the manuscript. All authors read and approved the final manuscript.

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Figures

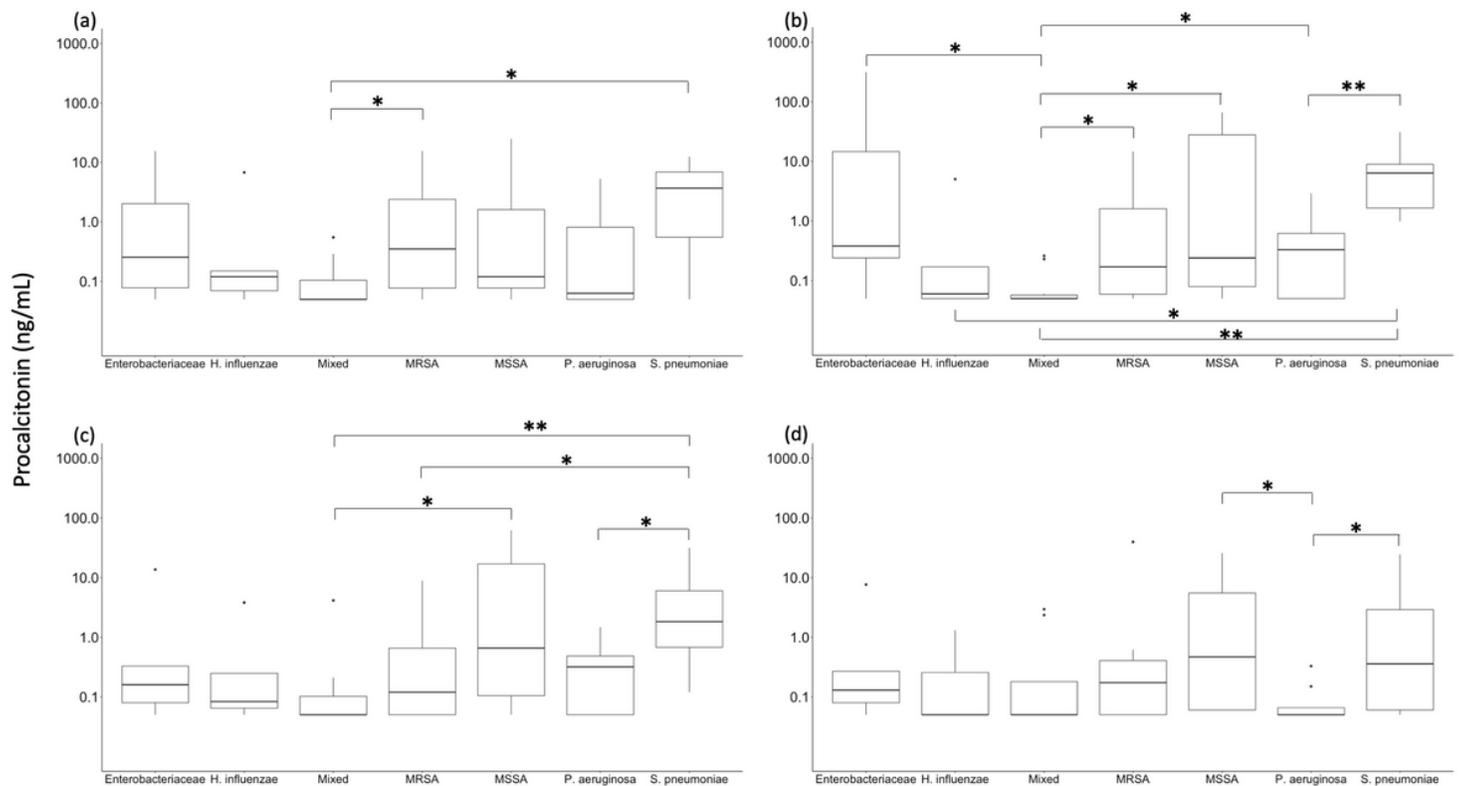


Figure 1

Box plots representing median and interquartile ranges of procalcitonin values for different bacteria on hospital days 1 (Panel a), 2 (Panel b), 3 (Panel c) and 4 (Panel d). * $p < 0.05$, ** $p < 0.01$

Supplementary Files

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- [TableS1.docx](#)