**Supplement for: Effects of Procalcitonin on Antimicrobial Treatment Decisions in Patients with COVID-19**

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**Supplemental Section 1: Detailed statistical methodology**

Baseline patient characteristics considered in multivariable modeling included gender, ethnicity, race, age, and weighted Elixhauser score1 as well as individual variables contained within the weighted Elixhauser score but with a zero contributing weight to this score, including hypertension, diabetes, hypothyroidism, peptic ulcer disease, HIV/AIDS, rheumatoid arthritis, alcohol abuse, and psychoses.

The multivariable model for antibiotic initiation included initial PCT (log-transformed to normalize the left-skewed distribution) and time from start of pandemic (March 1, 2020) as the main covariates of interest. Multivariable models for antibiotic duration, antibiotic risk classes, survival, and length of stay included these covariates as well as change in PCT over time and bPNA group. Patient-level baseline characteristics were then added to the models and assessed for their association with the outcome of interest and confounding effects on other model covariates. Change in PCT over time was derived from a mixed-effect linear regression model with subject-specific random intercepts and slopes. Log-transformed PCT value was the outcome in this model and days from initial PCT test was the independent variable. Subject-specific slopes were estimated and transformed to represent the estimated daily percentage change in PCT, which was then used as a covariate for subsequent analyses. A purposeful selection algorithm2 was utilized to determine the final multivariable model. This process included assessing univariable associations of covariates with the outcome of interest and retaining those with a p-value >0.25 as candidates for the final model. Retained variables were assessed for their individual significance as well as effects on other model covariates in a full multivariable model containing primary covariates of interest and all candidate predictors. Covariates with a p-value <0.1 in the multivariable model and those whose exclusion from the model resulted in >20% change in the parameter estimate of any other covariate were retained.

For secondary outcomes, a multivariable negative binomial model and Cox proportional hazards model, derived using the same purposeful selection algorithm as above, were used to assess associations between PCT and covariates with length of stay and survival, respectively. For secondary analyses, patients not initiated on antibiotics were classified as having no bPNA, as clinical suspicion for an underlying bacterial process was assumed to be very low when antibiotics were not begun.

**Supplemental Table 1: Bacterial pneumonia (bPNA) classification**

In cases where a note was present in the chart from an infectious diseases physician prior to the time of a PCT lab resulting, the patient assessment in this note was also used to inform bPNA classification. Patient charts were each evaluated independently by two reviewers (AC, SC, & ZC), with discrepant classifications adjudicated by an infectious diseases physician (KR).

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| **Clinical Criteria\*** | **Microbiologic criteria** |
| Fever (T>38°) or hypothermia (T<36°) | Pathogen identified on a respiratory culture |
| Elevated WBC count ≥12,000/mm3 | Positive *S. pneumoniae* bacterial urinary antigen |
| Chest imaging consistent with bacterial infection | Positive *Legionella* bacterial urinary antigen |
| Need for supplemental oxygen or oxygen saturation <90% |  |
| Purulent sputum production\*\* |  |

**\*Present in 1st 48 hours of hospital presentation**

**\*\***A**t least moderate PMNs on sputum Gram stain**

**Proven bPNA**: met all clinical and at least one microbiologic criterion

**Probable bPNA**: met all clinical criteria but had no microbiologic criteria and had clinical improvement on antibiotics within 48-72 hours

**Possible bPNA**: met at least one clinical criterion (except hypoxia alone, as this was the presenting symptom for nearly all patients with COVID-19)

**No bPNA**: met no clinical or microbiologic criteria or had hypoxia alone as their presenting symptom

**Supplemental Table 2: Antibiotic Risk Classification**

Antibiotics were classified into three risk categories based on published epidemiological data on their strength of association with *Clostridium difficile* infection.3-6

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| **High Risk** | **Intermediated Risk** | **Low Risk** |
| 3rd generation cephalosporins | aminoglycosides | 1st generation cephalosporins |
| 4th generation cephalosporins | penicillins | 2nd generation cephalosporins |
| fluoroquinolones | vancomycin | macrolides |
| β-lactam/β-lactamase inhibitor combinations |  | tetracyclines |
| carbapenems |  | metronidazole |
| clindamycin |  | trimethoprim/sulfamethoxazole |
|  |  | daptomycin |
|  |  | nitrofurantoin |
|  |  | aztreonam |
|  |  | fosfomycin |
|  |  | linezolid |

**Supplemental Table 3: Multivariable negative binomial model for covariate associations with length of stay**

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| **Negative Binomial Regression Covariate** | **RR (95% CI)** | **P-value** |
| bPNA, none → possible → probable/proven | 1.38 (1.23, 1.54) | <.001 |
| Initial PCT, per 50% increase | 1.07 (1.05, 1.09) | <.001 |
| % Change in Daily PCT, per unit increase | 1.02 (1.01, 1.03) | <.001 |
| Time from start of pandemic, per 2-week increase | 0.99 (0.98, 0.99) | <.001 |
| Weighted Elixhauser, per unit increase | 1.01 (1.00, 1.01) | 0.001 |
| Peptic Ulcer Disease, yes vs. no | 0.72 (0.57, 0.91) | 0.006 |
| Race, other vs. white | 0.87 (0.77, 0.99) | 0.05 |
|  unknown vs. white | 1.15 (0.82, 1.01) |  |
| Gender, female vs. male | 0.90 (0.81, 1.01) | 0.07 |
| Diabetes, yes vs. no | 1.05 (0.94, 1.19) | 0.39 |
| Hypertension, yes vs. no | 1.05 (0.91, 1.20) | 0.52 |

**Supplemental Table 4: Multivariable Cox proportional hazards model for covariate associations with overall survival**

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| **Cox Model Regression Covariate** | **HR (95% CI)** | **P-value** |
| bPNA, none → possible → probable/proven | 1.15 (0.77, 1.73) | 0.49 |
| Initial PCT, per 50% increase | 1.04 (0.98, 1.10) | 0.22 |
| % Change in Daily PCT, per unit increase | 1.05 (1.02, 1.08) | <.001 |
| Time from start of pandemic, per 2-week increase | 0.98 (0.96, 0.99) | 0.008 |
| Age, per year increase | 1.03 (1.01, 1.05) | 0.007 |
| Weighted Elixhauser, per unit increase | 1.02 (1.00, 1.03) | 0.008 |
| Diabetes, yes vs. no | 2.00 (1.08, 3.72) | 0.03 |
| Gender, female vs. male | 0.72 (0.46, 1.14) | 0.16 |
| Psychoses, yes vs. no | 1.54 (0.81, 2.93) | 0.19 |
| Hypertension, yes vs. no | 1.46 (0.71, 3.08) | 0.29 |
| Ethnicity, unknown vs. non-Hispanic/Latino | 0.97 (0.32, 2.96) | 0.37 |
|  Hispanic/Latino vs. non-Hispanic/Latino | 0.22 (0.03, 1.80) |  |
| Peptic Ulcer Disease, yes vs. no | 0.74 (0.31, 1.75) | 0.49 |

**Supplemental Table 5: Sensitivity analysis utilizing Cox proportional hazards model for antibiotic duration (n=224), with censoring at time of death or discharge if during antibiotic course (n=96)**

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| **Cox Model Regression Covariate** | **HR\* (95% CI)** | **P-value** |
| bPNA, none → possible → probable/proven | 1.61 (1.24, 2.09) | <.001 |
| Initial PCT, per 50% increase | 1.04 (1.00, 1.08) | 0.04 |
| % Change in Daily PCT, per unit increase | 1.05 (1.02, 1.07) | <.001 |
| Time from start of pandemic, per 2-week increase | 1.00 (0.98, 1.01) | 0.87 |
| Age, per year increase | 0.99 (0.98, 1.00) | 0.02 |
| Gender, female vs. male | 0.78 (0.55, 1.10) | 0.16 |

\*Hazard ratio for continuing antibiotic treatment

**References**

1. Thompson NR, Fan Y, Dalton JE, et al. A new Elixhauser-based comorbidity summary measure to predict in-hospital mortality. *Med Care.* 2015;53(4):374-379.

2. Bursac Z, Gauss CH, Williams DK, Hosmer DW. Purposeful selection of variables in logistic regression. *Source Code for Biology and Medicine.* 2008;3(1):17.

3. Baggs J, Jernigan JA, Halpin AL, Epstein L, Hatfield KM, McDonald LC. Risk of Subsequent Sepsis Within 90 Days After a Hospital Stay by Type of Antibiotic Exposure. *Clinical Infectious Diseases.* 2017;66(7):1004-1012.

4. Slimings C, Riley TV. Antibiotics and hospital-acquired Clostridium difficile infection: update of systematic review and meta-analysis. *J Antimicrob Chemother.* 2014;69(4):881-891.

5. Brown KA, Khanafer N, Daneman N, Fisman DN. Meta-analysis of antibiotics and the risk of community-associated Clostridium difficile infection. *Antimicrob Agents Chemother.* 2013;57(5):2326-2332.

6. Isaac S, Scher JU, Djukovic A, et al. Short- and long-term effects of oral vancomycin on the human intestinal microbiota. *J Antimicrob Chemother.* 2017;72(1):128-136.