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MICROBIAL DYNAMICS AND IMMUNOLOGICAL RESPONSES IN THE LUNGS IN SECONDARY BACTERIAL PNEUMONIA CAUSED BY COVID-19

Abstract. Although it is still poorly understood, secondary bacterial pneumonia (secondary bacterial pneumonia) is linked to substantial morbidity after respiratory virus infection. We compare the pulmonary transcriptome and longterm airway microbiome dynamics of patients who developed secondary bacterial pneumonia to controls who did not in a prospective cohort of 112 critically sick people who were intubated for COVID-19. We discover a substantial correlation with secondary bacterial pneumonia and corticosteroid treatment as well as death. Increased bacterial RNA mass and the predominance of culture-confirmed pathogens, which can be found days before a secondary bacterial pneumonia clinical diagnosis and are commonly also seen in nasal swabs, are characteristics of the pulmonary microbiome in secondary bacterial pneumonia.

Key words: Bacterial pneumonia, COVID-19, immune response.

Patients with secondary bacterial pneumonia had reduced TNFα signaling, according to pulmonary transcriptome analysis, and sensitivity studies indicate that corticosteroid therapy is the mechanism underlying this finding. Additionally, we discover that in both secondary bacterial pneumonia patients and controls, lower expression of innate and adaptive immune genes is correlated with increased bacterial RNA mass. When combined, our results offer new understandings of the host immunological characteristics and microbial dynamics of COVID-19-associated secondary bacterial pneumonia. They also imply that opportunistic bacterial pathogens can proliferate due to immune signaling suppression, which may be caused by corticosteroid therapy.

Severe COVID-19 is characterized by a dysregulated inflammatory response in both the airways and systemic circulation yet whether secondary bacterial pneumonia is associated with further alterations in this pathologic immune state remains unclear. For instance, secondary bacterial pneumonia might lead to activation of innate immune signaling pathways important for bacterial defense, which has been observed in patients with ventilator-associated pneumonia prior to the COVID-19 pandemic. Alternatively, secondary bacterial pneumonia might arise from suppressed immune signaling, which is well described in mouse models of post-influenza secondary bacterial pneumonia and in patients with sepsis who acquire nosocomial infections [2]. It is also possible that the host response to secondary bacterial pneumonia may simply be overshadowed by the inflammatory state of severe SARS-CoV-2 infection. Despite their interconnected roles, few studies have assessed both the lower respiratory tract microbiome and host immune responses in critically ill patients, and none for the explicit purpose of studying post-viral secondary bacterial pneumonia. A recent elegant study showcased how lower respiratory metatranscriptomics can effectively identify connections between host and microbial factors with clinical outcomes in COVID19[2], however it did not focus on clinically confirmed secondary bacterial pneumonia. Two recent diagnostic test studies demonstrated the potential of respiratory metatranscriptomics to improve the detection of pathogens in COVID19 patients with ventilator associated pneumonia[8] but did not evaluate biological features of secondary bacterial pneumonia. The burden of secondary infections in patients with COVID-19 and other viral pneumonias, as well as gaps in our mechanistic understanding of secondary bacterial pneumonia, motivated us to carry out this study[4]. We assessed lung microbiome dynamics and host immune

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responses using metatranscriptomics in a large cohort of hospitalized COVID-19 patients with rigorous secondary bacterial pneumonia adjudication by three physicians. We observed disruption of the lung microbiome in patients with secondary bacterial pneumonia, characterized by increased bacterial RNA mass and dominance of culture-identified pathogens, as well as changes in host immune signaling involving genes important for bacterial defense. Together, our findings provide fresh insights into the biology of secondary bacterial pneumonia, suggesting potential new therapeutic targets and approaches to secondary bacterial pneumonia diagnosis. Analysis of clinical and demographic data demonstrated that hospital mortality was significantly greater in patients with secondary bacterial pneumonia than in those without (47.7% vs 7.3%, $P < 0.0001$).[5] Patients with secondary bacterial pneumonia were also more likely to have received corticosteroids during their hospitalizations (97.7% vs 82.9%, $P = 0.026$). All patients received antibiotics during their hospitalizations, and total days of antibiotic therapy in the first week of hospitalization did not differ between groups. A minority of patients had received one or more SARS-CoV-2 vaccines prior to admission (9.1% vs 12.2%, $P = 0.61$); most patients were recruited prior to vaccine availability [6]. We found that secondary bacterial pneumonia pathogens were not only detectable in the lower airway, but also in the upper airway in more than half of the cases, including prior to clinical pneumonia diagnosis. More broadly, however, we found only low-moderate correlation between the nasal and lower respiratory tract microbiomes, and did not observe any differences based on secondary bacterial pneumonia status. A prior study using 16S rRNA gene sequencing to profile the microbiome of paired nasal and lower respiratory tract samples from children found significant correlations in taxonomic abundance between sites [4,5]. In contrast, a recent metatranscriptomic study of mechanically ventilated COVID-19 patients reported significant differences in the microbial composition of the upper and lower airways [7], as did a 16S study comparing the lower airway microbiome to that of the oropharynx and upper respiratory tract46. Additional studies are needed to more comprehensively investigate the relationships between the upper and lower airway microbiome, and how they differ based on sequencing technique or on the presence of bacterial pneumonia. Taken together, our study sheds light on the microbial dynamics and host immune responses of secondary bacterial pneumonia, a clinically important and serious complication of COVID-19 and other viral respiratory illnesses. Future studies are needed to validate these findings, clarify mechanisms in cohorts with other viral infections, and evaluate the diagnostic potential of metatranscriptomics for early detection of secondary bacterial pneumonia. Strengths of our work include the use of host/microbe metatranscriptomics to study secondary bacterial infections, rigorous clinical adjudication of secondary bacterial pneumonia, longitudinal sampling, and measurement of bacterial RNA mass, a biomarker not previously evaluated in studies of pneumonia. Limitations include a relatively small sample size and incomplete longitudinal sampling for all patients, which reduced the number of patients with analyzable samples near the date of secondary bacterial pneumonia onset, and the number of analyzable longitudinal samples. This likely limited our ability to detect microbiome and host transcriptional differences that may have existed between secondary bacterial pneumonia patients and controls. Our findings require further validation in independent cohorts. While several public COVID-19 respiratory transcriptomic datasets exist, none include adjudication of secondary bacterial pneumonia status using a rigorous and standardized definition. Taken together, our study sheds light on the microbial dynamics and host immune responses of secondary bacterial pneumonia, a clinically important and serious complication of COVID-19 and other viral respiratory illnesses. Future studies are needed to validate these findings, clarify mechanisms in cohorts with other viral infections, and evaluate the diagnostic potential of metatranscriptomics for early detection of secondary bacterial pneumonia.

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