Seek and Ye Shall Find: COVID-19 and Bacterial Superinfection

Since the onset of the coronavirus disease (COVID-19) pandemic and the massive influx of sick patients requiring mechanical ventilation in ICUs around the globe, frontline clinicians have repeatedly faced the same question: "*Is it all just COVID-19 or does my patient have a secondary bacterial pneumonia?*" Providing a timely and concrete answer at the bedside has proven difficult. COVID-19 pneumonia shares many of the radiographic, physiologic, and clinical features of severe bacterial pneumonias, often with a protracted course and variable evolution of severity, making objective microbiologic data necessary for the diagnosis of superinfections. However, dedicated diagnostic workup with lower respiratory tract (LRT) sampling has been variably performed, and earlier in the pandemic, it was often avoided because of (now largely allayed) concerns of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission. Consistent with clinical practice guidelines (1), about 85% of critically ill patients with COVID-19 receive systemic antibiotics (2, 3), which are often empiric and of broad spectrum. Such management guided by well-intentioned "best guesses" is destined to offer no benefit in many patients and may even cause harm in some. Empiric antibiotics given to patients with an isolated SARS-CoV-2 infection are not only unnecessary, but may also expose patients to unwarranted adverse effects and promote the selection of resistant pathogens. Furthermore, premature diagnostic closure on presumed secondary pneumonia will neglect investigation of competing etiologies for respiratory decline (e.g., pulmonary embolism or congestive heart failure). On the other hand, patients with COVID-19 with a true superinfecting pathogen require the timely initiation of targeted antibiotics of appropriate spectrum and duration (Figure 1).

Given these uncertainties, in this issue of the *Journal*, Pickens and the NU COVID (Northwestern University COVID-19) Investigators (pp. 921–932) provide influential and practice-informing data on bacterial superinfection in mechanically ventilated patients with COVID-19 (4). Capitalizing on an institutional practice of routine bronchoscopic sampling in patients after intubation or with clinical suspicion of ventilator-associated pneumonia (VAP), the authors enrolled 179 patients with COVID-19 and captured a comprehensive data set of 389 BAL samples. These samples were collected either early (within 48 h of intubation, $n = 133$), while looking for a community- or hospital-acquired superinfection, or late (>48 h, $n = 246$), while looking for an incident VAP (Figure 1). BAL fluid was analyzed for host cellular composition, as well as for respiratory pathogens by quantitative microbiologic cultures and a rapid multiplex PCR panel.

The results were striking. Early BAL samples revealed bacterial superinfections in 21% of patients, and these infections were overwhelmingly caused by antibiotic-sensitive, community-type pathogens (e.g., *Streptococcus* species and methicillin-sensitive *S. aureus*), with marginal sensitivity improvement by the PCR test over cultures. These superinfections were indistinguishable by clinical measures or blood biomarkers and, surprisingly, were not characterized by the typical alveolar neutrophilia usually associated with bacterial pneumonias (5). Nonetheless, clinical microbiologic results alone led to timely antibiotic adjustments (cessation or de-escalation), as quantified by a daily antibiotic scoring system. Late BAL samples uncovered a first episode of VAP in 44% of patients, of whom 21% went on to develop a second VAP at about 10 days after the first one, creating a linear incidence rate of 45.2 VAP episodes per 1,000 mechanical ventilation days. Patients with VAP were also clinically indistinguishable from those without VAP, but demonstrated higher alveolar neutrophilia and a lower percentage of BAL lymphocytes. Notably, only the minority of initial (21%) or subsequent (33%) VAP episodes were caused by difficult-to-treat nosocomial pathogens. Although there was no comparison group to judge their practice against, the overall low hospital mortality in this cohort (19%) suggested that active antibiotic adjustments and de-escalation based on BAL microbiology did not lead to harm despite the overall high incidence rate of secondary pneumonias.

On first glance, the high burdens of bacterial superinfections reported in this study (21% early and 42.5 VAPs/1,000 d) appear as numerical outliers compared with published estimates for early COVID-19 superinfections (about 9% [6]), VAP incidence rates (28/1,000 d in COVID-19 [7] and 6–16/1,000 d in the pre-COVID-19 era [8]), or combined meta-analytic estimates for COVID-19 secondary pneumonias (14% [9]). Nonetheless, the results reported by Pickens and colleagues (4) appear to derive from the meticulous, systematic bronchoscopic workup and not from a biological or clinical aberrancy. The authors detected the pathogens because they looked hard to find them. On closer inspection, the same holds true for prior studies of COVID-19 as well: when analyses were limited to patients with the most comprehensive workup (e.g., at least one LRT sample available or BAL culture and PCR), both early superinfection and VAP rates were higher and approximated the ones reported by the NU COVID team (6, 7, 10). Of note, the routine use of the multiplex PCR test in the NU COVID study did not account for much of the higher rate of pathogen detection, but led to more rapid therapeutic adjustments, with results available within 3 hours of sample acquisition.

Despite its notable strengths, this study has limitations and inevitably leaves many questions unanswered. The observational

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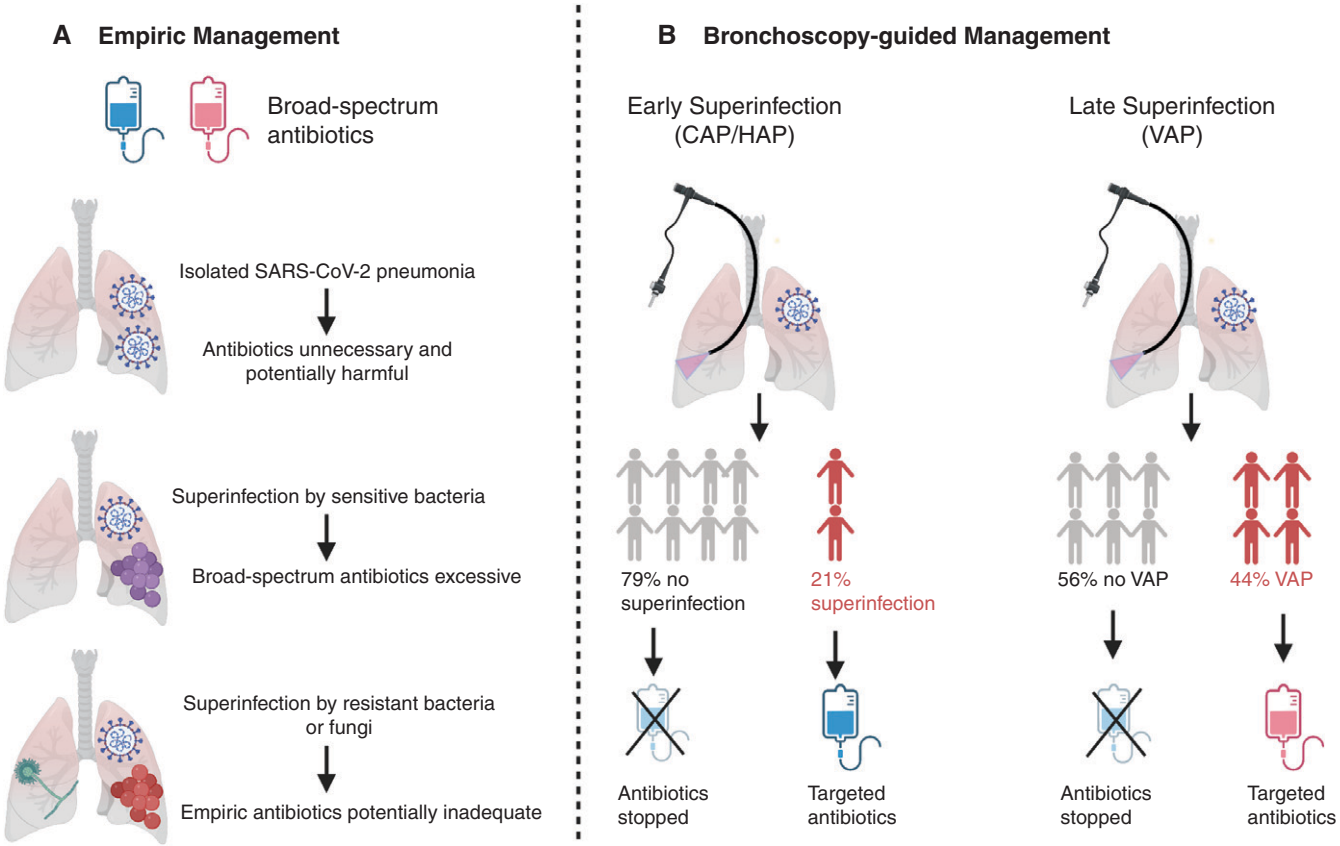

Figure 1. Empiric versus bronchoscopy-guided antibiotic management for bacterial superinfections in coronavirus disease (COVID-19). (*A*) Possible scenarios for the clinical utility of empiric broad-spectrum antibiotics in the case of isolated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, superinfection by sensitive bacteria, and superinfection by resistant bacteria or fungi. (*B*) Bronchoscopy-guided antibiotic management as per the study by Pickens and colleagues (4). For early superinfections for which bronchoscopy was performed within 48 hours of intubation (for diagnosis of CAP or HAP), microbiologic studies of BAL samples revealed bacterial superinfections by mostly sensitive bacteria in 21% of subjects. For late superinfections for which bronchoscopy was performed in patients intubated for >48 hours (for diagnosis of VAP), bacterial superinfection was detected in 44% of subjects, allowing for targeted antibiotic prescriptions. CAP = community-acquired pneumonia; HAP = hospital-acquired pneumonia; VAP = ventilator-associated pneumonia.

study design does not allow drawing inferences on the causal effects of a bronchoscopic workup on patient outcomes. Whether less invasive tracheal aspirates could offer similarly accurate and actionable diagnostic data is unknown, yet it would be relevant for many healthcare systems with limited access to bronchoscopy, and especially during surge operations. Detection of microbial cell–free DNA in peripheral blood may also offer diagnostic sensitivity in easily obtainable specimens, as we have recently shown in a small group of patients with COVID-19 by using plasma metagenomics. These patients had a high incidence of secondary infections, and there was an association between the plasma DNA levels from typical pathogens and higher 30-day mortality (11).

Clinically available metrics of the host response (blood biomarkers and BAL cellular composition) were not discriminatory for superinfections, and key questions thus remain regarding the diagnostic and/or prognostic value of systemic and lung biomarkers as well as whether a small proportion of positive microbiologic cultures represented colonization instead of invasive infection. It also remains unclear whether the linear increase in the VAP rate over time is a function of the prolonged ventilatory course observed in patients with COVID-19 versus non-COVID acute respiratory distress syndrome (12) or is reflective of SARS-CoV-2–specific disruption of host defenses. The current analysis did not provide data on fungal superinfections, which is an area of major diagnostic uncertainty and active investigation. Finally, this study was conducted in a period prior to wide adoption of steroids and anti–IL-6 receptor antibodies for COVID-19; it is possible that secondary infections have increased with these immunosuppressive therapies.

In summary, the NU COVID Investigators, through an enormous effort in the midst of the pandemic, demonstrate that diagnostic thoroughness delivers actionable information. The high rates of early and late superinfections in this study mandate vigilance and a systematic response. Among the many complications that can develop in critically ill patients with COVID-19, secondary pneumonias can be etiologically diagnosed and treated in a timely fashion. Most patients can be treated with appropriately de-escalated narrow-spectrum antibiotics, whereas antibiotics can be limited or avoided in those patients in whom LRT studies are negative. Given the group's findings that bronchoscopy can be safely performed in patients with COVID-19 (13), hospitals with such capacity should not

be dissuaded from performing BAL when clinically indicated. The study by Pickens and colleagues (4) reminds us that diagnostic inertia and therapeutic empiricism for secondary pneumonias can be overcome in the care of critically ill patients with COVID-19 because if we seek for pathogens, we shall find them. ■

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