FAQ: Should Antibiotic Therapy be Continued in Patients Diagnosed with COVID-19?

The ability to streamline and de-escalate empiric antibiotic therapy remains a challenge for antimicrobial stewardship programs. This challenge is further complicated by the ongoing pandemic and increased concern for COVID-19 infection, especially in light of reported mortality rates associated with severe disease presentation. Providers may decide to continue antibiotic therapy in the setting of viral illness due to a concern for bacterial co-infection.

Viral and bacterial co-infections have been largely described in clinical literature for influenza although data can be found for other respiratory illnesses (i.e. RSV, rhinovirus, adenovirus).[1] Prompt identification of bacterial infection in viral illness is critical as coinfection has been associated with increased rates of shock, required mechanical ventilation, prolonged ICU stay, and increased mortality.[2]

Our understanding of the incidence of bacterial co-infection in patients diagnosed with COVID-19 was largely shaped by published experiences at the very beginning of the pandemic. An early case series of 41 patients with COVID-19 described by Huang et al. noted that of the 12 patients who required ICU care, only 3 (7% of total) of them were diagnosed with bacterial superinfection.[3] In addition, another study describing 99 patients with COVID-19 in China, found only 1 patient diagnosed with a bacterial super-infection.[4] These findings are highlighted by a description of a larger case series of 1099 published by Guan et al. where 58% of all patients received IV antibiotics, suggesting we have opportunities for antibiotic de-escalation.[5] Subsequently, additional publications have shed further light on this topic:

- A single-center, retrospective analysis of 321 patients with confirmed COVID-19 infection assessed rates of community-acquired co-infection and found this to be an infrequent finding.[6] Microbiologically proven co-infection was identified in 12 (3.7%) of patients with only 7 (1.2%) attributed to bacterial infections. Co-infection was more frequent in patients admitted to the ICU 7/17 (41%, $p<0.005$).
- Langford et al. published results of a "living" rapid review and meta-analysis designed to determine the prevalence of bacterial co-infection (at presentation) and secondary infection (occurring after presentation) in patients with COVID-19.[7] A total of 28 studies met eligibility criteria which included evaluating patients with confirmed COVID-19 infection and reporting prevalence of acute bacterial infection. Bacterial co-infection was identified in 3.5% of patients (95%CI 0.6 to 6.5%) and secondary bacterial infection in 15.5% of patients (95%CI 10.9 to 20.1%). Bacterial infection was more common in critically ill patients 8.1% (95%CI 2.3 to 13.8). Notably 71.3% of the patients with COVID-19 received antibiotics.
- Stevens et al. retrospectively reviewed inpatient, emergency department (ED), and outpatient encounters at a single center in order to analyze the prevalence and duration of antimicrobial therapy in patients with confirmed COVID-19 infection.[8] A total of 346 patients were included and 59% (23/39) of inpatients received antimicrobials, with higher rates in the severe disease. Although not the intent of this study, the authors noted increased antimicrobial prescribing did not coincide with increased observation of bacterial co-infection among eight patients with respiratory culture results. Of note, approximately 3% (10/307) of ambulatory patients received antimicrobial therapy.
- Nori et al. published results from a retrospective observational study of 4,267 patients with COVID-19 admitted to a single hospital in the Bronx between March 1st and April 18th.[9] Approximately 3.6% (152) had a bacterial or fungal co-infection. Among patients with confirmed co-infection, 33% had preceding healthcare exposure, 65%

were admitted to an ICU, 74% received mechanical ventilation, 17% received biologics (or placebo as part of a randomized trial), and 29% received corticosteroids. The most common respiratory isolates were *S. aureus* (44%), *P. aeruginosa* (16%), and *Klebsiella spp*. (10%), and the most common blood culture isolates were *S. aureus* (30%), *S. epidermidis* (12%), and *Streptococcus spp*. (10%). Of note, 8 patients developed candidemia, 7 of which had an indwelling central venous catheter. Despite the low (3.6%) incidence of confirmed co-infection, 98% of patients hospitalized with COVID-19 received inpatient antimicrobial therapy for a median of 8.5 days, and local antibiogram data revealed a significant reduction in Enterobacteriaceae susceptibilities to multiple antibiotics as compared with the prior two years.

- A recent single center observational study in Ireland, 72% of COVID-19 patients received empiric antimicrobial therapy. However respiratory pathogens were identified in only 6% of these patients.[10]
- Vaughn et al. reviewed 1705 hospitalized patients with COVID-19 in a network of 38 hospitals in Michigan and found the majority (56%) of them were prescribed early empiric antibacterial therapy.[11] The most common antibiotics were ceftriaxone, vancomycin, doxycycline, and cefepime. The majority, 63.4%, were only prescribed antibacterials targeting community-acquired pathogens, however 25.8% received antibacterials targeting MRSA and 26.3% received anti-Pseudomonal therapy. Median duration of therapy was 3 days (IQR 2-6) and only 11.4% of all those receiving antibacterials were prescribed antibiotics at discharge. Similar to other studies, there were only 3.5% patients with confirmed bacterial co-infections, 1.8% had a positive blood culture and 1.7% had a positive respiratory culture. Risk factors for bacterial co-infection were older age, lower BMI, kidney disease, residing in a SNF, admitted to the ICU, and higher white blood cell count. Notably, the positive predictive value for a procalcitonin value of >0.5 ng/mL was only 9.3% but the negative predictive value was 98.3%. Interestingly, the majority of patients receiving antibiotic had them stopped within one day of the positive COVID-19 test, therefore as the test turnaround time improved the antibiotic use decreased.
- In a Letter to the Editor, in late August 2020, Punjabi et al. described 4,221 adult patients with COVID-19 and 21.4% received IV vancomycin within 48 hours of presentation. Of the 158 patients who had respiratory cultures throughout their stay, only 0.6% were positive for MRSA and 5.7% cumulative positive by day 28. They found the MRSA PCR tests had a negative predictive value of 100%.

Although empiric antibiotic therapy is often initiated upon presentation, particularly in those with severe COVID-19 pneumonia, consideration can be given to antibiotic discontinuation at 48 to 72 hours for patients with a positive test for SARS-CoV-2, no evidence of a bacterial pathogen, and early clinical stability.[12] The prevalence of bacterial co-infection on presentation seems to be very low, based on the above studies. Additionally, available data suggests that community-acquired bacterial pathogens in patients with COVID-19 and pneumonia are the same as would be suspected in CAP. MRSA and Pseudomonas become more prevalent when including co-infections not present on admission. And as described in the Letter to the Editor by Punjabi et al, the nasal MRSA PCR swab appears to be very helpful in being able to de-escalate anti-MRSA therapy with a NPV of 100%.

COVID-19 treatment guidance from the National Institutes of Health on empiric broad-spectrum antimicrobial therapy recommends that “In patients with COVID-19 and severe or critical illness, there are insufficient data to recommend empiric broad-spectrum antimicrobial therapy in the absence of another indication. If antimicrobials are initiated, the Panel recommends that their use should be reassessed daily in order to minimize the adverse consequences of unnecessary antimicrobial therapy.”[13] Continued use of antibiotics may increase the risk of antibiotic resistance, alter normal gut flora increasing the risk of *Clostridium difficile* infection, and increase the risk of adverse drug effects which may all negatively impact a patient’s clinical course. If bacterial infection has been excluded or is unlikely, there is minimal risk associated with discontinuing antibiotics even in the setting of COVID-19 infection.

References:
1. Crotty MP, Meyers S, Hampton N, et al. Epidemiology, Co-Infections, and Outcomes of Viral Pneumonia in Adults: An Observational Cohort Study. *Medicine (Baltimore)*. 2015;94(50):e2332.
2. Rice TW, Rubinson L, Uyeki TM, et al. Critical illness from 2009 pandemic influenza A virus and bacterial coinfection in the United States. *Crit Care Med*. 2012;40(5):1487-1498.
3. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*. 2020;395(10223):497-506.
4. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The Lancet*. 2020;395(10223):507-513.
5. Guan W, Ni Z, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *New England Journal of Medicine*. 2020;382(18):1708-1720.
6. Cj L, Mt P, D P, Jp R, Nn P. Community Acquired Co-infection in COVID-19: A Retrospective Observational Experience. *Clin Infect Dis*. Published online July 1, 2020.
7. Langford BJ, So M, Raybardhan S, et al. Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. *Clinical Microbiology and Infection*. 2020;0(0).
8. Stevens RW, Jensen K, O'Horo JC, Shah A. Antimicrobial prescribing practices at a tertiary care center in patients diagnosed with COVID-19 across the continuum of care. *Infection Control & Hospital Epidemiology*. Published online undefined/ed:1-14.
9. Nori P, Cowman K, Chen V, et al. Bacterial and Fungal Co-Infections in COVID-19 Patients Hospitalized During the New York City Pandemic Surge. *Infection Control & Hospital Epidemiology*. Published online undefined/ed:1-13.
10. Townsend L, Hughes G, Kerr C, et al. Bacterial pneumonia coinfection and antimicrobial therapy duration in SARS-CoV-2 (COVID-19) infection. *JAC Antimicrob Resist*. 2020;2(3).
11. Vaughn VM, Gandhi T, Petty LA, et al. Empiric Antibacterial Therapy and Community-onset Bacterial Co-infection in Patients Hospitalized with COVID-19: A Multi-Hospital Cohort Study. *Clin Infect Dis*.
12. Metlay JP, Waterer GW. Treatment of Community-Acquired Pneumonia During the Coronavirus Disease 2019 (COVID-19) Pandemic. *Ann Intern Med*. 2020;173(4):304-305.
13. Information on COVID-19 Treatment, Prevention and Research. COVID-19 Treatment Guidelines.

Reviewed on 8/28/20.