Reply to Casalini et al., "Bacterial Coinfections in COVID-19 Patients without a Positive Microbiologic Result: a Word of Caution"

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We thank Casalini et al. for their letter to the editor (1) and their interest in our recent publication "Antibiotic Use and Bacterial Infection among Inpatients in the First Wave of COVID-19: a Retrospective Cohort Study of 64,691 Patients" (2) and appreciate the opportunity to extend the conversation related to antibiotic use among hospitalized patients with COVID-19.

Casalini et al. note that we likely overestimated the true incidence of bacterial infections among hospitalized patients with COVID-19. As stated in our publication, we agree with them. The premise of our study was that prior research, which relied primarily on microbiologic cultures, underestimates the true incidence of bacterial infections among hospitalized patients with COVID-19. We used clinical diagnoses of infection, represented by diagnosis codes, as an alternative approach. Discharge diagnosis codes are associated with a positive predictive value for bacterial infection of ≥80% (3). In our study, diagnosis codes consistent with either bacterial coinfection or bacterial secondary infection were independently associated with increased mortality, suggesting that these codes have clinical significance and are not just a by-product of overcoding. However, we acknowledge that not all patients who are diagnosed with (and treated for) bacterial infections actually have bacterial infections. In particular, urinary tract infections may be overdiagnosed among patients with COVID-19 (4). The true incidence of bacterial infection among hospitalized patients with COVID-19 likely lies somewhere between our estimate and what has previously been reported.

It is worth restating a key point. We used a permissive definition of bacterial infection that likely captured some patients who were believed by clinicians to have bacterial infection but who would have tested negative by culture. Among patients who did not meet this broad definition of bacterial infection, 71% received antibiotics while hospitalized. When excluding any patient meeting our definition of bacterial infection or any patient with a non-specific diagnosis of pneumonia or sepsis, 63% received antibiotics while hospitalized. During the first phase of the pandemic, most hospitalized patients with COVID-19 received antibiotics, regardless of whether bacterial infection was diagnosed.

In response to other points made by Casalini et al., we state the following.

- We agree that cultures from blood or the site of infection are an important component of the diagnostic workup. However, because the sensitivities of clinical cultures vary by context, many patients with bacterial infections will not have positive cultures but will nonetheless require antibiotics.
- Hospitalized patients with COVID-19 are often immunosuppressed or critically ill. When a urinary tract infection develops in that context, it may be causally linked to COVID-19.
- We had not foreseen that, by reporting a high rate of bacterial infections among hospitalized patients with COVID-19, our findings might increase antibiotic prescribing. Though it has been our clinical experience that COVID-19 is associated with bacterial infections more frequently than was reported initially in the literature, we sought to highlight the overuse of antibiotics in an effort to encourage antibiotic stewardship.

Hospitalized patients with COVID-19 often receive unnecessary antibiotics. This population represents both a challenge and an opportunity for infectious disease physicians and antibiotic stewardship teams.

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