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How Much Early Empiric Antibiotic Use Is Valuable for COVID-19 Hospitalized Patients?

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The proper use of empiric antibiotics is challenging for severe COVID-19 patients. At the beginning of the pandemic, there were concerns about bacterial coinfection influencing mortality and morbidity, supported by the evidence from previous pandemics. The majority of deaths throughout the influenza pandemic in 1918 were because of bacterial coinfections (1). Likewise, in the H1N1 influenza pandemic in 2009, 29 to 59% of global mortality was because of bacterial superinfections (2). Data obtained from the COVID-19 pandemic suggests that the bacterial coinfection is not common. In a meta-analysis of 3,338 COVID-19 patients, only 3.5% of patients were found with bacterial coinfection on admission. The bacterial coinfection rate was higher in cases that needed intensive care (8.1%) (3). In a study, 76% of hospitalized patients with COVID-19 received antibiotics (4). Early empiric antibiotic use (EEAU) is associated with risk. Excessive use of empiric antibiotics increases antibiotic resistance (5), *Clostridioides difficile* infection (6), and death rate (7). Early anaerobic antibiotics change the pulmonary microbiome, enhance hyperoxia lethality, and cause adverse outcomes (8). Changes in the respiratory microbiome have been reported in long-term acute respiratory distress syndrome in COVID-19 (9). Our hypotheses were: (1) EEAU rates would be different between centers and reduce over time; and (2) EEAU would increase the rates of antimicrobial resistance, *C. difficile* infection, and death.

A large retrospective study demonstrated that many hospitalized COVID-19 patients received EEAU during the COVID-19 pandemic, and the centers and indications showed a high rate of variation. The reported rates were lower compared to the previous report (76%) (4) but their cohort was 10-fold larger compared to previous cohorts and included two years of additional information. However, the authors did not estimate the bacterial superinfection rate, and the actual rate is unknown. Early empiric antibiotic use in COVID-19 represents a treatment with remarkable potential harms and unknown advantages, as many patients have no bacterial infection and cannot benefit from antimicrobial compounds. Early empiric antibiotic use is different remarkably between centers indicating clinical equipoise regarding the use of EEAU, but many centers have the same trends over time. These differences can be attributed to center volumes or can indicate different antibiotic stewardship practices, incomplete mapping of data from the source to the research record, or uncertainty of the clinicians regarding EEAU benefits (4).

Early empiric antibiotic use is associated with an increase in late CDI, rate of later broad-spectrum antibiotic use, long-term mechanical ventilation, and death rate. Despite receiving EEAU, patients were still more likely to die. Although the mechanism that links EEAU to greater antibiotic exposure and CDI seems plausible, the mechanism that links EEAU to death and long-term mechanical ventilation is less known. Alterations in the lung microbiome are associated with worse outcomes in critical disease (9). Hence, possibly increased mortality can partially be owing to EEAU-induced respiratory tract dysbiosis. Likewise, critically ill patients receiving early anti-anerobic antibiotics were found with less ventilator-related pneumonia-free and infection-free days and overall survival (8). The use of anti-anerobic antimicrobials in their subjects may explain the variations in mortality; however, more studies are needed. Their results are subject to the limitations of

all attempts to make causal inferences in observational information; residual confounding might bias their estimates. Unneeded antibiotics are associated with harms. Nonetheless, there is no clear guidance on EEAU indications and secondary bacterial infection rate. *Staphylococcus aureus* causes secondary bacterial infection (10). Nonetheless, regarding the pulmonary microbiome, it is suggested that hyperoxia can confer a selective growth advantage for *S. aureus* compared to other less tolerant oxygen species (11). Distinguishing between infection and dysbiosis when a common but pathogenic organism is obtained from respiratory cultures in cases with different possible causes of acute respiratory failure is beyond their current diagnostic scope. They suggested equipoise concerning EEAU in severe COVID-19 and harms caused by antimicrobials in respiratory failure.

The treatment of patients with COVID-19 using empiric intravenous antibiotics has been reduced throughout the pandemic, but the usage frequency is higher compared to the rate of bacterial superinfection, with remarkable inter-center variation in antibiotic-prescribing practices. Such patterns can be linked to extensive harm, and our findings are hypothesis-generating. Future studies should compare adverse events and outcomes in patients with COVID-19 treated with/without empiric antibiotics.

Footnote

Conflict of Interests: The author is Editor-in-Chief of the journal.

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