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The Mystery of Futility of Appropriate Antibiotics for Coinfection in COVID-19

To the Editor:

We read with great interest the article by Rouze and colleagues about comparing early bacterial identification between mechanically ventilated coronavirus disease (COVID-19) and influenza (1). We want to congratulate the authors for their dedication to their work. The lower COVID-19 detection rate of culture suggested that appropriate spectrum antibiotics should be chosen based on microbiological findings at the start of mechanical ventilation. However, when incorporating the results of this study into daily practice, it is necessary to solve the following knowledge gaps, in addition to the methodological issues of this study, such as standardized sampling in the prospective trial.

First, the appropriate use of antibiotics is warranted if early bacterial coinfection is suspected. However, appropriate antibiotic coverage did not modify the prognostic impact of bacterial infection in COVID-19 (1). The definition of appropriate antibiotic treatment included unnecessary use of broad-spectrum antibiotics that was reported to increase mortality (2). The finding in this study may be due to two hypotheses. First, overuse of broad-spectrum antibiotics for early bacterial infection triggers microbiome change, resulting in late-phase ventilator-associated pneumonia and influences the prognosis mediated by ventilator-associated pneumonia (3). Although it was not presented by Rouze and colleagues, investigating the effect of unnecessary initial broad-spectrum antibiotics use on the outcome might be an important future research question. Second, the local antibiotic concentration was inadequate to control the coinfection because of pulmonary macro- and/or microthrombosis (4). Thus, to determine the appropriate antibiotic strategy, both the effect of antibiotics on the prognosis and the capability of the local antimicrobial concentration to reach the effective threshold in COVID-19 should be investigated.

Although the study reported the incidence of bacterial detection, externalization of the result should be cautious for the different populations who receive different treatments. Since the initial COVID-19 pandemic, the treatment and vaccination have rapidly developed. Currently, various antiinflammatory therapies were employed in COVID-19 before intubation. Tocilizumab, for example, was associated with bloodstream infection (5). Antiinflammatory drugs mask signs of infection, making it difficult to diagnose infections in the earlier phase. The rapid distribution of the vaccine effectively addressed the issues of the pandemic. On the other hand, the new population of critically ill patients with COVID-19 will possibly be shifted from relatively healthy individuals into those who have not received the vaccine or have not acquired sufficient immunity due to their comorbidities. Rouze and colleagues reported that chronic obstructive pulmonary disease was less frequent than influenza pneumonia in patients with COVID-19, but gram-negative rods were more frequent (1). Future researchers need to address the following question: "In a world where vaccines and antiinflammatory treatments are ubiquitous, does the type of virus matter, or is the patient background more important?" ■

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Reply to Kasugai *et al.*

From the Authors:

We thank Dr. Kasugai and colleagues for their insightful comment following our comparative cohort study (1), which raises, in

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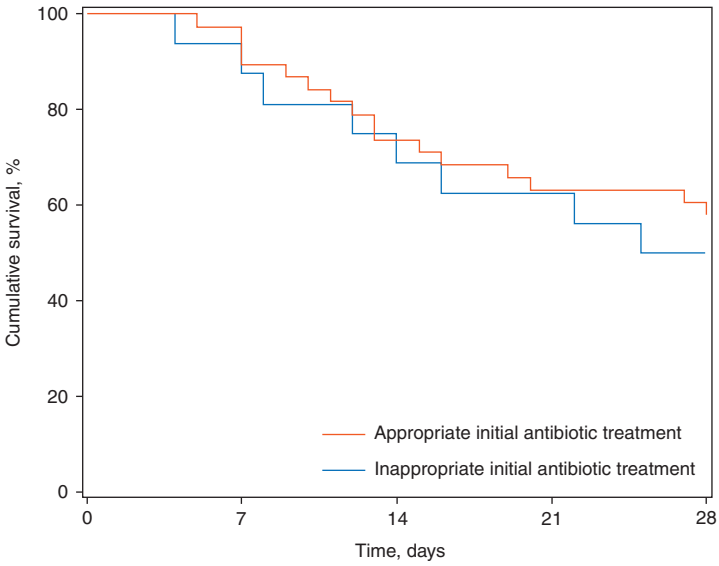
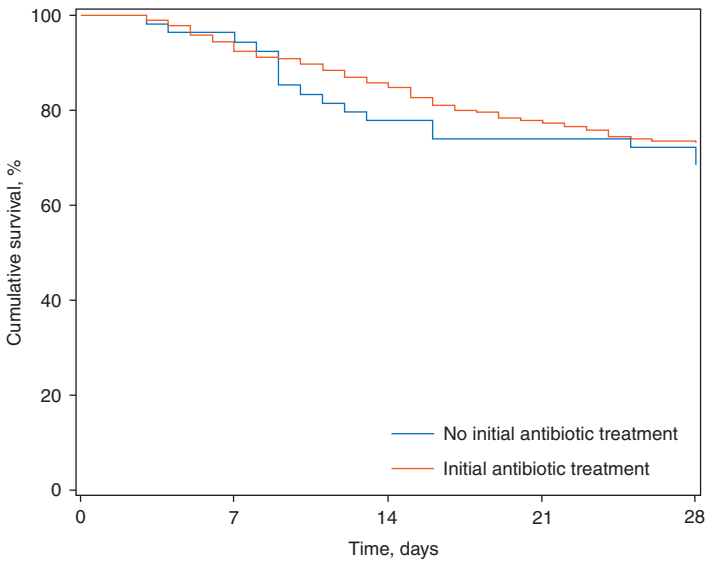


Number at risk

Appropriate initial antibiotic treatment	38	37	28	24	22
Inappropriate initial antibiotic treatment	16	15	12	10	8

Figure 1. Kaplan-Meier 28-day survival curves for patients with coronavirus disease (COVID-19) with early bacterial identification, according to appropriateness of initial antibiotic treatment.



Number at risk

No initial antibiotic treatment	54	52	42	40	37
Initial antibiotic treatment	450	425	386	350	329

Figure 2. Kaplan-Meier 28-day survival for patients with coronavirus disease (COVID-19) without early bacterial identification, according to the presence or not of initial antibiotic treatment (within the first 24 h of ICU admission).

particular, the question of the futility, and even the potential harmfulness, of empirical antibiotics for suspected early bacterial coinfection among critically ill patients with coronavirus disease (COVID-19). We take this opportunity to further discuss some additional data regarding the impact of "appropriate" early antibiotic therapy on the outcome of patients with COVID-19 requiring mechanical ventilation.

Antibiotic prescribing in patients with COVID-19 is substantial. Data from first waves worldwide show a rate of antibiotic use of 75%, with antibiotics mainly being started on admission, use being significantly higher in ICU settings (up to 85%), and an increasing proportion of use being shown in mechanically ventilated patients (2). Although a trend toward reduced antibiotic use is noted as the pandemic progresses, this rate is far higher than the reported

prevalence, below 10%, of early bacterial coinfection among hospitalized patients, even in the ICU (1, 2). However, we agree with Dr. Kasugai and colleagues on the hypothesis of a future shift in the prevalence, etiology, and severity of early bacterial coinfection in patients with COVID-19 owing to the generalized use of antiinflammatory therapies and the evolution of patients' underlying conditions, selecting those with a poor immune response to the vaccine.

Initial antibiotic therapy to treat suspected early bacterial coinfection can be retrospectively considered as "inappropriate" when *1*) no antibiotic matched the *in vitro* susceptibility of the identified bacteria (3), and *2*) no subsequent bacterial documentation occurred, leading to the conclusion of a possibly unnecessary initial antibiotic therapy. This last situation, the most frequent in daily practice, greatly depends on the effective microbiological diagnosis of coinfection. Bacterial identification may underestimate the true coinfection status owing to a lack of a quality microbiological specimen or antibiotics at the time of sampling.

Ultimately, Dr. Kasugai and colleagues address two distinct research questions. First, is appropriate early antibiotic treatment among coinfected patients with COVID-19 ineffective and, therefore, futile? As reported, only 70% of coinfected patients with COVID-19 received appropriate antibiotics. Surprisingly, although early bacterial identification was associated with an increased risk for 28-day mortality in patients with COVID-19, we did not observe an association between appropriate antibiotics and survival (28-day mortality: 42% [16/38] and 50% [8/16] in the case of appropriate and inappropriate initial antibiotic treatment, respectively; Figure 1), as one could expect (3). Interestingly, appropriate antibiotic use did not result in better survival in coinfected critically ill patients with influenza despite coinfection being an independent risk factor of death in this population (4). Second, is unnecessary initial antibiotic therapy among patients with no proven early bacterial coinfection harmful? Reducing antibiotic exposure is the cornerstone of the fight against antimicrobial resistance and nosocomial infections in the ICU (5). However, again, no association was found between antibiotics started or continued in the first 24 hours of ICU admission and mortality among patients without documented early bacterial coinfection (28-day mortality: 31% [17/54] and 27% [121/450] in the absence and presence of initial antibiotic treatment, respectively; Figure 2). However, our study was clearly underpowered to detect an effect of early antibiotics on outcome, as the number of coinfected patients with COVID-19, as well as the number of noncoinfected patients without any antibiotic upon ICU admission, was limited.

Critically ill patients with COVID-19 under mechanical ventilation may not all benefit from systematic early empirical antibiotics. Indication for antimicrobial treatment should be individualized at ICU admission after microbiological sampling, including respiratory secretions, before any antibiotic administration if possible. Toward better antimicrobial stewardship, a reasonable strategy could be to wait for the microbiological findings before prescribing antibiotics in patients with less severe disease and to initiate antibiotics with quick discontinuation based on microbiological results in patients with more severe disease, such as those with severe acute respiratory distress syndrome or septic shock. ■

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Initial Triple Combination Therapy for Intermediate- and High-Risk Pulmonary Arterial Hypertension: Standard of Care or Still Too Soon to Tell?

To the Editor:

Current guidelines recommend initial oral combination therapy for patients with low- or intermediate-risk pulmonary arterial hypertension (PAH) and initial combination therapy including intravenous prostacyclin for high-risk patients, but whether dual or triple combination therapy is preferable remains an open question (1, 2). We read with great interest the perfect retrospective study from

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