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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Boucly and colleagues (3), which investigated the impact of initial treatment strategy on the long-term prognosis of PAH by a comprehensive subgroup analysis and propensity score matching method and demonstrated tremendous survival benefits of initial triple combination therapy including parenteral prostacyclin for high-risk patients with PAH at the time of diagnosis. Excitingly, this is the first study showing a favorable profile of initial triple combination therapy with parenteral prostacyclin in intermediate-risk patients with PAH. However, the initial triple combination strategy is highly controversial among patients with intermediate- and high-risk PAH.

Three differential signaling pathways integrated in triple combination therapy, namely, the endothelin, nitric oxide, and prostacyclin pathways, may complement each other and produce superimposed or even synergistic effects (1). Gone are the days when patients with PAH had no available effective medicines, and with multiple accessible drugs advancing side by side and vying for the light, we have ushered in a new era of prosperity, so why not choose an optimized initial triple combination strategy? Moreover, a high proportion of triple combination therapies (including epoprostenol) enabled Japanese patients with idiopathic/heritable PAH to obtain a good long-term prognosis, with a 10-year survival rate of nearly 80%, suggesting more effectiveness of a relatively aggressive treatment strategy to rapidly reach low-risk status or hemodynamic normalization, especially for intermediate- and high-risk PAH (4). Additionally, although initial dual combination of PAH-targeted medications brought clinical benefits (5), the overall 10-year survival rate reported in the related study was only 43%, with 25% of patients with PAH receiving initial dual therapy escalated to triple combination therapy after a median follow up of 17 months (3), indicating the former strategy may result in disease progression and delayed optimal treatment.

Nonetheless, medication administration complexity, high drug expenses, targeted agent accessibility, and various adverse effects make initial triple combination strategy contentious and challenging. Unlike widely accepted oral medication, subcutaneous or intravenous administration of treprostinil requires complex up-titration to achieve an optimally tolerated dose. Regarding cost burden and drug accessibility, bosentan, macitentan, riociguat, and selexipag were already covered by Chinese national health insurance in 2019, but treprostinil has not been included. Furthermore, epoprostenol is not currently marketed in China, thus greatly limiting the therapeutic measures of critically ill patients. Last but not least, 19.0% of patients with PAH treated with selexipag, in the *post hoc* analysis of GRIPHON Study (evaluating a selexipag add-on to background dual combination therapy), prematurely discontinued their study regimen because of an adverse event, implying more side effects with more drugs (6).

Further prospective, multicenter, randomized controlled trials are needed to conclusively determine the optimal triple drug combination, and the role of initial triple therapy in other PAH subtypes, such as congenital heart disease or connective tissue disease–associated PAH, is also worth exploring. ■

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Treatment of Pulmonary Hypertension: Is Triple Therapy Necessarily Better than Monotherapy?

To the Editor:

Recently, Boucly and colleagues (1) found that long-term survival was independently related to the initial treatment strategy in a large cohort of patients newly diagnosed with idiopathic, hereditary, or anorexin-induced pulmonary arterial hypertension (PAH). Initial triple therapy treatment, including parenteral prostacyclin, was associated with a better overall survival rate than monotherapy or dual therapy with or without parenteral prostacyclin. The authors further clarified the relationship between the initial treatment strategy and long-term survival rate in patients with PAH, providing a new

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