the environment are always skewed, and analyses that use the mean data can lead to very strange conclusions. The reader would benefit from knowing the median and interquartile range in order to better understand the distribution of the results. The reduction of 79% appears large, but calculation of the colony-forming units (CFU) from 208 to 74.6 results in a reduction of 0.4 log_{10} CFU. We have performed similar studies, and analyses of the mean provide quite different results since many samples of microbiological swabs are below the level of detection and some CFU values are extremely high [2, 3]. Therefore, we strongly suggest use of the median and range for such studies and calculation of the log_{10} CFU reduction. The editorial by Dancer [4] also suggests that environmental control is unlikely to result in an impressive decrease in healthcare-associated infections; it was considered as “implausible.” Quaternary ammonium organosilane is highly effective against gram-positive pathogens but has, in general, low effectiveness against nonfermenting gram-negative bacteria as well as some Enterobacterales. In addition, it is ineffective against Clostridioides difficile spores [5]. We strongly believe that environmental control has an influence on transmission of multidrug-resistant pathogens. However, the effect on hospital-acquired infections may have been overestimated in the study by Ellingson et al, and are more likely influenced by other factors as outlined in the editorial [4].

Note

Potential conflicts of interest. The authors: No reported conflicts of interest. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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To the Editor—We read with interest the paper by Naseer et al, providing the US Food and Drug Administration’s (FDA) assessment of the benefit-risk of cefiderocol for its initial complicated urinary tract infection (cUTI) indication published in Clinical Infectious Diseases 2 December 2020 [1]. This manuscript was submitted in March 2020, the same month Shionogi submitted the cefiderocol supplemental New Drug Application for the hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP) indication. Because the paper is written in the present tense and was published after the FDA-approved HABP/VABP label update for cefiderocol [2] (September 2020), several statements in the manuscript are no longer current and may be confusing or misinterpreted by journal readers with respect to the following:

- The summary paragraph states cefiderocol is approved for cUTI when in fact cefiderocol is now approved for both cUTI and HABP/VABP.
- The statement that “the product labeling states cefiderocol should be reserved for use in patients who have limited or no alternative treatment options for the treatment of cUTI” when in fact this “limited use” restriction has been removed from the label.
- The statement that “The safety and efficacy of cefiderocol has not been established for the treatment of nosocomial pneumonia, [bloodstream infection], or sepsis” when in fact it is now approved for HABP/VABP.
- That “susceptibility breakpoints have not been established for [Acinetobacter] baumannii” when in fact breakpoints have been registered with the new indication that includes A baumannii [3].
- Describing the results of the CREDIBLE-CR study as unpublished, when in fact results were published in Lancet Infectious Disease in October 2020, along with the results of the APEKS-NP study [4, 5]. Results are also available on ClinicalTrials.gov: NCT03032380 for Clinical Study of Cefiderocol (S-649266) for the Treatment of Nosocomial Pneumonia Caused by Gram-negative Pathogens (APEKS-NP), NCT02714595 for Study of Cefiderocol (S-649266) or Best Available Therapy for the Treatment of Severe Infections Caused by Carbapenem-resistant Gram-negative Pathogens (CREDIBLE-CR), and NCT02321800 for A Study of Efficacy and Safety of Intravenous Cefiderocol (S-649266) Versus Imipenem/Cilastatin in Complicated Urinary Tract Infections (APEKS-cUTI).

We appreciate the FDA’s positive assessment of the benefit-risk of cefiderocol for the initial New Drug Application submission for the cUTI indication and its balanced view on the CREDIBLE-CR study. The CREDIBLE-CR study provided
supporting evidence for the cefiderocol pathogen-focused indication approved by the European Medicines Agency in the European Union [6].

We hope this letter provides important context to the current indications for cefiderocol in the United States and will serve to eliminate potential confusion or misinterpretation in reading the FDA's well-described assessment of cefiderocol, which was based on the initial approval for cUTI.

Note

Potential conflicts of interest. Both authors are employees of Shionogi & Co., Ltd. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Pneumocystis jirovecii Pneumonia and Use of mTOR Inhibitors in Kidney Transplantation

To the Editor—We read with interest the study by Kaminski and colleagues [1] regarding Pneumocystis jirovecii pneumonia (PJP) in kidney transplant recipients. While universal prophylaxis given for 6–12 months post-transplant is highly effective, PJP may still occur after discontinuation of prophylaxis. The primary objective of the study by Kaminski et al was to identify risk factors for late-onset PJP. Their main conclusion is that chronic lymphopenia and use of corticosteroid boluses are independent risk factors for PJP and that these 2 criteria may be used to restart prophylaxis or extend its duration [1]. We commend the authors on undertaking this important study.

The study also found that the use of mechanistic target of rapamycin (mTOR) inhibitors (mTORi) was independently associated with PJP occurrence [1]. This association was relatively unexpected, given that the use of mTORi was not considered as a risk factor for PJP in international guidelines [2–4]. These guidelines were, however, based on limited evidence. According to a recent systematic review, 15 studies have assessed the relationship between mTORi and PJP in organ transplant recipients [5]. Unfortunately, the number of cases included in these studies was often too low to draw accurate conclusions. Of note, the only study with a larger number of cases than the study by Kaminski and colleagues is a retrospective cohort study of US Renal Data System data in which the use of mTORi was found to be independently associated with the development of PJP [6]. However, this study had major limitations including the method used to define PJP and incomplete reporting of important microbiological and therapeutic data. We believe that the data provided by Kaminski and coworkers are the best available to date regarding this research question.

Two important questions remain regarding the relationship between mTORi and PJP. First, mTORi may cause an interstitial pneumonitis easily confused with PJP [4, 7]. Even if all patients included by Kaminski and colleagues had detection of Pneumocystis in a respiratory specimen, some had a positive polymerase chain reaction (PCR) test only. Conversely, Pneumocystis PCR has low specificity for the diagnosis of PJP and, even if quantitative PCR is used, there is no consensual threshold to distinguish infection from carriage [8]. Therefore, we would be interested to know the percentage of patients who developed PJP while receiving mTORi and had microscopic detection of Pneumocystis [8]. For those without proven PJP (ie, those who had a positive PCR only), it would be interesting to know how many had resolution of PJP without cessation of mTORi.

The use of additional diagnostic assays, such as serum (1,3)-β-D-glucan, may help differentiating between PJP and mTORi-induced pneumonitis [9].

Second, we would be interested to know the authors' thoughts on the cost-effectiveness of universal PJP prophylaxis in transplant recipients receiving mTORi. Despite being a relatively rare infection, it is important to consider the significant mortality associated with PJP compared with the availability of cotrimoxazole, a very cheap, effective, and well-tolerated drug. In addition to preventing post-transplant PJP, the systematic use of PJP prophylaxis may simplify the management of interstitial pneumonitis in patients receiving mTORi.

Notes

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