Reply to Macesic et al

To the Editor—We thank Macesic and colleagues for their interest in our work. The additional data that they present in their letter adds to the growing body of knowledge regarding polymyxin resistance in multidrug-resistant gram-negative bacteria.

Carbapenem-resistant *Klebsiella pneumoniae* (CRKp)—or any pathogen that displays an antibiotic-resistant phenotype—can be recovered from a patient as a result of a variety of clinical circumstances. The most direct and intuitive way is that exposure to polymyxins will inevitably lead to resistance to polymyxins in a certain number of cases. This is highlighted by the experience summarized by Macesic and colleagues, in which about half of patients were treated with a polymyxin before the detection of polymyxin resistance in CRKp. This circumstantial link between polymyxin exposure and subsequent resistance was also shown in cases of colistin resistance in *Acinetobacter baumannii* [1]. We agree that for a certain proportion of patients in our study, this is likely the mechanism by which polymyxin resistance arose. We also agree that evaluation for a period of time beyond 14 days before the index culture would have uncovered more cases with colistin exposure. As we reported, we were able to collect such data in a small subset of patients. In these 27 patients, 6 (22%) were exposed to colistin. However, even assuming that all patients with documented polymyxin exposure are examples of de novo polymyxin resistance development, the data presented in the letter by Macesic et al and our data still leave between 51% and 78% of patients without documented exposure. Undoubtedly, limitations in electronic medical records and clinical research data collection may be at fault. Nonetheless, alternative mechanisms of spread of colistin resistance should be considered as well.

As importantly, polymyxin-resistant CRKp may be transmitted from one patient to another or from the environment to a

patient. A striking example of this mechanism is seen in China, where polymyxins have not been available for clinical use. However, agricultural application presumably resulted in a favorable environment for the dissemination of plasmid-borne *mcr-1*–mediated colistin resistance, which subsequently found its way into clinical isolates [2]. While we did not find any genetic evidence for *mcr-1*–mediated resistance. CRKp with chromosomally encoded polymyxin resistance may obviously also be transmitted from person to person. Furthermore, for several antibiotics, exposure to one antibiotic leads to increased resistance to another antibiotic [3].

Ongoing work in the Consortium on Resistance against Carbapenems in *Klebsiella pneumoniae* and other Enterobacteriaceae (CRACKLE) study will hopefully shed some light on the relative contributions of resistance developing within bacterial strains of antibiotic-exposed patients vs transmission of resistant strains from one patient to the next [4]. Data such as this and the data that is being generated by Macesic and colleagues will be crucial to stem not only the rise of polymyxin resistance but more importantly of resistance to more novel anti-CRKp agents as well.

Note

Potential conflicts of interest. Both authors: No reported conflicts. The 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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