Reply to Dr Hatipoglu et al and to Dr Mancini et al

To the Editor—We thank Dr Hatipoglu et al [1] for their interest in our study [2]. Nephrotoxic agents are among the few modifiable risk factors for acute kidney injury (AKI), and we agree on the potential incremental risk of renal toxicity associated to colistin and aminoglycosides in combination. Unfortunately, we failed to find a link between their concomitant

use and AKI, because only covariates that met the statistical criteria of a $P < .05$ at univariate analysis were retained in the multivariate model. This was not the case for aminoglycosides ($P = .05$). In our opinion, in patients who receive colistin it would be prudent to choose a different second agent, if possible.

Mortality was not among the study outcomes, and it was recorded only during intensive care unit stay. Six patients died, 3 of them with (and not due to) AKI.

We appreciate the comments by Dr Mancini et al [3], who address the relationship between colistin exposure and potential resistance selection. This is a very intriguing and multifaceted issue.

First, we would like to remark that our study aim was uniquely to investigate the renal toxicity of a pharmacokinetics-pharmacodynamics (PK/PD)-driven colistin dosing approach for critically ill patients [2, 4] and was not to assess colistin efficacy. Accordingly, it was not a "resistance study": because sequential samples for cultures were not routinely performed, and therapeutic drug monitoring was not available, the study was not aimed to relate colistin minimal inhibitory concentration (MIC) with individual drug exposure. Moreover, a colistin unexposed group was lacking and control for confounders in the spread of colistin resistance (eg, cross-transmission) was not allowed.

That said, we strongly agree on the potential risk of inducing colistin-resistance by our PK/PD-based dosing algorithm. We are aware that translating experimental targets of efficacy to clinical field would require an average colistin steady state concentration ($C_{ss,avg}$) exceeding our target of 2.5 mg/L and that by capping colistin dose at 9 million international units (MIU) and 12 MIU in normal and augmented renal clearance conditions [2], respectively, may result in modest bactericidal or even bacteriostatic effects for pathogens with an MIC near to the current colistin susceptibility breakpoint. However, these remain only theoretical concerns, because actual colistin C_{ss} in our patients was not measured. Moreover, the validity of these targets in the critically ill patient has not yet been proven, and the optimal colistin $C_{ss,avg}$ for clinical efficacy is currently unknown. Among the few clinical investigations assessing colistin dosing and efficacy a significant clinical benefit by using colistin at 9 MIU (approximately 270 mg colistin-base activity [CBA]) [5] or at 5 mg/kg/day CBA (approximately 11.5 MIU/day for a 70-kg patient) per day [6] has been found, and our dosing approach [2] resulted in very similar median daily doses. Whether higher doses could confer a greater clinical benefit is actually unknown. More importantly, we are aware of the wide mutant selection window (MSW) and of the high mutant prevention concentration found for colistin against multidrug-resistant (MDR) gram-negative pathogens in in vitro studies [7, 8]. In MDR *A. baumannii*, the MSW for colistin ranged from 1 mg/L to 128 mg/L, with concentration exceeding 128 mg/L preventing mutation in more than 90% of all isolates [7]. If confirmed in in vivo studies, these findings would mean that even very high colistin daily doses might still lie within the MSW and, consequently, might still be unable to overcome resistance selection. On the other side, a greater colistin intensity of exposure (5 mg/L vs 2 mg/L) has resulted in faster emergence of antibiotic-resistant subpopulations [8]. Of note, combination therapy at clinically achievable concentrations of 0.5 mg/L and 2 mg/L [4, 9] may enhance colistin bactericidal efficacy, narrow its MSW, and prevent the in vitro emergence of resistant strains [8, 9].

In line with the above considerations, recently the US Food and Drug Administration [10] and the European Medicines Agency [11] suggested to employ colistin in combination with other active agents at a maximum daily dose of 5 mg CBA/kg (approximately 350 mg CBA or 11.5 MIU for a 70-kg patient) [10] and of 9 MIU (approximately 300 mg CBA) [11], respectively, for creatinine clearance ≥80 mL/min.

We are still far from having certainty on the most appropriate use of colistin. However, according to current knowledge, a conservative dosing of colistin in combination with a second active or synergystic drug, as performed in our study [2], seems to provide the best balance of efficacy and resistance prevention. Undoubtedly, rigorous prevention of cross-transmission of resistant strains and early microbiological diagnosis to avoid inappropriate empiric use of colistin may substantially contribute to prolong the lifespan of colistin.

Notes

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