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EDITORIAL

# Pitfalls of defining combination therapy for carbapenem-resistant Enterobacteriaceae in observational studies

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Carbapenem-resistant Enterobacteriaceae (CRE) are now endemic in several countries [1]. Infections caused by these organisms are associated with high mortality, with the frequently multidrug-resistant phenotype of CRE being deemed as one of the major culprits [2, 3]. Indeed, clinicians have usually little choice but to use antibiotics with reduced activity; sometimes they do not have any active choice at all. Many clinicians, including ourselves, have therefore started to administer combinations of antimicrobials, mainly with the aim of taking advantage of possible additive or synergistic effects [2].

Several observational studies have been published in recent years that explore the impact of combinations on survival of CRE infections, with most suggesting favorable effects [3]. The recent interesting article of Papadimitriou-Olivgeris and colleagues is in line with these findings, indicating that administration of combinations might be favorably associated with survival in critically-ill patients with bloodstream infections due to CRE in intensive care units [4]. Nonetheless, despite both this and other studies were conducted with rigorous design and methods, their high heterogeneity remains a double-edged sword, which on the one hand enriches our knowledge about the use of combinations in different populations and settings, but on the other prevents us from obtaining a generalizable proof of any definitive advantage of combinations over monotherapy [4]. Notably, also systematic reviews are still somewhat inconclusive on this topic, since they suffer in part from the methodological limitations of the same studies they summarized. In this regard, an important bias already observed by Paul and colleagues is the presence of various definitions of combination therapy (e.g., any combination of drugs, at least one in-vitro active drug, at least two in-vitro active drugs) that might unpredictably confound the results [5]. Indeed, this does not only reflect a possible true difference across studies which is accounted for in a random-effect model, but also makes us greatly unsure of whether we are really observing the effect of an antibiotic combination, further increasing the already high risk of misclassification of intervention [6]. In other words, some effect sizes might erroneously reflect, in part or completely, the effect of monotherapies (an active drug plus an inactive drug), or of no active therapy at all (two inactive drugs). This might deviate our estimate of any possible favorable effect of combinations from its true value, or even completely change its direction. It is indeed plausible that inactive agents might sometimes increase only toxicity and not efficacy.

Certainly, a reasonable compromise in observational studies might be that of focusing only on the effect of *adequate* combinations, as we and others have done [2, 7], but experience have taught us that troubles come as we try to define *what* is adequate. For example, deeming as adequate only those combinations that include at least two in-vitro active agents (often the best among the feasible options) might seem a good compromise at first glance, but it raises other possible confounding factors. For example, antibiotic combinations might have a synergistic effect. In their systematic review and meta-analysis of in-vitro interactions between polymyxins and carbapenems, Zusman and colleagues observed that among carbapenem- and polymyxin-resistant Gram negatives, the rate of bactericidal activity increased from 14% (95% CI:

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7–27%) with monotherapy to 43% (95% CI: 21–68%) with combination therapy [8]. This implies that the presence of various degrees of synergism involving inactive agents might confound our definition of adequateness, in the sense that some "inadequate" combinations might well be "adequate" for some patients. In this regard, although it is true that in-vitro synergism might not always be predictive of in-vivo interactions and outcome, the existence of a clinical benefit by combining in-vitro inactive drugs for treating CRE infections has been suggested in case series, and deserves further investigation [9, 10] . We therefore think efforts should be made to include synergism information in future comparative studies, both for assessing possible differences of effect across subgroups and for adjusting comparisons between studies.

The second source of confusion is the frequently unknown percentage of achievement of therapeutic concentrations in vivo by some last-resort agents commonly used for treating CRE. Indeed, agents which prove adequate in vitro might sometimes be inadequate in vivo, or vice versa. The former case is well exemplified by colistin, whose serum concentrations can vary up to 10-fold irrespective of dose and renal function [11]. Consequently, full activity in vitro might not always guarantee therapeutic concentrations in vivo. The order of terms is inverted for carbapenems, but the potential for confusion remains the same. Indeed, despite being inactive in vitro by definition, meropenem might sometimes achieve therapeutic concentrations in vivo against CRE with minimum inhibitory concentration (MIC) up to 32–64 mg/l, when administered as a prolonged or continuous high-dose infusion [12, 13]. In summary, these examples create another important source of uncertainty in ascertaining whether (and to what extent) combinations are *adequate*. In support of this hypothesis, Pea and colleagues recently suggested that therapeutic drug monitoring (TDM) of meropenem might be a reasonable way for improving the outcome of infections due to CRE with meropenem MICs ≤64 mg/l [13]. Of course, as also observed for in-vitro synergism just above, the relationship between serum levels and clinical effectiveness is not straightforward, and PK/PD parameters might not always be predictive of outcome, as recently argued for colistin [14]. However, until we extensively include PK/PD information in observational studies, its true influence on the outcome of CRE infections (and thus on the definition of adequateness) will remain unknown.

In conclusion, randomized trials and other multinational studies (NCT01732250, NCT01597973, NCT01764490, and NCT02709408) are ongoing or have been recently completed that might ultimately shed light on the real impact of combination therapies for treating CRE and other multidrug-resistant Gram negatives. However, other similar threats might appear in the future. If they do, it would be important to concert our efforts to collect more information on in-vitro synergism and in-vivo PK/PD data from the very first observational experiences, for better classifying and summarizing early evidence pending randomized studies. We should not be unprepared.

**Compliance with ethical standards**

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