Challenges to Conducting a Clinical Trial of Combination Therapy of Colistin and Rifampicin for Extensively Drug-Resistant Acinetobacter baumannii

TO THE EDITOR—We commend Durante-Mangoni and colleagues [1] for conducting a study of examining the potential role of combination therapy of colistin and rifampicin for the treatment of serious infections due to extensively drug-resistant (XDR) Acinetobacter baumanii. Identifying treatments for XDR A. baumannii is an obvious high unmet medical need because of the increased mortality rates identified in critically ill patients and the dearth of antibiotics available to treat these patients.

Durante-Mangoni and colleagues [1] randomized 210 patients with life-threatening infections due to XDR A. baumannii at a 1:1 ratio to either colistin alone (2 MU every 8 hours) or colistin plus rifampicin (600 mg every 12 hours), both given intravenously. The treatment duration was left up to the investigator. The primary endpoint was overall 30-day mortality. Results indicated that the 30-day mortality was 43%, without difference between treatment arms ($P = .95$). The authors conclude that “[i]n serious XDR A. baumannii infections, 30-day mortality is not reduced by addition of rifampicin to colistin."

We believe that 3 confounding variables were not addressed a priori before the initiation of this head-to-head comparison of colistin versus colistin plus rifampicin. Because of these confounding variables, it is difficult to determine whether or not there is a true lack of difference between these 2 treatments.

First, the patient population enrolled and randomized was a very heterogeneous population. The population was inherently complex, as evidenced by the percentage of patients with a Charlson comorbidity index of $\geq 3$ (33% of all patients) and the severity of the underlying illness (mean Simplified Acute Physiology Score II, 39.9). It is unknown whether the combination therapy would be effective in a specific primary diagnosis or a homogenous population.

Second, the patients were not stratified by the additional antibiotics that are known to be effective for A. baumannii (eg, tigecycline and carbapenems [meropenem]). Although patients were infected with XDR A. baumannii (ie, resistance to tigecycline and carbapenems), in combination with colistin, these additional antibiotics may result in a synergistic effect [2]. The authors acknowledge that “Mero-penem was employed in the control arm more frequently than in the experimental arm (15.9% vs 3.9%), whereas the reverse occurred with tigecycline (4.9% in the control arm vs 10.9% in the experimental arm).” Although these differences were not statistically significant, post hoc analyses to evaluate the contribution of these antibiotics on 30-day mortality are necessary to see what impact, if any, they have on the primary end point of 30-day mortality. Furthermore, mortality differences are known to be increased with the use of tigecycline compared with comparator antibiotics, especially for the indication of ventilator-associated pneumonia, bloodstream infections, or hospital-acquired pneumonia. In patients with ventilator-associated pneumonia and baseline bacteremia, mortality was 50.0% (9 of 18 patients) for tigecycline [3]. Patients with these primary diagnoses made up 98.5% of all patients in the trial.

Third, therapeutic drug monitoring for colistin was not available. It is widely known that rifampicin causes drug-drug interactions. It causes drug-drug interactions with other concomitantly administered medications for diagnoses that were most likely the reasons for hospital admission in the first place. Consequently, drug-drug interactions with these medications may have affected the primary endpoint in this study—30-day mortality. Importantly, rifampicin mediates cytochrome P450 enzyme induction and the P-glycoprotein transport system, which may have altered drug clearance and consequently therapeutic treatment outcome of colistin or additional antimicrobial agents used in this study [4].

Despite these confounding variables in this study, XDR A. baumannii eradication from the primary source of infection was more frequently observed with the combination of colistin and rifampicin than with colistin alone, consistent with previous in vitro findings. There are other examples of antibiotics that show statistically significant differences in microbiological outcomes but not in clinical outcomes [5]. These examples reinforce findings indicating that microbiological outcomes do not always translate into clinical outcomes and that studies in a heterogeneous patient population may be difficult to interpret.

It is also important to note that just because the authors concluded that 30-day mortality did not differ between

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**References**


combination therapy with colistin and rifampicin and therapy with colistin alone, it does not mean that there is no utility for combination therapy. For example, the microbiological findings seen in this trial may support a study to examine whether a decreased dose of colistin both in amount and duration of therapy when combined with rifampicin compared to colistin used alone for XDR A. baumannii may yield different results. As another example, the microbiological findings also support a trial to study whether combination therapy with colistin and rifampicin may prevent relapses of XDR A. baumannii infections. Therefore, although no 30-day mortality differences were seen between the combination therapy with colistin and rifampicin and therapy with colistin alone, other studies examining potential utilities with combination colistin and rifampicin therapy may be clinically relevant.

In conclusion, we commend Durante-Mangoni and colleagues [1] for conducting a challenging study for a highly unmet need: treatment of serious and life-threatening infections caused by XDR A. baumannii. Although they saw no differences in 30-day mortality between combination therapy with colistin and rifampicin and therapy with colistin alone, additional studies are needed to evaluate whether there are other potential uses for combination therapy with colistin and rifampicin. Finally, we fully support the authors’ statement that “As the clinical development of novel antimicrobial agents progresses slowly, any effort should be made to optimize the use of already available drugs. This should only be pursued, however, through adequately powered, randomized clinical trials.”

Note

Potential conflicts of interest. All authors: No reported conflicts.

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