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Hot Topic

Post-MERINO trial: Any role for piperacillin-tazobactam in treating bloodstream infections caused by extended-spectrum beta-lactamase producing Enterobacteriaceae?

The long-awaited MERINO trial results were published recently by Harris et al. [1]. This multi-national, multi-centre, non-inferiority randomized clinical trial (RCT) found that the 30-day mortality rate for patients with ceftriaxone-resistant *Escherichia coli* or *Klebsiella pneumoniae* bloodstream infections (BSI) treated with piperacillin-tazobactam (PTZ) was 12.3%, compared with 3.7% for patients who received meropenem as definitive therapy. The difference in the 30-day mortality rate exceeded the non-inferiority margin of 5%. To that end, the authors recommended against the use of PTZ as a carbapenem-sparing option to treat ceftriaxone-resistant *E. coli* or *K. pneumoniae* BSI [1].

Interestingly, selection of the appropriate antibiotic is essential to improve patient outcomes, stem antibiotic overuse, and reduce the emergence of microbial resistance. Until the results of the MERINO trial, treatment of ceftriaxone-resistant *E. coli* or *K. pneumoniae* was considered contestable. Carbapenems have shown excellent activity against these infections; however, a recent meta-analysis compiling 25 observational studies showed non-inferiority of PTZ compared with carbapenems [2]. Although observational studies are prone to biases, the generalizability of the RCT results might be limited due to issues of external validity, such as differences in the pharmacokinetics of antibiotics between the MERINO participants and the North American population that was under-represented in the trial.

Designing and analysing non-inferiority trials relies mainly on the predefined non-inferiority margin, which represents the largest clinically acceptable difference between the test medication and the active comparator [3]. However, it is often highly challenging to define the non-inferiority margin, which is essential in the design of non-inferiority trials [3]. The prespecified non-inferiority margin in the MERINO trial was predefined by the MERINO Protocol Development Committee as -5%, which is considerably narrower than the TANGO I trial non-inferiority margin of -15% [4]. Consequently, it was difficult to prove the non-inferiority of PTZ compared with carbapenems for treatment of ceftriaxone-resistant *E. coli* or *K. pneumoniae* BSI. Moreover, the MERINO trial was stopped prematurely after enrolment of a fraction of the planned sample size (340 patients were enrolled, planned sample size 454 patients), and that created complex challenges to demonstrate non-inferiority [1].

It is important to highlight that the trial lacked a plausible explanation for the difference in all-cause mortality at 30 days between the PTZ and carbapenem arms. All deaths in the MERINO trial were unrelated to infections, but were due to malignancies or other comorbidities. Consequently, this created noise due to non-infection-related deaths because of the choice of all-cause mortality as the primary outcome rather than other clinical outcomes [1]. Besides, it is known that the appropriate antimicrobial treatment during the first 48 h is a crucial prognostic factor for improved outcome in patients with BSI [5]. However, randomization in the MERINO trial occurred after the 48-h window of empiric therapy, and 40.7% of enrolled patients had resolved objective markers of infection at the time of enrolment. By day 4 of randomization, there was no significant difference in clinical and microbiological resolution between the two groups [1]. Although the median treatment duration was 7 days, the difference in mortality continued to increase beyond the 2 weeks following randomization [1].

A subgroup analysis of the MERINO trial showed lower risk associated with PTZ in patients with a urinary tract source, low Pitt scores or without evidence of immunocompromise, but the trial was not powered to demonstrate non-inferiority in these subgroups [1]. Therefore, larger studies comparing PTZ with carbapenems in this patient population are warranted.

Moreover, in the setting of wide use of advanced rapid molecular diagnostics, correlation between resistance gene type and outcome is missing from the MERINO results. Inoculum effects with PTZ occur in SHV and/or AmpC β-lactamases, potentially leading to worse outcomes compared with carbapenems [2,6]. On the other hand, PTZ is a weak inducer of bla_{AmpC}, and its clinical effectiveness for treatment of AmpC β-lactamase-producing Gram-negative bacteria remains poorly understood [2]. The geographical differences in resistance rates would also have affected the endpoint results, as bla_{SHV}-producing Enterobacteriaceae have been widespread in many of the countries where the MERINO trial was conducted, including Turkey which accounted for eight of the 23 deaths (35%) in the PTZ arm [1]. Harris et al. also highlighted the frequent presence of narrow-spectrum oxacillinases (e.g. bla_{OXA-1}), seen in 67.6% of the strains, as a possible explanation for the decreased effectiveness of PTZ [1].

Furthermore, previous observational studies and a meta-analysis showed lower mortality rates when the minimum inhibitory concentration (MIC) of PTZ was $\leq$0.5/4 μg/L [2]. However, only a fraction of patients enrolled in the PTZ group had isolates available for PTZ MIC testing to evaluate the correlation of

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clinical outcomes and PTZ MIC. Similarly, the MERINO trial did not study the extended infusion of antibiotics and impact on mortality [1]. Additionally, a substantial proportion of patients randomized to the carbapenem arm received PTZ or other antibiotics and vice versa. It would be interesting to exclude the 'contamination' of antibiotic exposure between the two groups, and run a subgroup analysis comparing the patients who received PTZ as empiric and postrandomization treatment with the patients who were treated with carbapenems as empiric and postrandomization treatment [1].

Finally, a major concern of the results of this trial might be the overprescription of carbapenems at a time when carbapenem-sparing antibiotics remain a pressing need. It is important to note that the MERINO trial showed that subsequent detection of carbapenem-resistant bacteria recorded up to 30 days after enrolment was infrequent, and was not significantly lower in patients who received PTZ (3.2% vs 2.1%) [1]. However, studies found a correlation between the use of carbapenems and increasing incidence of carbapenem resistance in Gram-negative bacteria [7]. Accordingly, incentives to re-evaluate and/or discover carbapenem-sparing antimicrobial agents to treat ceftriaxone-resistant Enterobacteriaceae are urgently needed to limit the global use of carbapenems and reduce carbapenem resistance [8]. In conclusion, awaiting the subgroup analyses of the influence of different resistance genes, carbapenems should be considered as first-line treatment for ceftriaxone-resistant *E. coli* or *K. pneumoniae* BSI, especially in patients with multiple comorbidities, septic shock or poor source control. However, one could consider PTZ as a carbapenem-sparing alternative for treatment of ceftriaxone-resistant *E. coli* or *K. pneumoniae* BSI in other circumstances.

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Competing interests

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Ethical approval

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