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O1121 The MERINO Trial: piperacillin-tazobactam versus meropenem for the definitive treatment of bloodstream infections caused by third-generation cephalosporin non-susceptible Escherichia coli or Klebsiella spp.: an international multi-centre open-label non-inferiority randomised controlled trial

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Background: *Escherichia coli* or *Klebsiella pneumoniae* may express extended-spectrum β-lactamases (ESBLs) mediating resistance to third-generation cephalosporins (3GCs). Whether piperacillin-tazobactam is effective carbapenem-sparing therapy for bloodstream infection (BSI) caused by these organisms is uncertain. We aimed to test this concept in a randomised controlled trial (RCT) (ACTRN12615000403538; NCT02176122).

Methods: We enrolled adult patients from 32 sites in 9 countries with BSI caused by 3GC non-susceptible, piperacillin-tazobactam susceptible, *E. coli* or *K. pneumoniae*. Participants were randomized within 72 hours of initial blood culture collection 1:1 to piperacillin-tazobactam 4.5g 6-hourly or meropenem 1g 8-hourly for a minimum of 4 days. Treating clinicians were not blinded to treatment allocation. The primary outcome was all-cause mortality at 30 days post-randomisation. Secondary outcomes included days to clinical and microbiological resolution, clinical and microbiological success at day 4, relapsed BSI and secondary infection with a piperacillin-tazobactam or meropenem-resistant organism or *Clostridium difficile*. Our hypothesis was that definitive therapy with piperacillin-tazobactam was non-inferior to meropenem, using a margin of 5% for the primary outcome.

Results: Between February 2014 and July 2017, 391 patients were enrolled, from 1,646 screened. Of these 379 were randomized appropriately, received at least one dose of study drug and were included in the modified intention to treat (mITT) population (piperacillin-tazobactam=188, meropenem=191). One patient was lost to follow-up. The majority of patients were enrolled in Singapore (40.6%), Australia (22.4%) and Turkey (12.1%). BSIs were most frequently healthcare-associated (56.4%), of urinary tract origin (60.9%) and caused by *E. coli* (86.5%). A total of 23/187 (12.3%) patients randomized to piperacillin-tazobactam met the primary outcome of mortality at 30 days, compared with 7/191 (3.7%) randomized to meropenem (risk difference 8.6%, 95% CI 3.4% to 14.5%; RR 3.4, 95% CI 1.5 to 7.6; p=0.002). Effects were consistent in an analysis of the per-protocol population. There were no significant differences in subsequent infection with carbapenem resistant gram-negative organisms or *C. difficile* between treatment arms.

Conclusions: The use of piperacillin-tazobactam as definitive therapy for BSI caused by *E. coli* or *K. pneumoniae* with non-susceptibility to 3GCs was inferior to meropenem and should be avoided in this context.