

LETTER

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Comparison between meropenem and ceftolozane/tazobactam: possible influence of CRRT

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In their recent study [1], Timsit et al. conclude that mortality risk with ventilator hospital-acquired bacterial pneumonia (vHABP) was over twice as high when treated with meropenem compared to ceftolozane/tazobactam (C/T). However, the percentage of patients in the database with vHABP who had a creatinine clearance (CrCl) between 15 and 30 ml/min was 12% in both groups [1]. Of these, around 40% had a sequential organ failure assessment (SOFA) score > 7 with vasopressor use in more than 50% in both groups. Consequently, it is reasonable to assume that most of these patients were undergoing renal replacement therapy (RRT), most likely continuous RRT (CRRT) though this was not reported [1]. While a dose of C/T of 3 gr (2 g ceftolozane and 1 g tazobactam) three times a day will surely be above the minimal inhibitory concentration (MIC) most of the time even on CRRT [2], this is not the case for meropenem 1 gr three times a day, as in a number of cases this dose will fall below the MIC when undergoing CRRT [1]. Kothekar et al. concluded that in septic shock patients, extended infusions (EI) of 1000 mg of meropenem over 3 h, administered every 8 h,

provided adequate coverage against sensitive strains of Enterobacteriaceae, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* [3]. However, this dosing regimen failed to achieve a fraction of time (fT) > 4 µg/mL > 40 for activity against more resistant strains of these organisms in more than one-third of patients [3]. A bolus of 500 mg followed by EI of 1500 mg every 8 h was predicted to achieve this target in all patients [3]. If drug dose adaptation was not adhered to in CRRT patients and continuous infusion (CI) not used in cases of pathogens with a MIC ≥ 4, as recommended [4] some patients may have been underdosed, even with 1 g every 8 h [3, 4], as meropenem is significantly eliminated by CRRT [4]. In addition, in the same study adjunctive therapy with amikacin 15 mg/kg was permitted for the first 72 h of study treatment where ≥ 15% of *Pseudomonas aeruginosa* were known to be meropenem resistant [1]. Under CRRT, the recommended dose of amikacin to avoid failure is 25 mg/kg [5]. In conclusion, underdosing of antibiotics in patients undergoing CRRT may go some way to explaining the findings reported by Timsit et al.

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Authors Response

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Dear Editor,

We appreciate the letter from Honore et al. expressing concern about the potential for underdosing meropenem in participants who may have received renal replacement therapy (RRT) in our study [1]. Honore et al. assumed that because 40% of participants in our subgroup analysis had sequential organ failure assessment scores > 7 and ≈50% received concomitant vasopressors, most would have undergone continuous RRT (CRRT). However, this was not the case.

Per the study protocol, any requirement for peritoneal dialysis or hemodialysis or hemofiltration were exclusion criteria and RRT was not permitted during study treatment. Any participant who developed creatinine clearance (CrCl) < 15 mL/min or was placed on RRT was required to be withdrawn from randomized study treatment and switched to standard-of-care antibacterial therapy, because optimal dosing recommendations for participants with renal impairment receiving RRT had not been determined for ceftolozane/tazobactam or meropenem at the time the study was conducted. The current meropenem label still lacks dosing recommendations for patients undergoing RRT [6]. We agree with Honore et al. that inclusion of participants receiving RRT in the meropenem arm would have been of concern.

Recently, several studies have been conducted to determine optimal dosing of ceftolozane/tazobactam in adults with hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia (HABP/VABP) and renal impairment or augmented renal clearance (ARC). The results suggest that the following ceftolozane/tazobactam doses, administered every 8 h according to renal function, are recommended for adults with HABP/VABP [7–9]: CrCl > 50 mL/min (including critically ill patients with ARC): 3 g; CrCl 30 to ≤ 50 mL/min: 1.5 g; CrCl 15

to < 30 mL/min: 750 mg; and end-stage renal disease on hemodialysis: single loading dose of 2.25 g, followed by 450 mg every 8 h.

Importantly, among the ventilated HABP (vHABP) subgroup, only 1 of the 108 participants in the meropenem arm underwent RRT, including CRRT, while on study treatment (i.e., a protocol deviation). Thus, the influence of RRT on the analysis and interpretation of results reported for participants with vHABP treated with meropenem was exceedingly small. None of the 99 participants with vHABP in the ceftolozane/tazobactam treatment arm received RRT while on treatment.

In conclusion, RRT was not permitted during study treatment, and only 1 participant in the vHABP subgroup deviated from the protocol and received CRRT during study treatment. Therefore, underdosing of meropenem in the setting of RRT did not appreciably affect the findings of our recently published analysis of participants with vHABP [1].

Abbreviations

vHABP: Ventilator hospital-acquired bacterial pneumonia; C/T: Ceftolozane/tazobactam; CLCr: Creatinine clearance; SOFA: Sequential organ failure assessment; RRT: Renal replacement therapy; Continuous RRT: Continuous renal replacement therapy; MIC: Minimal inhibitory concentration; EI: Extended infusions; FT: Fraction of time; CI: Continuous infusion.

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PMH, SM, SR, WB, and DDB designed the paper. All authors participated in drafting and reviewing. All authors read and approved the final version of the manuscript.

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Competing interests

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