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Letter to the Editor

Re: "Comparison of antipseudomonal betalactams for febrile neutropenia empiric therapy: systematic review and network metaanalysis" by Horita et al.

Dear Sir,

We read with interest the recent network meta-analysis published by Horita et al. comparing different β-lactams in the empirical treatment of febrile neutropenia (FN) [1]. We consider that the authors draw debatable conclusions that could encourage unjustifiably wide use of imipenem/cilastatin in individuals with FN. Another meta-analysis, published in 2010 [2] on the same issue, drew different conclusions, showing lower all-cause mortality with piperacillin/tazobactam versus cefepime or carbapenems. Several reasons can explain these different findings. Most obviously, some studies included by Horita et al., simply post-dated Paul et al.; but, perhaps more importantly, the newly available studies included by Horita et al. are often from high-resistance countries and often analysed piperacillin/tazobactam, whereas much of the imipenem/cilastatin data come from relatively old studies. As resistance varies with place and time, these factors have major potential impact.

Overall, 15 studies representing 4026 patients and comparing piperacillin/tazobactam with other antibiotics were included in Horita et al.'s meta-analysis, but not in that of Paul et al.; ten of these were published since 2010, variously originating from Turkey, India, Japan, China and Spain. A recent multinational study of bacteraemia in individuals undergoing haematopoietic stem cell transplants found significantly higher rates of resistance to non-carbapenem β-lactams among Gram-negative rods (GNRs) isolated from patients in southeast Europe (55.3%) or China (76%) versus those in northwest Europe (27.6%) [3]. In this study, 33.9%, 56.5% and 52.0% of GNR reported from Spain, Turkey and China, respectively, were resistant to non-carbapenem anti-*Pseudomonas* penicillin β-lactamase inhibitors. In an Indian study, fully 82.7% of *Escherichia coli* and 74.3% of *Klebsiella* spp. isolated from individuals with cancer were extended spectrum β-lactamase producers [4]. One would expect to see an advantage for imipenem/cilastatin over other β-lactams at sites with such high rates of resistance, where empirical treatment with piperacillin/tazobactam may be insufficient. Basing the approach to FN on local epidemiology is crucial. In our recent study in haematopoietic stem cell transplant patients, a half of GNR were resistant to non-carbapenem β-lactams [3]; however, the rates in individual countries ranged from 0% to 100%.

Underpinning the high rates of resistance among GNRs in some parts of the world are changes in the global molecular epidemiology, mainly since 2000, notably including the proliferation of *Escherichia coli* ST131 and the common co-presence of CTX-M-15 (an extended spectrum β-lactamase) with OXA-1/30 (a sulphone/clavam-resistant penicillinase) enzymes in this and other *Enterobacteriaceae*. In some European regions, over 50% of bloodstream *E. coli* isolates were reported to be resistant to third-generation cephalosporins in the 2016 WHO Antimicrobial Resistance report (http://www.euro.who.int/__data/assets/pdf_file/0005/354434/WHO_CAESAR_AnnualReport_2017.pdf?ua=1). Piperacillin/tazobactam may be less effective in this situation and most (19/23) of these studies assessing piperacillin/tazobactam in Horita et al.'s meta-analysis were published after 2000.

Ten studies included in Horita et al.'s meta-analysis compared imipenem/cilastatin to other antibiotics; these included 2156 patients. Seven of these studies (1496 patients, 70%) were published between 1990 and 2004, before the global spread of carbapenem-resistant *Enterobacteriaceae*. Several countries have, largely since 2007, seen proliferation of carbapenemases, though the predominant types (KPC, OXA-48, VIM, NDM or IMP) vary with the particular country.

Thirteen of the 50 studies selected by Horita et al. were published between 1990 and 2000. Significant changes occurred in bacterial resistance since 90s to present day. This is a common problem of network meta-analysis on antibacterials, where efficacy may change with time and place. In simple language, this means that one must be very wary of statistical comparison of agents that were not compared head-to-head in the same time and place. In the present case, mortality data on imipenem, based on studies mainly published before the emergence of carbapenem-resistance, are compared with mortality data on piperacillin/tazobactam based on more recent studies, mainly from countries with high rates of extended spectrum β-lactamase infections.

Another concern is the dosing regimens of β-lactams, which was not considered in Horita et al.'s meta-analysis. Individuals with FN have an increased volume of distribution and increased clearance, resulting in a decreased time above MIC. Therefore, using a maximal dosage is crucial. In the studies selected by Horita et al., piperacillin/tazobactam was dosed at 4.5 g thrice daily in 6/23 studies and 24% of the patients, and meropenem was dosed at ≤2 g/day (in adults) in 2/14 studies and 24% of the patients. These regimens, which were not enhanced by prolonged/continuous infusion, may be insufficient.

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The authors' conclusion that 'Among guideline-recommend medications, imipenem/cilastatin was related to the highest treatment success rate and the lowest all-cause death' may encourage preferential use of imipenem/cilastatin as the primary choice for any FN. However, no significant differences were reported according to the primary end point (treatment success without modification) between cefepime, meropenem, imipenem/cilastatin and piperacillin/tazobactam, nor for a secondary end point (all-cause death) between meropenem, imipenem/cilastatin, ceftazidime and piperacillin/tazobactam. Moreover, there are no significant differences in the spectrum of coverage between meropenem and imipenem/cilastatin.

In conclusion, the ECIL group wishes to reiterate its previous position that, although we have no doubt as to the efficacy and safety profile of imipenem/cilastatin in patients with FN, carbapenems should, whenever possible, be avoided in individuals without severe clinical presentation and risk factors for bacterial resistance to other agents, so as to preserve their activity [5]. The wide range of resistance rates among GNRs in different countries warrants a customized approach in patients with FN, combined with rigorous infection control in settings where resistance has become or is becoming prevalent. Universal deployment of carbapenems without de-escalation in all individuals with FN, half of whom have neither clinical nor microbiological infection, is only likely to lead to an increase in carbapenem-resistant infections, and should be discouraged.

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References

[1] Horita N, Shibata Y, Watanabe H, Namkoong H, Kaneko T. Comparison of anti-pseudomonal β-lactams for febrile neutropenia empiric therapy: systematic review and network meta-analysis. Clin Microbiol Infect 2017;23:723–9.
[2] Paul M, Yahav D, Bivas A, Fraser A, Leibovici L. Anti-pseudomonal β-lactams for the initial, empirical, treatment of febrile neutropenia: comparison of β-lactams. Cochrane Database Syst Rev 2010:CD005197.
[3] Averbuch D, Tridello G, Hoek J, Mikulska M, Akan H, Yanez San Segundo L, et al. Antimicrobial resistance in gram-negative rods causing bacteremia in haematopoietic stem cell transplant patients: intercontinental prospective study of Infectious Diseases Working Party of the European Bone Marrow Transplantation group. Clin Infect Dis 2017;65:1819–28.
[4] Abdul K, Vidyalakshmi P, Jayalakshmi V, Poojary I. Susceptibility profile of gram-negative bacteremic isolates to β lactam-β lactamase inhibitor agents in comparison to other antibiotics. Indian J Cancer 2014;51:450–2.
[5] Averbuch D, Orasch C, Cordonnier C, Livermore DM, Mikulska M, Viscoli C, et al. European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: summary of the 2011 4th European Conference on Infections in Leukemia. Haematologica 2013;98:1826–35.

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