Comment on: Best in class: a good principle for antibiotic usage to limit resistance development?

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Sir,

We wish to comment on the article by Amyes \textit{et al.},\textsuperscript{1} in which we are referenced\textsuperscript{2} as stating that ‘the concept that ertapenem is unlikely to increase resistance in non-fermenters is flawed’. We in fact did not state this and, on the contrary, we agree with the conclusions of Livermore \textit{et al.}\textsuperscript{3} that selection (of carbapenem-resistant \textit{Pseudomonas aeruginosa} in particular) is unlikely under physiologically relevant ertapenem concentrations.

In this regard, the following points are critical. First, the BSAC/EUCAST ertapenem breakpoint for susceptibility is ≤0.5 mg/L and for resistance is >2 mg/L. The former value is far below the MICs for most \textit{P. aeruginosa} strains, which range between 2 and 32 mg/L with MIC\textsubscript{50} and MIC\textsubscript{90} values of 4–8 and ≥16 mg/L, respectively.\textsuperscript{4} Secondly, the free ertapenem plasma concentration is less than the MIC\textsubscript{90} by 4 h post-dose.\textsuperscript{5} In critically ill patients, the protein-unbound plasma concentration after a single intravenous administration of 1 g has been documented to be 0.87 ± 0.76 mg/L 12 h after infusion and 0.24 ± 0.43 mg/L 24 h after infusion.\textsuperscript{6} In other words, relevant ertapenem concentrations are below those likely to be active against \textit{Pseudomonas} (let alone \textit{Acinetobacter}), implying that selection pressure for specific resistance is minimal. Thirdly, the OASIS (Optimizing Abdominal Surgery with Invanz Study) studies indicated no significant colonization by \textit{P. aeruginosa}, either with imipenem-resistant or imipenem-susceptible strains, during ertapenem therapy.\textsuperscript{6}

We acknowledge that under laboratory conditions with high drug concentrations, it is possible to select for imipenem-resistant \textit{P. aeruginosa} with ertapenem, but the clinical relevance seems doubtful, because in the clinical scenario adequate concentrations are not maintained for a sufficiently long duration.

It seems relevant to ask whether, using similar logic, the authors of this article would restrict the use of cefotaxime and ceftriaxone in that they might undermine ceftazidime against \textit{P. aeruginosa}, or similarly levofloxacin with regard to ciprofloxacin?

We would still recommend that ertapenem be used as the preferred therapy for infections due to extended-spectrum β-lactamase producers and, in certain specific settings as outlined in our article, for intra-abdominal sepsis, pneumonia and skin and soft tissue (including diabetic foot) infections.

Transparency declarations

A. J. B. is on the advisory board for Merck. C. F. and G. A. R. are on the advisory board for Merck and speakers bureau for Astra Zeneca.

References


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Best in class: a good principle for antibiotic usage to limit resistance development?—author’s response

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Sir,

The point that we were emphasizing in our Leading article was that the use of weaker drugs may select for bacteria resistant to stronger members of the same class.\textsuperscript{1} In their comment, Brink \textit{et al.}\textsuperscript{2} identify that the clinical use of ertapenem is likely to deliver concentrations below the MIC of ertapenem for...