Proposed disc zone breakpoints for doripenem for use with the BSAC disc susceptibility testing method

Russell Hope*, Teresa Pllana, Marina Warner and David M. Livermore

Antibiotic Resistance Monitoring and Reference Laboratory, Centre for Infections, Health Protection Agency, 61 Colindale Avenue, London NW9 5HT, UK

*Corresponding author. Tel: +44-20-8327-6493; Fax: +44-20-8327-6264; E-mail: russell.hope@hpa.org.uk

Keywords: MICs, carbapenems, EUCAST

Sir,

Doripenem is a new carbapenem, recently licensed in the European Union for treatment of nosocomial pneumonia (including ventilator-associated pneumonia), complicated intra-abdominal infections and complicated urinary tract infections. A 10 µg doripenem disc has been proposed for routine susceptibility testing. We determined provisional zone breakpoints corresponding to European Committee on Antimicrobial Susceptibility Testing (EUCAST) MIC breakpoints for these 10 µg doripenem discs in the BSAC disc method.

Isolates (n=810) were selected from the BSAC Bacteraemia Resistance Surveillance Project (2005–06), supplemented with additional, more-resistant, isolates from other survey collections and reference submissions held by the UK HPA’s Antibiotic Resistance Monitoring and Reference Laboratory. Care was taken, whenever possible, to select isolates for which the MICs corresponded with or were within one or two dilutions of the breakpoints. Zones and agar dilution MICs were determined by the BSAC methods. Results were reviewed against EUCAST/European Medicines Agency (EMEA) MIC breakpoints, as also adopted by the BSAC methods. Results were reviewed against EUCAST/European Medicines Agency (EMEA) MIC breakpoints, as also adopted by the BSAC, of: susceptible, ≤1 mg/L and resistant, >1 mg/L for streptococci; and susceptible, ≤1 mg/L and resistant, >4 mg/L for staphylococci, enterococci, Enterobacteriaceae, Acinetobacter spp. and Pseudomonas spp. Error minimization was used to optimize the values.

Zone breakpoints corresponding to these MIC breakpoints were as follows:

(i) Enterobacteriaceae (n=237): susceptible, ≥24 mm; and resistant, ≤18 mm (Figure 1).
(ii) Acinetobacter (n=61): susceptible, ≥24 mm; and resistant, ≤17 mm (Figure 1).
(iii) Pseudomonas (n=63): susceptible, ≥32 mm; and resistant, ≤24 mm (Figure 1).

Figure 1. Scatter diagram showing the correlation between zones of inhibition caused by the 10 µg doripenem disc and doripenem MICs for Gram-negative organisms.
(iv) α- and β-Haemolytic streptococci and Streptococcus pneumoniae \( (n = 167) \): susceptible, \( \geq 23 \) mm; and resistant, \( \leq 22 \) mm. A caveat is that these breakpoints were determined by extrapolation from highly susceptible populations, and their robustness cannot be fully evaluated until streptococci with doripenem MICs of \( \geq 1 \) mg/L emerge (Figure 2).

(v) Staphylococcus aureus and coagulase-negative staphylococci \( (n = 200) \): susceptible, \( \geq 32 \) mm; and resistant, \( \leq 27 \) mm. However, non-susceptibility to doripenem was best inferred from methicillin resistance (Figure 2).

(vi) Enterococcus spp. \( (n = 82) \): susceptible, \( \geq 22 \) mm; and resistant, \( \leq 18 \) mm (Figure 2).

Using the above breakpoints there was only one major error (a susceptible isolate reported as resistant) and one very major error (a resistant isolate reported as susceptible) among all 810 organisms tested. These comprised a meca-positive coagulase-negative Staphylococcus and an Enterococcus durans for which doripenem MICs were 1 and 16 mg/L, respectively. There were 38 minor errors, half of which \( (n = 19) \) concerned staphylococci, which would not be routinely tested with doripenem.

The 10 μg doripenem discs effectively differentiated between susceptible, intermediate and resistant for most bacterial groups. As with all antibiotics, MIC determinations (for example by Etest) should be performed on isolates with zones close to the susceptible breakpoint if the drug is intended for clinical use.

Acknowledgements
The majority of isolates for this work were provided by the BSAC Resistance Surveillance Project.

Funding
This work was supported by Johnson & Johnson.

Transparency declarations
D. M. L. has shareholdings, or acts as enduring attorney for a shareholder, in AstraZeneca, Dechra, EcoAnimal Health, GlaxoSmithKline, Schering-Plough and Pfizer, and he has had research contracts or conference finance in the past 3 years from AstraZeneca, Calixa, Cerexa, Johnson & Johnson, Merck, Novartis, Novexel, Pfizer, Phico, Theravance and Wyeth. All authors are employed by the HPA and are influenced by their views on antibiotic usage.

References