

EUCAST Technical Note on daptomycin

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) Steering Committee*

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INTRODUCTION

Daptomycin is a lipopeptide antimicrobial agent, first described in the early 1980s, but not developed for clinical use until more recently in response to increased resistance to other agents. Daptomycin was registered by the European Medicines Agency (EMA) in November 2005 for skin and soft-tissue infections caused by *Staphylococcus* spp. and *Streptococcus* spp., with the exception of *Streptococcus pneumoniae*. This technical note is based on the daptomycin rationale document (available on the EUCAST website, <http://www.eucast.org>). The rationale document includes more details, as well as published references related to the selection of EUCAST breakpoints.

DOSAGE

EUCAST has determined clinical breakpoints for the parenteral use of daptomycin 250 mg × 1. Daptomycin has not been licensed previously in Europe, so there is no history of differences in dosage among different European countries.

MIC DISTRIBUTIONS

The daptomycin MICs for wild-type staphylococci and streptococci are ≤ 1 mg/L. The epidemiological cut-off value was set at 1 mg/L for staphylococci, at 0.25, 0.5 and 1 mg/L for streptococci, depending on the species, and at 4 mg/L for both *Enterococcus faecalis* and *Enterococcus faecium* (see <http://www.eucast.org>).

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ESTABLISHED BREAKPOINTS

None of the European breakpoint committees recommended breakpoints for daptomycin before the establishment of the EUCAST breakpoint.

PHARMACOKINETIC DATA

Based on a standard once-daily parenteral dose of 4 mg/kg/day, the pharmacokinetic data used to evaluate daptomycin are shown in Table 1.

PHARMACODYNAMIC DATA

The pharmacodynamic data are summarised in Table 2. There is considerable variation in the pharmacodynamic target (AUC/MIC) required for antibacterial effect in different studies. The total drug AUC/MIC for bacteriostatic effect against *Staphylococcus aureus* is 438 ± 67 (range 120–537). If a two-log reduction in bacterial count after 24 h dosing is chosen as the antibacterial effect endpoint, the AUC/MIC target increases more than two-fold. This higher target may be more appropriate for inpatient intravenous therapy; hence, the target selected is favourable to the drug.

Monte Carlo simulation was performed based on the parameter values listed in Table 1 since

Table 1. Pharmacokinetic data for daptomycin

Parameter	Data
Dosage	4 mg/kg/day (250 mg × 1) IV
C _{max} (mg/L)	57
C _{min} (mg/L)	Not defined
Total body clearance (L/h), mean (range)	0.86 (0.41–2.19)
T _{1/2} (h), mean (range)	8.3 (4.64–48.01)
AUC _{24 h} (mg.h/L), mean (range)	400.8 (160.6–1143.7)
Fraction unbound (%)	8–10
Volume of distribution (L)	9.7 (5.1–32.8)

IV, intravenous.

Table 2. Pharmacodynamic data for daptomycin

Pharmacodynamic parameter	Staphylococci	Streptococci
AUC/MIC for stasis	250–550	75–237
AUC/MIC for 2 log drop	800–4000	157–815

AUC distributions from neither volunteers nor patients were available. Using a mean target AUC/MIC of 438, a probability of target attainment of 100 is obtained for MICs of ≤ 0.5 mg/L (Table 3). A pharmacodynamic susceptible breakpoint of ≤ 0.5 mg/L is therefore most appropriate. If a lower AUC/MIC target for staphylococci and streptococci was used, as in some publications and in additional data supplied by the manufacturer, a susceptibility breakpoint of ≤ 1 mg/L would be appropriate.

CLINICAL EFFICACY

Clinical efficacy data for staphylococci and streptococci indicate eradication of the organisms in 80% of patients (similar to comparator treatments) and no difference in eradication rates for strains with different MICs ≤ 0.5 mg/L. No data are available for strains with MICs > 0.5 mg/L.

BREAKPOINTS

Breakpoints are summarised in Table 4.

Non-species-related breakpoints

Non-species-related breakpoints are generally determined on the basis of Pk/Pd data and are independent of MIC distributions of specific species. The non-species-related breakpoints are for use only with species for which specific breakpoints are not given. Pharmacodynamic data suggest a non-species-related breakpoint in the region of 0.5 or 1 mg/L for daptomycin, but as there is insufficient evidence related to infections other than those caused by staphylococci and streptococci, no non-species-specific breakpoint is given.

Table 3. Monte Carlo simulation of target attainment for daptomycin 4 mg/kg/day

Daptomycin MIC (mg/L)	Probability of target attainment with an AUC/MIC target of		
	373 (- one standard deviation)	438 (mean)	503 (+ one standard deviation)
≥ 4	0	0	0
2	0	0	0
1	96.8	77.2	42.9
0.5	100.0	100.0	100.0
≤ 0.25	100.0	100.0	100.0

Table 4. Summary of EUCAST clinical MIC breakpoints for daptomycin. Daptomycin – EUCAST clinical MIC breakpoints, 22 November 2005

Species-related breakpoints (S \leq / R $>$)	Species-related breakpoints ² (S \leq / R $>$)				Non-species related breakpoints ² (S \leq / R $>$)				
	Enterobacteriaceae	<i>Pseudomonas</i>	<i>Acinetobacter</i>	<i>Staphylococcus</i>	<i>Streptococcus</i> A,B,C,G	<i>Streptococcus pneumoniae</i>	<i>Haemophilus influenzae</i> <i>Moraxella catarrhalis</i>	<i>Neisseria gonorrhoeae</i> <i>Neisseria meningitidis</i>	Gram-negative anaerobes
Daptomycin	-	-	-	1/1 ¹	1/1 ¹	IE	-	-	IE

1. Strains with MIC values above the S/I breakpoints are rare or not yet reported. The identification and susceptibility tests for any such isolate must be repeated, and if the result is confirmed the isolate should be sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MICs above the current resistant breakpoint (in *italics*), the isolates should be reported as resistant.

2. Non-species-related breakpoints have been determined mainly on the basis of Pk/Pd data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint, and not for those species where susceptibility testing is not recommended (marked with - or IE in the table).

- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug. IE = There is insufficient evidence that the species in question is a good target for therapy with the drug.
Breakpoints finalised November 2005.

Species-related breakpoints

For *Staph. aureus*, coagulase-negative staphylococci and streptococci, the wild-type distributions of MICs range up to 1 mg/L. Hence a susceptible breakpoint of 1 mg/L would render wild-type *Staphylococcus* spp. and *Streptococcus* spp. susceptible to daptomycin, would be compatible with the pharmacodynamic and clinical data, and would not divide wild-type populations. Resistant isolates are rare, but MICs are reproducible for the few isolates of *Staph. aureus* with MICs ≥ 2 mg/L. Therefore the following breakpoints are suggested for staphylococci and streptococci:

Susceptible ≤ 1 mg/L

Intermediate -

Resistant > 1 mg/L

Isolates with MICs above the resistant breakpoint are rare. The identification and susceptibility tests on any such isolate must be repeated and, if the result is confirmed, the isolate should be sent to a reference laboratory. Until there is evidence regarding clinical response, such isolates should be reported as resistant.

Species without breakpoints

No breakpoint is given for enterococci, as true skin and soft-tissue infections with enterococci are rare and their presence may more likely reflect colonisation. There is insufficient clinical evidence to set a breakpoint for enterococci. There is also insufficient evidence to determine whether *Strep. pneumoniae* would be an appropriate target.

Daptomycin is not active against Enterobacteriaceae, *Pseudomonas* spp., *Acinetobacter* spp., *Haemophilus* spp., *Moraxella* spp., *Neisseria* spp. or anaerobic bacteria.

Additional comment

Daptomycin activity is markedly affected *in vitro* by the concentration of calcium ions, and there are unresolved questions concerning routine testing of susceptibility to daptomycin. At present, EUCAST recommends that the MIC must be determined to allow susceptibility categorisation.