

Daptomycin: Rationale for EUCAST Clinical Breakpoints

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Foreword

EUCAST

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) is organised by the European Society for Clinical Microbiology and Infectious Diseases (ESCMID), the European Centre for Disease Prevention and Control (ECDC), and the active national antimicrobial breakpoint committees in Europe.

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EUCAST rationale documents

EUCAST rationale documents summarise the information on which the EUCAST clinical breakpoints are based.

Availability of EUCAST documents

All EUCAST documents are freely available from the EUCAST website at <http://www.eucast.org>.

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This rationale document should be cited as: "European Committee on Antimicrobial Susceptibility Testing. Daptomycin Rationale Document, version 1.1, 2021. <http://www.eucast.org/rd>.

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 the increased resistance to current agents.

Daptomycin acts in a bactericidal manner through insertion into and subsequent depolarisation of the bacterial cell membrane, a unique mode of action. Cross-resistance between daptomycin and other antibiotic classes is not observed. Daptomycin is active in vitro against a range of Gram-positive pathogens, including both susceptible and multidrug-resistant staphylococci and enterococci. Two pivotal clinical studies comparing daptomycin 4 mg/kg per day intravenously with vancomycin or oxacillin-class antibiotics demonstrated the efficacy of daptomycin for treatment of cSSSIs. One pivotal study supported the use of daptomycin 6 mg/kg per day in bacteraemia and right-sided endocarditis caused by *S. aureus*.

Daptomycin therapy is registered for the treatment of complicated skin and soft tissue infections caused by *Staphylococcus aureus* and *Streptococcus pyogenes*, and right-sided endocarditis caused by *Staphylococcus aureus*. It is active against methicillin- and multi-drug resistant isolates of *S. aureus*. More recently, interest has developed in the use of daptomycin for the serious enterococcal infections, including endocarditis, especially caused by strains with resistant to vancomycin. In this case it has been recommended to increase the administered does of daptomycin ([https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X\(20\)30235-4/pdf](https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(20)30235-4/pdf)).

1. Dosages

	EMA Complicated SSTI	EMA Right-sided endocarditis
Available formulations	iv	iv
Most common dose	4 mg/kg once daily	6 mg/kg once daily
Maximum dose schedule	4 mg/kg once daily	6 mg/kg once daily

2. MIC distributions and epidemiological cut-off (ECOFF) values

MIC distributions and ECOFFs can be found at <https://mic.eucast.org/Eucast2/SearchController/search.jsp?action=init>

3. Breakpoints prior to harmonisation (mg/L)

Not applicable

4. Pharmacokinetics (PK)

Dosage	4 mg/kg/day	6 mg/kg/day	10 mg/kg/day	12 mg/kg/day
C _{max} (mg/L)	57	95.7	129.7	164.8
C _{min} (mg/L)	Not defined			
Total body clearance	0.86 (0.41-2.19) (L/h)	9.9 ml/h/kg	9.9 ml/h/kg	10.1 ml/h/kg
T _{1/2} (h), mean (range)	8.3 (4.64-48.01)	7.5	8.4	7.8
AUC ₀₋₂₄ (mg.h/L)	400.8 (160.6-1143.7)			
AUC _{0-∞} (mg.h/L)	–	729.8	1013.5	1269.2
Fraction unbound (%)	8-10	7-10	7-10	7-10
Volume of distribution	9.7 (5.1-32.8) L	0.105 L/kg	0.117 L/kg	0.111 L/kg
Comments	•			
References	<ol style="list-style-type: none"> 1. Woodworth J.R. et al. Antimicrob Agents Chemother 1992; 36: 318. 2. Dvorchick B. et al. Antimicrob Agents Chemother 2004; 48: 2799. 3. Louie A et al. Antimicrob Agents Chemother 2001; 45: 845. 4. Safdar N et al. Antimicrob Agents Chemother 2004; 48: 63. 5. Benvenuto et al., Antimicrob Agents Chemother 2006; 50:3245-9 			

5. Pharmacodynamics (PD)

Index	Murine Thigh Infection				
	<i>S. aureus</i> (n=1) ¹	<i>S. aureus</i> (n=4) ²	Van-R <i>E. faecium</i> (n=2) ²	<i>S. pneumoniae</i> (n=8)	
AUC/MIC for bacteriostasis	43.4	388 – 537 (mean = 438)	0.94 – 1.67	74.7 – 203 (mean = 160)	
AUC/MIC for 1-log ₁₀ reduction	–	588 – 750 (mean = 666)	4.1 – 33.8	108 – 467 (mean = 290)	
AUC/MIC for 2-log ₁₀ reduction	–	788 – 1460 (mean = 1061)	–	157 – 815 (mean = 498)	
Protein binding	91%	88 – 93%	88 – 93%	88 – 93%	
Index	Murine Thigh Infection				
	Meth-R <i>S. aureus</i> (n=2) ³	Van-S <i>E. faecalis</i> (n=1) ³	Van-R <i>E. faecium</i> (n=1) ³	<i>E. faecalis</i> (n=6) ⁴	<i>E. faecium</i> (n=12) ⁴
fAUC/MIC for bacteriostasis		13	5	Mean of 7.2	Mean of 0.85
fAUC/MIC for -log ₁₀ reduction		–	–	Not achieved	Mean of 12.9
Comments					
References	1) Louie et al., AAC 2001; 45:845-51 2) Safdar et al., AAC 2004; 48:63-8 3) Dandekar et al., 2003; 52:405-11 4) Kidd et al, AAC 2018; 62:e00506-18				

6. Monte Carlo simulations

There is considerable variation in the pharmacodynamic target AUC/MIC required for antibacterial effect in different studies and in different bacterial species.

Staphylococcus aureus

The pharmacodynamic target is taken from what is considered the best published data (reference 2, section 5). The total drug AUC/MIC required for a bacteriostatic effect against *S. aureus* is 438 ± 67 (range 120-537). If a 2-log drop is chosen, the target increases to 1061 ± 296 . This higher target may be more appropriate for patient iv therapy, hence again the target selected is favourable to the drug.

Monte Carlo simulation was performed using a virtual AUC distribution based on the mean, SD, maximum and minimum values as published (section 4). Using a mean target total AUC/MIC of 438, the probability of target attainment just misses a proposed target attainment of >80% for MICs of < 1mg/L, even using favourable PK data and a bacteriostatic AUC/MIC target (Table 1). A probability of target attainment of 100% is obtained for MICs of <0.5 mg/L and a pharmacodynamic breakpoint of S <0.5mg/L would therefore seem most appropriate from the data in reference 2, section 5. If a lower AUC/MIC target for staphylococci and streptococci were used, as in some publications and additional data supplied by Chiron, a susceptible breakpoint of <1 mg/L would be appropriate (Figure 1).

Table 1: Target attainment for 4mg/kg/day daptomycin

daptomycin MIC mg/L	% target attainment with a total 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 of probabilities of target attainments (PTAs) from Prof A. MacGowan, Bristol, UK]

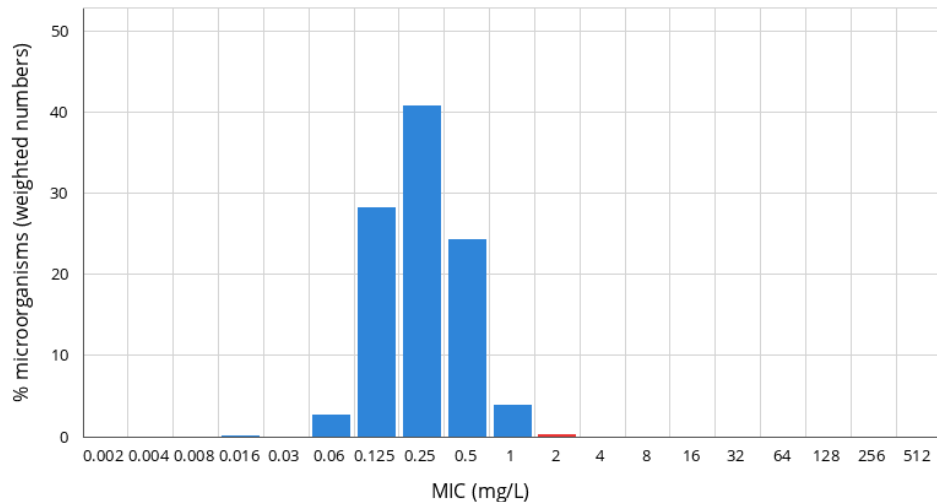
Figure 1: Daptomycin MIC distribution and probability of target attainment for *S. aureus*

Daptomycin / Staphylococcus aureus

International MIC distribution - Reference database 2021-03-09

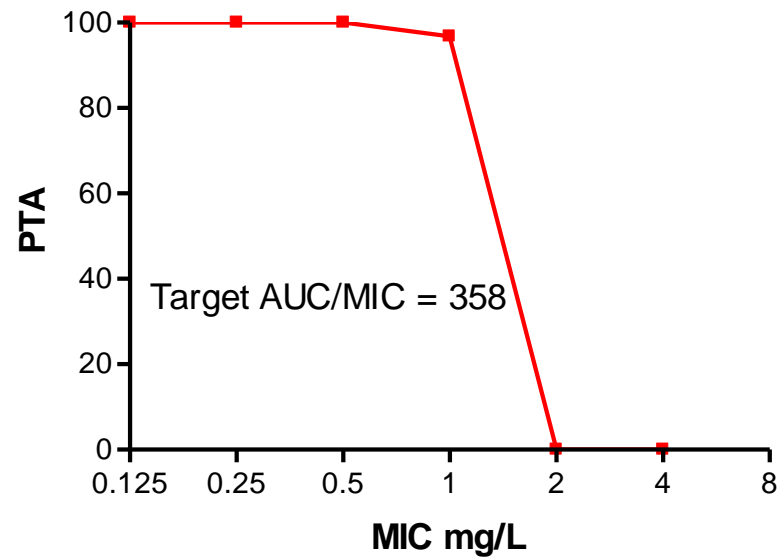
Based on aggregated distributions where each distribution has equal weight *

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



MIC Epidemiological cut-off (ECOFF): 1 mg/L
 Wildtype (WT) organisms: ≤ 1 mg/L
 Confidence interval: -
 36208 observations (28 data sources)
 * individual distributions were converted to percentages of their individual total and then aggregated

Probability of target attainment with AUC/MIC target of 358 for staphylococci



Enterococcus faecalis and E. faecium

The determinant of efficacy of daptomycin is the *fAUC/MIC* ratio [1]. In a recent study using the mouse thigh model, the target *fAUC/MIC* for a 1-log kill against *E. faecium* was 12.9 [2]. A 1-log reduction was not achieved against *E. faecalis*; a target of 7.2 achieved bacteriostasis with this species. With a human-simulated regimen of 6 mg/kg/day, a 1-log₁₀-CFU reduction was observed in 3/3 *E. faecium* isolates with MICs of <4 mg/L and 0/3 *E. faecium* isolates with MICs of ≥4 mg/L.

A recent investigation undertook a CART analysis of clinical outcome data from enterococcal bloodstream infection treatment studies using published PK data [3]. An *fAUC/MIC* of 27.4 best predicted survival at 30 days. This value was statistically significant in patients with low acuity (n=77, p=0.006) and nearly achieved statistical significance in all patients (n=114, p=0.051). CART analysis of microbiological clearance identified an *fAUC/MIC* target of 19.9, although this did not reach statistical significance in all patients (n=66) or the subset of those with low acuity (n=48). The results of Monte Carlo simulations using the data generated from these analyses are shown in Table 1. Some small differences were noted for males versus females. Satisfactory target attainment rates were only seen with a dose of 12 mg/kg/day and then only for strains with MICs up to 2 mg/L.

The high off-label doses required for enterococcal infections, and the failure to reach the ECOFFs with these doses means that the selection of breakpoints for these two enterococcal species is not possible at this time.

Table 1: Probability of survival threshold (*fAUC/MIC* >27.43) attainment using Monte Carlo simulation [4]

MIC (mg/L)	6 mg/kg/day	8 mg/kg/day	10 mg/kg/day	12 mg/kg/day
0.25	100	100	100	100
0.5	100	100	100	100
1	91.0, 97.9	98.7, 99.9	99.9, 100	100
2	32.4, 54.4	60.7, 80.4	80.4, 92.9	91.0, 97.9
4	1.5, 5.5	7.3, 18.1	18.1, 36.2	32.4, 54.4
8	0	0.0, 0.2	0.2, 2.0	1.5, 5.5
16	0	0	0	0

Males and females were simulated separately.

For MICs at which the probability differs, values are presented as 'male, female'.

References

1. Safdar N, Andes D, Craig WA. In vivo pharmacodynamic activity of daptomycin. *Antimicrob Agents Chemother* 2004; 48:63-8
2. Kidd JM, Abdelraouf K, Asempa TE, Humphries RM, Nicolau DP. Pharmacodynamics of Daptomycin against *Enterococcus faecium* and *Enterococcus faecalis* in the Murine Thigh Infection Model. *Antimicrob Agents Chemother*. 2018;62(10). pii: e00506-18
3. Avery LM, Kuti JL, Weisser M, Egli A, Rybak MJ, Zasowski EJ, Arias CA, Contreras GA, Chong PP, Aitken SL, DiPippo AJ, Wang JT, Britt NS, Nicolau DP. Pharmacodynamic Analysis of Daptomycin-Treated Enterococcal Bacteremia: It Is Time to Change the Breakpoint. *Clin Infect Dis*. 2019; 68(10):1650-7.

7. Clinical data

Clinical trial data demonstrating efficacy and supporting the registration of daptomycin were conducted in complicated skin and skin structure infections and *S. aureus* bacteraemia, including infections caused by methicillin-resistant strains. Studies have also demonstrated efficacy in staphylococcal osteomyelitis. Clinical efficacy data for staphylococci and streptococci indicate eradication in 80% of patients (similar to comparator treatments) and no difference in eradication rates for strains with different MICs up to 0.5 mg/L.

References

Arbeit et al., Clin Infect Dis 2004; 38:1673-81
Fowler et al., N Eng J Med 2006; 355:653-65
Davis et al., Pharmacotherapy 2007; 27:1611-8
Lalani et al., JAC 2008; 61:177-82
Rehm et al., JAC 2008; 62:1413-21.

8. Clinical breakpoints (<http://www.eucast.org>)

PK/PD breakpoints (non-species related)	Insufficient evidence (greatly differing targets depending on species)
Species-related breakpoints	<i>Staphylococcus aureus</i> : S ≤ 1, R >1 <i>Streptococcus</i> groups A, B, C and G: S ≤ 1, R >1
Species without breakpoints	<i>Streptococcus pneumoniae</i> : Insufficient evidence <i>Enterococcus</i> species: Insufficient evidence (see Additional comments below) Gram-positive anaerobes: Insufficient evidence Daptomycin is not active against <i>Enterobacterales</i> , <i>Pseudomonas</i> spp., <i>Acinetobacter</i> spp., <i>Haemophilus</i> spp., <i>Moraxella</i> spp. and <i>Neisseria</i> spp. and Gram-negative anaerobic organisms.
Clinical qualifications	Daptomycin failed in clinical trials of community-acquired pneumonia, and hence the <i>S. pneumoniae</i> breakpoints are listed as insufficient evidence
Dosage(s) linked to breakpoints	Complicated skin and skin structure infections: 4 mg/kg once daily Infective endocarditis: 6 mg/kg once daily
Additional comments	The management of serious enterococcal infections with daptomycin is addressed in a EUCAST guidance document: https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Guidance_documents/Daptomycin_guidance_note_-_revision_20200430.pdf

9. Exceptions noted for individual national committees

None