

Antibiotic Susceptibility Testing with Cubicin[®] (daptomycin)

Introduction

Cubicin (daptomycin) is a cyclic lipopeptide antibiotic against Gram-positive bacteria, approved for treatment of the following infections in adults:

- Complicated skin and soft tissue infections (cSSTI)¹
- *Staphylococcus aureus* bacteraemia when associated with right-sided infective endocarditis or cSSTI
- Right-sided infective endocarditis due to *S. aureus*¹

Cubicin is also indicated in paediatric patients aged 1 to 17 years for the treatment of complicated skin and soft tissue infections (cSSTI)¹²

- Paediatric patients below the age of one (1) year should not be given Cubicin due to the risk of potential effects on muscular, neuromuscular, and/or nervous systems (either peripheral and/or central) that were observed in neonatal dogs

Daptomycin has one characteristic that affects susceptibility testing:

- It requires appropriate concentrations of free calcium (Ca²⁺) ions for accurate assessment of its activity *in vitro*²⁻⁴

Effect of Calcium (Ca²⁺) on susceptibility testing

Daptomycin activity is dependent on the presence of physiological calcium (Ca²⁺) concentrations²⁻⁴

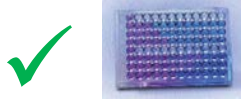

Other divalent and monovalent cations have negligible effects on activity^{2,5,6}

A Ca²⁺ concentration of 50 µg/ml (1.1 mM) in growth media provides optimal determination of daptomycin minimum inhibitory concentration (MIC) and correlates with physiological levels of free Ca²⁺ in human plasma (1.15–1.31 mM)^{7,8}

Therefore, reliable *in vitro* susceptibility testing of daptomycin in clinical laboratories requires appropriate standardization of test media to 50 µg/ml Ca²⁺

Summary of daptomycin susceptibility testing methods

Recommended methods for daptomycin susceptibility testing

<p>Broth microdilution (BMD)</p> 	<ul style="list-style-type: none"> The BMD is the Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommended method for determining MIC and susceptibility of pathogens to daptomycin Follow CLSI-approved method using Mueller–Hinton broth (with or without 2–5% lysed horse blood) adjusted to 50 µg/ml Ca²⁺ MIC determination using broths other than Mueller–Hinton broth has not been validated
<p>E test*</p> 	<ul style="list-style-type: none"> Daptomycin E test strips (bioMerieux SA), which contain a constant Ca²⁺ level throughout the daptomycin gradient, are also a recommended method Ca²⁺ content in the agar is also essential and should be in the range of 25–40 µg/ml The daptomycin E test strips are suitable for use on Mueller–Hinton agar (BBL™ Mueller–Hinton agar is recommended because the Ca²⁺ concentration is consistently within the required range)⁹




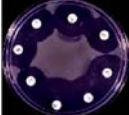
*FOR FURTHER INFORMATION AND LOCAL DISTRIBUTOR CONTACT DETAILS GO TO WWW.BIOMERIEUX-DIAGNOSTICS.COM/ETEST

Automated and semi-automated systems

<p>Automated and semi-automated systems</p>	<ul style="list-style-type: none"> Development of daptomycin panels and cards for BioMerieux ViTeK 1 and VITEK 2, BD Phoenix and Trek SensiTitre is complete Contact your local representative/customer services of the system manufacturer to obtain these systems and software updates as appropriate Other systems are in development
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Non-recommended methods for susceptibility testing

<p>Agar dilution</p>	<ul style="list-style-type: none"> This method is not recommended because there is no agar with consistent Ca²⁺ concentrations that is also appropriate for daptomycin testing. Supplementing agar with Ca²⁺ is problematic The variability in Ca²⁺ concentrations of agar between different batches
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 	<p>and manufacturers makes this method unpredictable</p>
 	<ul style="list-style-type: none"> • A 30 µg disk was withdrawn from the US market due to problems in distinguishing resistant isolates from susceptible strains • This method is currently not recommended

EUCAST-approved interpretive criteria¹⁰ (www.escmid.org)

	Susceptible	Resistant
<i>Staphylococcus</i> spp.	≤1 µg/ml	>1 µg/ml
<i>Streptococcus</i> spp. Groups A, B, C and G (excluding <i>S.pneumoniae</i>)	≤1 µg/ml	>1 µg/ml

Susceptibility to Cubicin

Of 2,977 European Gram-positive clinical isolates tested in a 2011 European surveillance programme, 99.9% were susceptible to Cubicin¹¹

Further information

Please contact your local MSD office (see www.msd.com.)

References

1. Cubicin EU SmPC.
2. Eliopoulos GM *et al.* *In vitro* and *in vivo* activity of LY 146032, a new cyclic lipopeptide antibiotic. *Antimicrob Agents Chemother* 1986;30:532–535.
3. Fuchs PC *et al.* Daptomycin susceptibility tests: interpretive criteria, quality control, and effect of calcium on *in vitro* tests. *Diagn Microbiol Infect Dis* 2000;38:51–58.
4. Fuchs PC *et al.* Evaluation of daptomycin susceptibility testing by Etest and the effect of different batches of media. *J Antimicrob Chemother* 2001;48:557–561.
5. Alborn WE Jr *et al.* Daptomycin disrupts membrane potential in growing *Staphylococcus aureus*. *Antimicrob Agents Chemother* 1991;35:2282–2287.
6. Eliopoulos *et al.* *In vitro* activity and mechanism of action of A21978C1, a novel cyclic lipopeptide antibiotic. *Antimicrob Agents Chemother* 1985;27:357–362.
7. Barry AL *et al.* *In vitro* activities of daptomycin against 2,789 clinical isolates from 11 North American medical centers. *Antimicrob Agents Chemother* 2001;45:1919–1922.

8. Wise R *et al.* Activity of daptomycin against Gram-positive pathogens: a comparison with other agents and the determination of a tentative breakpoint. *J Antimicrob Chemother* 2001;48:563–567.
9. bioMerieux SA. Etest daptomycin Customer Information Sheet. 2010/2011.
10. EUCAST. EUCAST Clinical Breakpoints- Daptomycin. Available at http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_6.0_Breakpoint_table.pdf [Accessed 19 July 2016].
11. Sader HS *et al.* Antimicrobial activity of daptomycin tested against Gram-positive pathogens collected in Europe, Latin America, and selected countries in the Asia-Pacific Region (2011). *Diagn Microbiol Infect Dis* 2013; 75: 417-422.
12. Study DAP-PEDS-07-03

Please refer to the Summary of Product Characteristics (SmPC) before prescribing Cubicin.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions for CUBICIN at ADR Reporting at: www.medicinesauthority.gov.mt/adrportal.

Adverse events should also be reported to Merck Sharp & Dohme Cyprus Ltd by calling **800 7 4433** or at malta_info@merck.com.