ANTIBIOTIC SUSCEPTIBILITY TESTING WITH DAPTOMYCIN

Introduction

Daptomycin is a cyclic lipopeptide antibiotic active against Gram positive bacteria. Daptomycin is approved for the treatment of the following infections in adults:

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

Daptomycin is also indicated for use in paediatric patients (aged between 2 and 17 years) for the treatment of cSSTI. Children under 1 year of age should not be given daptomycin due to the potential risk of effects on muscular, neuromuscular and/or nervous system (either peripheral or central), such effects have been observed in neonatal dogs

There is one characteristic of daptomycin which affects susceptibility testing namely that daptomycin requires an appropriate concentration of free calcium (Ca^{2+}) ions for accurate assessment of its activity *in vitro*

The effect of Ca^{2+} on susceptibility testing

Daptomycin activity is dependent on the physiological Ca^{2+} concentration.

Other divalent and monovalent cations have negligible effect on daptomycin activity

A Ca^{2+} concentration of 50 μg/ml (1.1 mM) in growth media provides the optimal determination of the daptomycin minimum inhibitory concentration (MIC) and correlates with the physiological levels of free Ca^{2+} in human plasma (1.15 – 1.31 mM)

Reliable *in vitro* susceptibility testing of daptomycin will therefore require the appropriate standardisation of the test media to 50 μg/ml Ca^{2+}

Summary of daptomycin susceptibility testing methods

Recommended Methods for daptomycin susceptibility testing

Broth Microdilution (BMD) √	The BMD method 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 Ca^{2+}
	MIC determination using broths other than Mueller-Hinton broth have not been validated
E test * √	Daptomycin e-test strips (BioMerieux SA) which contain a constant Ca^{2+} level throughout the daptomycin gradient are also a recommended method
	Ca^{2+} content in the agar is essential and should be in the range 25-40 μg/ml
	The daptomycin e-test strips are suitable for use on Mueller-Hinton agar (note BBL™ Mueller-Hinton agar is recommended because the Ca^{2+} concentration is consistently within the required range)

* For further information and local distributor contact details go to www.biomerieux-diagnostics.com/etest

Automated and Semi-automated systems

The development of daptomycin panels and cards for BioMerieux VITEK 1 and VITEK 2, BD Phoenix and TrekSensiTitre is complete
To obtain these systems and software updates contact your local representative/ customer services of the system manufacturer
Other systems are in development. Check with the representative/ customer services function as appropriate

Non-recommended methods for susceptibility testing

Agar dilution **X**	This method is not recommended because there is no agar with consistent Ca^{2+} concentrations that is also appropriate for daptomycin testing. Supplementation of agar with Ca^{2+} is problematical and not recommended
	The variability in Ca^{2+} concentrations of agar between different batches and manufacturers makes this method unpredictable
Disc diffusion **X**	A 30 μg disc was withdrawn from the US market due to problems in distinguishing resistant isolates from susceptible strains
	This method is currently not recommended

EU-CAST approved interpretative criteria (visit www.escmid.org for more information)

Gram-positive organism	**Susceptible**	**Resistant**
Staphylococcus spp.	≤ 1 μg/ml	> 1 μg/ml
Streptococcus spp. Groups A,B,C and G (excluding *S. pneumoniae*)	≤ 1 μg/ml	> 1 μg/ml

Susceptibility to daptomycin – of 2977 European Gram positive isolates tested in a 2011 European surveillance programme 99.9% were susceptible to daptomycin

Further information

BEFORE PRESCRIBING DAPTOMYCIN PLEASE ENSURE THAT YOU REFER TO THE SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)

Reporting of suspected adverse reactions

Please continue to report suspected adverse drug reactions (ADRs) including medication errors (any errors while prescribing, preparing or administering the drug) to the MHRA, through the Yellow Card scheme and to the company contact details stated below.

Please report all suspected ADRs that are serious or result in harm. Serious reactions are those that are fatal, life-threatening, disabling or incapacitating, those that cause a congenital abnormality or result in hospitalisation, and those that are considered medically significant for any other reason.

When making a report please provide us with as much information as possible, including the method of dilution, the dose administered and any side effects, medical history, concomitant medications etc.

MHRA contact point

The easiest and quickest way to report is online at www.mhra.gov.uk/yellowcard. Alternatively, prepaid Yellow Cards for reporting are available:

- by writing to FREEPOST YELLOW CARD (no other address details necessary)
- by emailing yellowcard@mhra.gov.uk
- at the back of the British National Formulary (BNF)
- by telephoning the Commission on Human Medicines (CHM) free phone line: 0800-731-6789
- or by downloading and printing a form from the Yellow Card section of the MHRA website

Company contact point:

Address

Actavis UK Ltd, a subsidiary of Accord Healthcare Ltd, Whiddon Valley, Barnstaple, Devon, EX32 8NS, UK

Medical Information Direct Line

+44 (0)1271 385 257

Medical Information e-mail

medinfo@accord-healthcare.com