Laboratory susceptibility testing leaflet

Antibiotic Susceptibility Testing with Daptomycin Xellia

Introduction

Daptomycin Xellia is a cyclic lipopeptide antibiotic against Gram-positive bacteria, approved for treatment of the following indications in adults:

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

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

- Paediatric patients below the age of one year should not be given Daptomycin Xellia 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 Ca^{2+} ions for accurate assessment of its activity *in vitro*

Effect of Ca^{2+} on susceptibility testing

Daptomycin activity is dependent on the presence of physiological Ca^{2+} concentrations

Other divalent and monovalent cations have negligible effects on activity

A Ca^{2+} 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 Ca^{2+} in human plasma (1.15-1.31 mM)

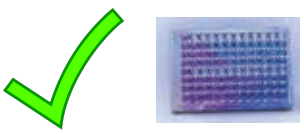
Therefore, reliable *in vitro* susceptibility testing of daptomycin in clinical laboratories requires appropriate standardization of test media to 50 µg/ml Ca^{2+}

Susceptibility to Daptomycin Xellia

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

Summary of daptomycin susceptibility testing methods

Recommended methods for daptomycin susceptibility testing

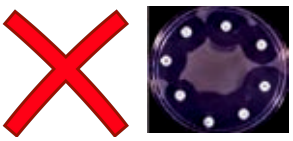
Broth microdilution (BMD) 	➢ The BMD is the Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommended method for determining MIC and susceptibility of pathogens to daptomycin ➢ Follow CLSI-approved method using Mueller–Hinton broth (with or without 2-5% lysed horse blood) adjusted to 50 µg/ml Ca^{2+} ➢ MIC determination using broths other than Mueller-Hinton broth has not been validated

Etest 	➢ Daptomycin Etest 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 also essential and should be in the range of 25-30 µg/ml ➢ The daptomycin Etest strips are suitable for use on Mueller-Hinton agar ➢ (BBL™ Mueller-Hinton agar is recommended because the Ca^{2+} concentration is consistently within the required range)

Automated and semi-automated systems

Automated and semi-automated systems	➢ 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

Non-recommended methods for susceptibility testing

Agar dilution 	➢ This method is not recommended because there is no agar with consistent Ca^{2+} concentrations that is also appropriate for daptomycin testing. Supplementing agar with Ca^{2+} is problematic ➢ The variability in Ca^{2+} concentrations of agar between different batches and manufacturers makes this method unpredictable
Disk diffusion 	➢ 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 criteria (www.escmid.org)

	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

Reporting suspected adverse reactions after authorisation 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 via National Reporting System.

Reporting can be done by contacting Xellia at:
Xellia Pharmaceuticals ApS
Dalslandsgade 11
2300 Copenhagen S
Denmark
via e-mail: safety@xellia.com

or by contacting

Xellia Medical Information at:
Lambda Therapeutic Limited
Sage House, 319 Pinner Road
North Harrow
London, HA1 4HF
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