

Multi-Site Evaluation of Daptomycin on the Sensititre® Dried Susceptibility Plate Compared to NCCLS Microdilution Method

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ABSTRACT

Background: A multi-site evaluation was undertaken to compare the performance of a new antimicrobial agent Daptomycin (DAP) on the Sensititre 18 – 24 hour susceptibility dried plate with its performance on the frozen NCCLS M7 broth microdilution reference method, testing both automated and manual reading methods. The drug range tested for Daptomycin was (0.03 – 64 µg/ml).

Methods: The clinical evaluation was conducted at three sites and consisted of 287 fresh clinical gram-positive isolates and 77 CDC challenge isolates. These isolates included *S. aureus*, *S. epidermidis*, *Staphylococcus species*, *Streptococcus species*, *E. faecalis*, *E. faecium*, and *Enterococcus species*. The recommended quality control organisms were tested daily and were within the NCCLS expected quality control range.

Results*: When the automated reading method was compared to the reference method the clinical isolates' Essential Agreement (EA) was 98.3%, while the challenge isolates' EA was 98.7%. When the manual reading method was compared to the reference method the clinical isolates' EA was 97.6% and 98.7% for the challenge isolates.

The reproducibility isolates' EA for the automated method were 99.0%, and for the manual method were 96.0%.

Conclusions: This multi-site evaluation indicates that the performance of Daptomycin on the Sensititre 18-24 hour susceptibility system, using either the automated or manual reading method, was equivalent to its performance using the NCCLS microdilution reference method.

*Abstract has been modified

PURPOSE OF THE STUDY

To evaluate the performance of Daptomycin on the Sensititre® 18 – 24 hour susceptibility panel compared to the NCCLS microdilution reference method (M7 – A6).

MATERIALS & METHODS

Organisms: The testing at 3 sites consisted of the following:

- 287 clinical gram-negative isolates
- 77 CDC challenge isolates
- 25 reproducibility isolates
- 4 Quality Control strains

Provisional interpretive criteria for susceptibility to Daptomycin provided by Cubist Pharmaceuticals.

Pathogen	Minimal Inhibitory Concentration (µg/ml) ^a		
	S	I	R
<i>Staphylococcus aureus</i> (methicillin-susceptible and methicillin resistant)	≤2	4	≥8
<i>Streptococcus spp.</i> Other than <i>S. pneumoniae</i>	≤2	(d)	(d)
<i>Enterococcus faecalis</i> (vancomycin susceptible only)	≤8	---	≥16

Antibiotics

Antimicrobials Tested	Range Tested	Supplied By
Daptomycin (DAP)	0.03 – 64	Cubist Pharmaceuticals

Susceptibility Testing Methods:

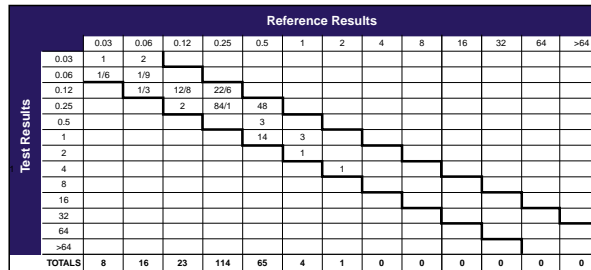
- Each isolate was tested using a Sensititre 18 – 24 hour susceptibility plate. The panels were set-up and tested according to the manufacturers' instructions.
- The reference panel was tested according to the microdilution methods published by the National Committee for Clinical Laboratory Standards (NCCLS, M7-A6).

Isolates Tested

Organisms	Clinical	Number Tested
<i>Staphylococcus aureus</i>	19	75
<i>Staphylococcus epidermidis</i>	13	70
<i>Staphylococcus species</i>	7	5
<i>Streptococcus species</i>	3	35
<i>Enterococcus faecalis</i>	17	35
<i>Enterococcus faecium</i>	14	26
<i>Enterococcus species</i>	4	41
Total	77	287

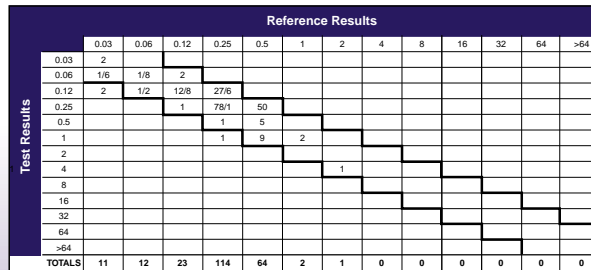
RESULTS

Staphylococcus/Streptococcus species – Manual Reading Method MIC distribution for clinical and challenge isolates vs. Daptomycin



Categorical Interpretations: (*S. aureus*) Susceptible ≤ 2, Intermediate = 4, Resistant ≥ 8
Categorical Interpretations: (*Streptococcus spp.*) Susceptible ≤ 2

Staphylococcus/Streptococcus species – Automated Reading Method MIC distribution for clinical and challenge isolates vs. Daptomycin

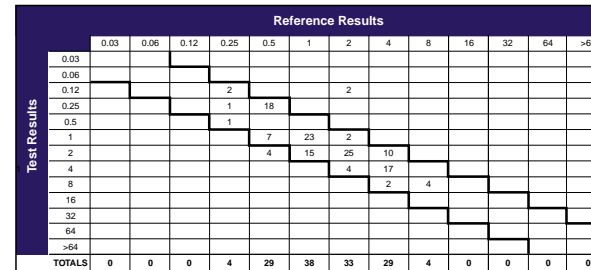


Categorical Interpretations: (*S. aureus*) Susceptible ≤ 2, Intermediate = 4, Resistant ≥ 8
Categorical Interpretations: (*Streptococcus spp.*) Susceptible ≤ 2

Reproducibility Isolates vs. Daptomycin Reference Agreement within +/-1 Dilution of Modal MIC

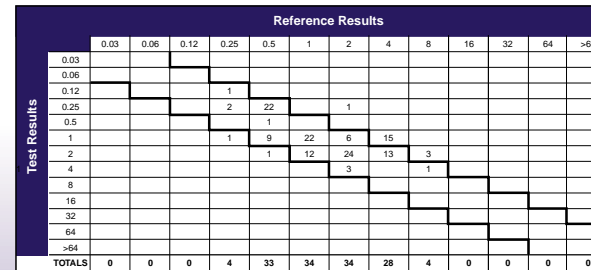
Site	# Agreement Manual	# Agreement Autoread	Total Isolates Tested	Manual %	Autoread %
TREK	25	25	25	100	100
Creighton	25	25	25	100	100
UH	22	24	25	88	96
Combined	72	74	75	96	99

Enterococcus species – Manual Reading Method MIC distribution for clinical and challenge isolates vs. Daptomycin



Categorical Interpretations: (*E. faecalis*) Susceptible ≤ 8, Intermediate ---, Resistant ≥ 16

Enterococcus species – Automated Reading Method MIC distribution for clinical and challenge isolates vs. Daptomycin



Categorical Interpretations: (*E. faecalis*) Susceptible ≤ 8, Intermediate ---, Resistant ≥ 16

Clinical Isolates vs. Daptomycin for *Staph.* and *Strep.* species

Read Method	Total Isolates Tested	% Essential Agreement	% Categorical Agreement	Number Resistant	Very Major Errors	Major Errors	Minor Errors
Manual	189	100	100	0	0	0	0
Automated	185	99	99.5	0	0	0	1

CDC Challenge Isolates vs. Daptomycin for *Staph.* and *Strep.* species

Read Method	Total Isolates Tested	% Essential Agreement	% Categorical Agreement	Number Resistant	Very Major Errors	Major Errors	Minor Errors
Manual	42	98	100	0	0	0	0
Automated	42	96	100	0	0	0	0

Clinical Isolates vs. Daptomycin for *Enterococcus* species

Read Method	Total Isolates Tested	% Essential Agreement	% Categorical Agreement	Number Resistant	Very Major Errors	Major Errors	Minor Errors
Manual	102	94	100	0	0	0	0
Automated	102	97	100	0	0	0	0

CDC Challenge Isolates vs. Daptomycin for *Enterococcus* species

Read Method	Total Isolates Tested	% Essential Agreement	% Categorical Agreement	Number Resistant	Very Major Errors	Major Errors	Minor Errors
Manual	35	100	100	0	0	0	0
Automated	35	100	100	0	0	0	0

CONCLUSIONS

This investigation compared the 18 – 24 hour Sensititre® susceptibility plate with the NCCLS reference microdilution frozen plate (M7 – A6). The Sensititre plate demonstrated a high level of agreement and was very reproducible.

Clinical Isolates:

- The overall essential agreement for Daptomycin, within a +/- one-well dilution range, was 98% for the manual method and 98% for the autoread method.
- The overall categorical agreement for Daptomycin was 100% for the manual method and 99.8% for the autoread method.

CDC Challenge Organisms:

- The overall essential agreement for Daptomycin, within a +/- one-well dilution range, was 99% for the manual method and 99% for the autoread method.
- The overall categorical agreement for Daptomycin, was 100% for the manual method and 100% for the autoread method.

Reproducibility:

- Interlaboratory reproducibility was 96% for the manual read method and 99% for the autoread method.