

A Multicenter Comparison Study of Various Ceftaroline MIC-Based Methods for *Staphylococcus aureus*

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INTRODUCTION: Ceftaroline, the active metabolite of the pro-drug ceftaroline fosamil, has in vitro activity against *Staphylococcus aureus* including methicillin-resistant *S. aureus* (MRSA). Commercial antimicrobial susceptibility testing (AST) devices are available for ceftaroline testing. The objective of this study was to compare the performance of these AST products against challenge isolates (selected to include 49% with MICs of 1 and 2 mg/L) and recent clinical *S. aureus* isolates.

METHODS: The challenge set consisted of 41 *S. aureus* (31 MRSA, 10 MSSA) reporting reference ceftaroline MICs of 0.12-4 mg/L (11 isolates inhibited by 1 mg/L, 9 by 2 mg/L and 1 by 4 mg/L of ceftaroline and *S. aureus* ATCC 29213). One site tested each isolate by ISO/CLSI broth microdilution (BMD) method to confirm reference MIC values. The challenge set and 30 *S. aureus* (prospectively collected consecutive isolates from each of 3 European sites) included 12, 12 and 3 MRSA from Germany, Spain and Austria, respectively) and a retrospective collection of 30 *S. aureus* with high prevalence of MRSA (28/30) from Italy were tested once by 3 AST BMD methods and by 3 gradient diffusion (GD) methods (Table 1) following manufacturer instructions on 2 lots of media at 4-5 laboratories (Austria, Germany, Italy, Spain, USA).

Product Name, Catalog No.	Manufacturer, location	Ceftaroline (mg/L)
Sensititre Gram Pos, GPALL2F	Trek Diagnostic Systems, Thermo-Fisher, E. Grinstead, UK	0.12-4
Microscan Gram Pos MIC 33, B1016-173	Siemens AG, Erlangen, Germany	0.5, 1
Micronaut MRSA/GP, M/E1-055-040	Merlin, Berlin, Germany	0.25-2
CPT Etest, 537548	bioMérieux, Marcy l'Etoile, France	0.002-32
CPT M.I.C.Evaluator, MA0127F	Oxoid Ltd., Thermo-Fisher, Basingstoke, UK	0.002-32
CPT MIC Strip, 920490	Liofilchem, Roseto degli Abruzzi, Italy	0.016-256

RESULTS (Challenge Isolates):

Consolidated ceftaroline MICs for each method compared to the reference BMD are shown in Figure 1. Range of category agreement (CA) rates for method/site data sets were:

- Micronaut: 82.9% (USA) – 92.7% (Germany)
- Microscan 87.8% (Austria) – 97.6% (Italy)
- Sensititre 85.4% (Austria, Spain) – 100% (USA)
- Etest 82.9% (Spain) – 92.7% (Italy)
- Liofilchem 82.9% (Spain) – 90.2% (Italy)
- M.I.C.E. 75.6% (Spain) – 90.2% (Austria).

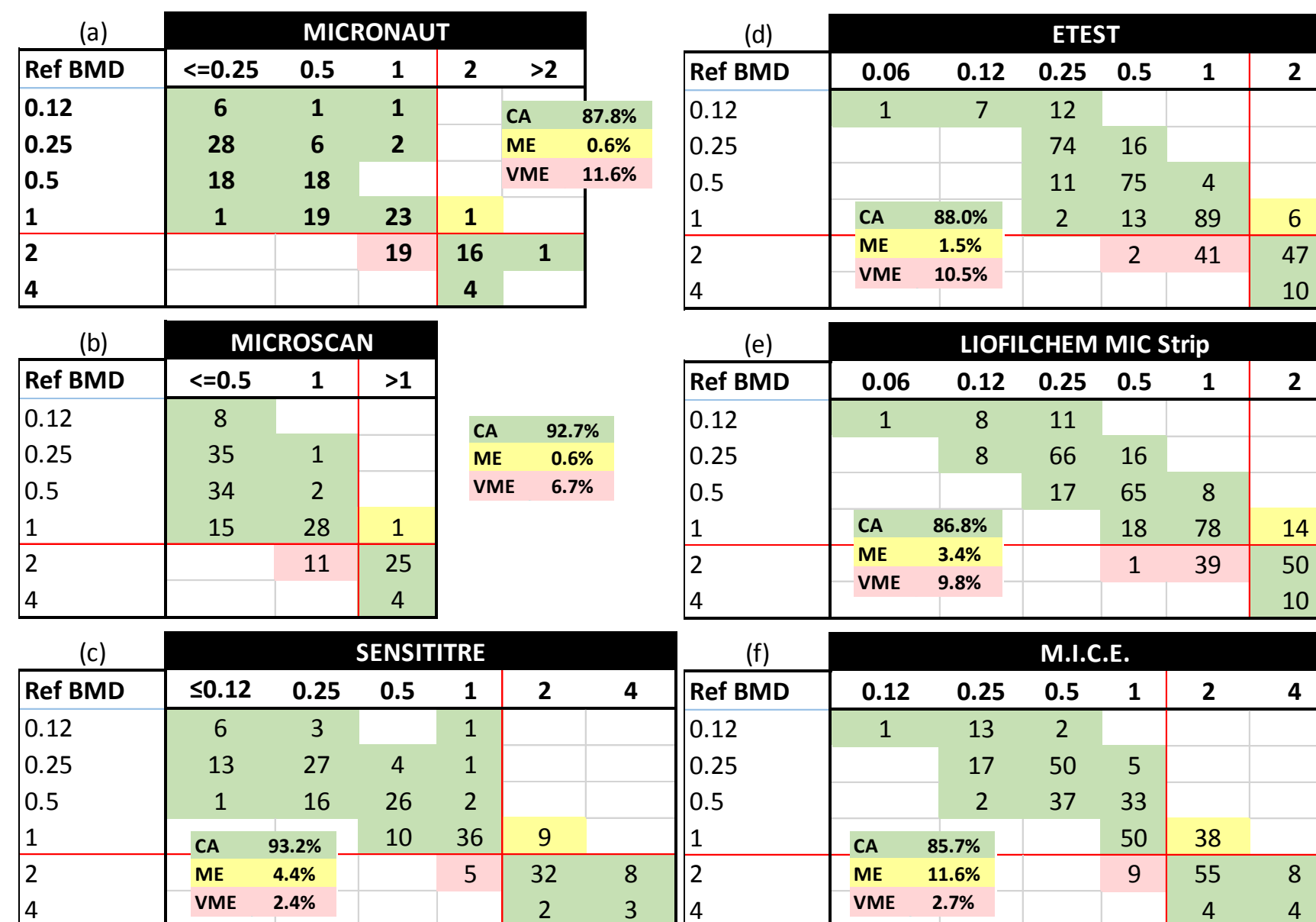
The ceftaroline susceptibility rate by BMD for the challenge set was 75.6% and for the test methods susceptibility rates varied from 56.0% (M.I.C.E., Spain) to 92.7% (Micronaut, USA). Essential agreement (EA) rates were 98-100% (Table 2).

RESULTS (Site Specific Isolates):

Ceftaroline susceptibility rates for the site specific set of *S. aureus* were high for Austria, Germany and Spain (100%, 93.3-100% and 96.7%-100%, respectively). The susceptibility rates for the retrospective set of primarily MRSA from Italy were much lower and similar to the challenge set, susceptibility rates varied depending on method (66.7-93.3%).

With a few exceptions and off-scale results with Micronaut and Microscan (due to limited concentrations), ceftaroline MICs for ATCC 29213 were within the EUCAST quality control range of 0.12-0.5 mg/L.

Figure 1: Consolidated 5 site ceftaroline MIC results (mg/L) for 6 methods compared to reference BMD MIC results for 41 challenge isolates



CA = Category Agreement (results for both methods agree by interpretive category), ME = Major Error (susceptible by Ref BMD, resistant by Test Method), VME = Very Major Error (resistant by Ref BMD, susceptible by Test Method); Red lines are EUCAST MIC and disk susceptible breakpoints

Table 2 Dilution difference of ceftaroline commercial MIC method compared to reference BMD for 41 challenge *S. aureus* (2 results/isolate for GD methods tested on 2 MHA lots)

AUSTRIA	3	2	1	0	-1	-2	EA
Sensititre			13	28			100%
Liofilchem			7	48	27		100%
Etest			12	59	11		100%
M.I.C.E.			26	52	4		100%
GERMANY	3	2	1	0	-1	-2	
Sensititre			3	28	10		100%
Liofilchem			6	56	20		100%
Etest			8	61	13		100%
M.I.C.E.			26	47	9		100%
ITALY	3	2	1	0	-1	-2	
Sensititre			8	27	6		100%
Liofilchem			6	53	23		100%
Etest			5	56	21		100%
M.I.C.E.		2	33	47			97.6%
SPAIN	3	2	1	0	-1	-2	
Sensititre	1		2	18	19	1	95.1%
Liofilchem			19	49	14		100%
Etest			5	51	22	4	95.1%
M.I.C.E.		5	56	19	2		93.9%
USA	3	2	1	0	-1	-2	
Sensititre				32	9		100%
Liofilchem			8	61	12	1	98.8%
Etest			8	65	9		100%
TOTALS	1	7	251	857	231	6	99.0%

EA= Essential Agreement (+/- 1 dilution of reference BMD MIC)

CONCLUSIONS:

In this multi-method/site study, essential agreement rates were exceptionally good. This study showed very clearly that even though results for different methods agree with regard to the typical ± 1 dilution variability, if an MIC falls near the susceptible/resistant breakpoint, considerable categorical result differences can be expected. The categorical discrepancies that occurred were attributed solely to isolates with ceftaroline MIC results of 1 and 2 mg/L.

Disclosures: This study was supported by a grant from AstraZeneca; Laboratory Specialists, Inc., Westlake, also received a fee for service in relation to preparation of the abstract and poster. Jane Ambler is a former employee of AstraZeneca.

References:

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