Comparative Evaluation of Cefepime-Taniborbactam MIC Testing with Gradient Strip and CLSI Broth Microdilution Methods

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BACKGROUND

Cefepime is a fourth-generation cephalosporin antibiotic approved for clinical use since 1994. Taniborbactam is a new boronate-based β-lactamase inhibitor to be combined with cefepime. Cefepime-taniborbactam (FTB) is active against most isolates of serine- and metallo-β-lactamase producing *Enterobacterales* and *Pseudomonas aeruginosa* and is in development for the treatment of complicated urinary tract infections/acute pyelonephritis and hospital-acquired/ventilator-associated bacterial pneumonia.

OBJECTIVE

The aim of this study was to perform a comparative evaluation of ETEST® cefepime-taniborbactam (ETEST FTB) with the Clinical and Laboratory Standards Institute (CLSI) broth microdilution (BMD) reference method using a large panel of clinical strains.

METHODS

- A panel of 99 *Enterobacterales* and 27 *P. aeruginosa* with different resistance mechanisms (including ESBL, high level cephalosporinase, carbapenemase production and porin alteration/impermeability) and 4 ATCC quality control strains were tested. The details of species and QC strains are presented in tables 1 and 2.
- The strains were provided by bioMérieux's internal collection, supplemented by strains supplied by Venatorx pharmaceuticals.

Species	Number of strains
Enterobacter cloacae complex	12
Escherichia coli	16
Klebsiella pneumoniae	12
Proteus mirabilis	10
Pseudomonas aeruginosa	27
Serratia marcescens	10
Citrobacter freundii complex	5
Citrobacter koseri	5
Klebsiella aerogenes	5
Klebsiella oxytoca	5
Morganella morganii	5
Proteus vulgaris	5
Providencia rettgeri	5
Providencia stuartii	4

Table 1 – Detail of species

QC Strains	Collection number	QC Range CLSI M100 – Ed34 (µg/mL)
Escherichia coli	ATCC® 25922™	0.032/4 – 0.125/4
Escherichia coli	NCTC® 13353™	0.125/4 – 1/4
Klebsiella pneumoniae	ATCC® 700603™	0.125/4 – 0.5/4
Pseudomonas aeruginosa	ATCC® 27853™	0.5/4 – 4/4

Table 2 – CLSI QC strains for cefepime-taniborbactam

- BMD was performed using the CLSI standards M100 – 34th Edition – 2024 and M07 – 12th Edition – 2024. ETEST® FTB was evaluated using the standard ETEST® MIC procedure for aerobic strains (inoculum 0.5 McFarland from 18/24h cultures on Columbia agar + 5% sheep blood, testing on Mueller Hinton agar medium, incubation at 35°C during 16-20h in ambient air).
- For BMD, the MIC endpoint corresponded to the lowest concentration of cefepime-taniborbactam that showed complete inhibition of growth. For ETEST® FTB, the MIC endpoint corresponded to the value where the respective inhibition ellipses intersected the strip or where haze, macrocolonies or microcolonies within 3mm of the strip disappeared (bactericidal reading).
- Results were analysed using ISO standard 20776-2 (2021) for essential agreement (EA) and bias, and FDA AST Guidance (2009) for essential agreement (EA), category agreement (CA), major error rate (ME) and very major error rate (VME) using cefepime-taniborbactam provisional breakpoints (S≤16/4 and R≥32/4 µg/mL).

RESULTS

- The MICs for QC strains were within the CLSI ranges (EUCAST ranges not yet published) with reproducible results.

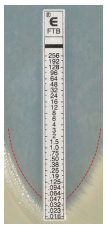


Figure 1
E. coli ATCC 25922
MIC = 0.047 µg/mL
Read at complete inhibition of haze

Figure 2
E. coli NCTC 13353
MIC = 0.38 µg/mL

Figure 3
K. pneumoniae ATCC 700603
MIC = 0.19 µg/mL

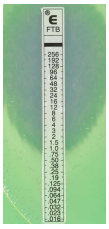


Figure 4
P. aeruginosa ATCC 27853
MIC = 1 µg/mL

- The essential agreement [± 1 dilution] for all strains between ETEST® FTB and BMD MICs was **92.1%**, with no significant bias (-19.2% for *Enterobacterales* and - 4.9% for *Pseudomonas aeruginosa*).

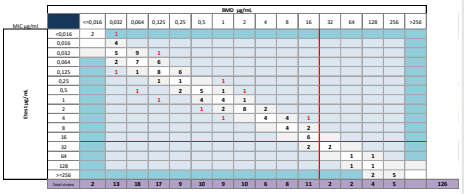
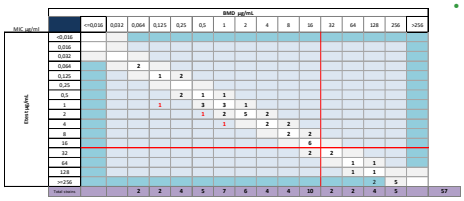


Table 3 : Distribution diagram between ETEST® FTB and BMD – All strains

- Cefepime-taniborbactam exhibits activity against most carbapenem-resistant strains of *Enterobacterales* and *P. aeruginosa*. Among the 126 strains tested, 57 were Intermediate or Resistant to meropenem (i.e., meropenem CLSI breakpoints: MIC ≥2 µg/mL for *Enterobacterales* and MIC ≥ 4 µg/mL for *P. aeruginosa*). ETEST® FTB performance was therefore also assessed against these strains of interest (strains with elevated carbapenem MICs).



- For these strains of interest, the essential agreement [± 1 dilution] between ETEST® FTB and BMD MICs was **94.7%,** with no significant bias (+7.9% for *Enterobacterales* and +10.9% for *Pseudomonas aeruginosa*).

Table 4 : Distribution diagram between ETEST® FTB and BMD – Strains of interest (i.e., meropenem MIC ≥2 µg/mL for *Enterobacterales* and MIC ≥ 4 µg/mL for *P. aeruginosa*)

The list of strains not within essential agreement is presented in Table 5 (all strains).

Species	Resistance profile	ETEST® FTB MIC (µg/mL)	BMD FTB MIC (µg/mL)	Doubling dilution difference
Enterobacter cloacae complex	Carbapenemase (VIM)	2	0.5	+ 2
Escherichia coli	Acquired cephalosporinase	0.032	0.125	- 2
Klebsiella pneumoniae	Carbapenemase (KPC)	0.25	1	- 2
Serratia marcescens	Undetermined	4	16	- 2
Pseudomonas aeruginosa	Wild type	0.5	2	- 2
Citrobacter freundii complex	ESBL	< 0.016	0.032	- 2
Citrobacter freundii complex	Carbapenemase (KPC)	4	1	+ 2
Morganella morganii	Carbapenemase (NDM)	1	0.125	+ 3
Proteus vulgaris	Undetermined	0.5	0.064	+ 3
Proteus vulgaris	Undetermined	0.125	0.032	+ 2

Table 5 : Detail of discrepant strains in terms of essential agreement

- The categorical agreement was **98.4%** with 124/126 concordant strains between both methods (see tables 6a and 6b).
  The major error rate was 1.8%. Only 2 strains showed category discrepant results although they are concordants in essential agreement (see detail in table 7).
  There were no very major errors observed.

ETEST® FTB / BMD		ETEST S	ETEST R	ETEST Total
BMD	S	111	2	113
	R	0	13	13
	Total	111	15	126

ETEST® FTB / BMD	%	Number of strains	Total
Category agreement	**98,4**	124	126
Major Error	**1,8**	2	113
Very Major Error	**0,0**	0	13

Tables 6a and 6b : Category agreement between ETEST® FTB and BMD

Species	Resistance profile	ETEST® FTB MIC (µg/mL)	BMD FTB MIC (µg/mL)	ETEST® category	BMD category
Escherichia coli	Carbapenemase (IMP)	32	16	R	S
Escherichia coli	Carbapenemase (NDM)	32	16	R	S

Table 7 : Detail of discrepant strains in terms of category agreement

CONCLUSION

ETEST® FTB performed similarly to the CLSI reference BMD method and MIC endpoints for both methods were generally easy to read. With a 15 doubling dilution range and simplicity of use, ETEST® FTB may become a valuable tool for MIC testing to inform clinical drug use for *Enterobacterales* and *P. aeruginosa* once cefepime-taniborbactam is approved for clinical use. These results still need to be validated by clinical trials before review and clearance by regulatory authorities for *in vitro* diagnostic use.

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