Influence of Genotype on the Activity of Cefepime/Enmetazobactam against Beta-lactam Resistant Enterobacterales collected from Europe in 2019-2021

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INTRODUCTION

Cefepime/enmetazobactam is a novel beta-lactam/beta-lactamase inhibitor combination intended as empiric therapy for serious infections proven or suspected to be caused by Gram-negative pathogens. In a phase 3 study of complicated urinary tract infections and acute pyelonephritis, cefepime/enmetazobactam met criteria for non-inferiority and superiority compared to piperacillin/tazobactam (1).

The purpose of this study was to assess the *in vitro* activity of cefepime/enmetazobactam against recent, genotyped beta-lactamase-producing Enterobacterales clinical isolates.

MATERIALS AND METHODS

A total of 453 Enterobacterales clinical isolates from a global collection from 2019 to 2021 screened positive for beta-lactamase-genes using a PCR method (2). These originated from Italy (IT), France (FR), Germany (DE), Spain (ES), the United Kingdom (UK), Belgium (BE), Sweden (SW), the Netherlands (NL and Denmark (DK) (Figure 1).

Minimum inhibitory concentrations (MICs) were determined by Clinical and Laboratory Standards Institute (CLSI) broth microdilution methodology (3).

Cefepime/enmetazobactam was tested at a fixed concentration of 8 mg/L enmetazobactam.

Antimicrobial susceptibility was determined using the 2022 European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints 43). Cefepime/enmetazobactam breakpoints are yet to be established, so the EUCAST cefepime breakpoints of susceptible ≤1 mg/L and susceptible-increased exposure ≤4 mg/L (assigned for a cefepime dose of 2 g every 8 hours) were used for comparative purposes.

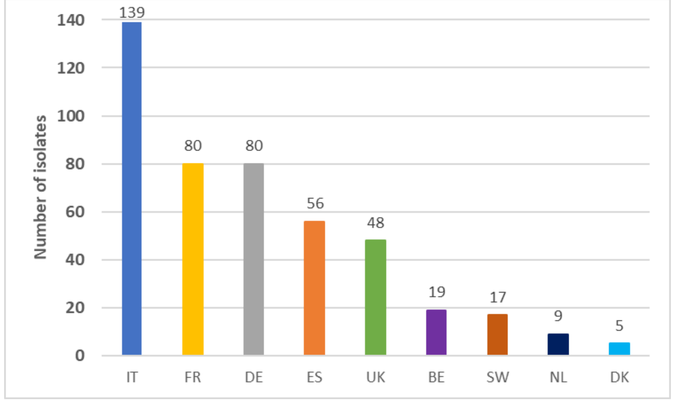

FIGURE 1: Isolate country of origin

RESULTS

TABLE 1: Summary of activity of cefepime/enmetazobactam and comparators against ESBL-positive Enterobacterales.

Antimicrobial	ESBL Enterobacterales (n=252)				ESBL *E. coli* (n=118)				ESBL *K. pneumoniae* (n=110)				ESBL *E. cloacae* (n=17)			
	MIC_{50}	MIC_{90}	%SUS	%SIE	MIC_{50}	MIC_{90}	%SUS	%SIE	MIC_{50}	MIC_{90}	%SUS	%SIE	MIC_{50}	MIC_{90}	%SUS	%SIE
Cefepime	>16	>16	4.0	20.6	>16	>16	0.0	21.2	>16	>16	0.9	10.0	2	>16	41.2	70.6
Cefepime/enmetazobactam (8 mg/L)	**0.06**	**0.25**	**98.4**	**100.0**	**0.06**	**0.12**	**99.2**	**100.0**	**0.06**	**0.5**	**97.3**	**100.0**	**0.25**	**1**	**100.0**	**100.0**
Ceftazidime	16	>16	2.4	16.7	16	>16	4.2	24.6	>16	>16	0.0	4.5	16	>16	0.0	41.2
Ceftazidime/avibactam (4 mg/L)	0.25	1	100.0	-	0.25	1	100.0	-	0.25	1	100.0	-	0.5	1	100.0	-
Ceftriaxone	>4	>4	1.6	1.6	>4	>4	0.0	0.0	>4	>4	0.0	0.0	>4	>4	17.6	17.6
Meropenem	0.03	0.06	98.8	100.0	0.03	0.03	100.0	100.0	0.03	0.12	97.3	100.0	0.03	0.12	100.0	100.0
Piperacillin/tazobactam (4 mg/L)	4	64	63.5	-	4	32	78.0	-	8	64	53.6	-	16	>128	23.5	-

$MIC_{50/90}$, concentration required to inhibit 50%/90% of isolates; SUS, susceptible; SIE, susceptible increased exposure.

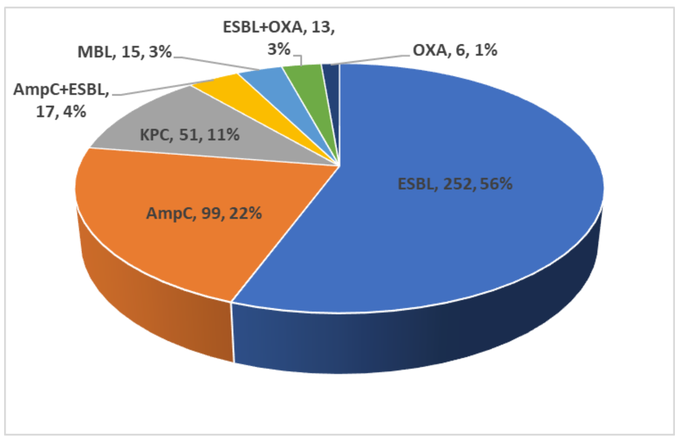

FIGURE 2: Genotype distribution (n, %)

TABLE 2: Summary of activity of cefepime/enmetazobactam and comparators against AmpC- and KPC-positive Enterobacterales

Antimicrobial	AmpC+ESBL Enterobacterales (n=17)				AmpC Enterobacterales (n=99)				AmpC *E. cloacae* (n=46				AmpC *C. freundii* (n=29)				KPC Enterobacterales (n=51)			
	MIC_{50}	MIC_{90}	%SUS	%SIE	MIC_{50}	MIC_{90}	%SUS	%SIE	MIC_{50}	MIC_{90}	%SUS	%SIE	MIC_{50}	MIC_{90}	%SUS	%SIE	MIC_{50}	MIC_{90}	%SUS	%SIE
Cefepime	>16	>16	17.6	23.5	1	4	61.6	94.9	2	4	45.7	93.5	1	2	75.9	100.0	>16	>16	2.0	2.0
Cefepime/enmetazobactam (8 mg/L)	**0.12**	**1**	**100.0**	**100.0**	**0.25**	**1**	**96.0**	**99.0**	**0.5**	**1**	**93.5**	**97.8**	**0.25**	**0.5**	**100.0**	**100.0**	**64**	**>64**	**17.6**	**27.5**
Ceftazidime	>16	>16	0.0	0.0	>16	>16	9.1	12.1	>16	>16	6.5	10.9	>16	>16	13.8	13.8	>16	>16	2.0	2.0
Ceftazidime/avibactam (4 mg/L)	0.5	2	100.0	-	0.5	2	100.0	-	0.5	2	100.0	-	0.5	1	100.0	-	2	4	100.0	-
Ceftriaxone	>4	>4	0.0	0.0	>4	>4	9.1	10.1	>4	>4	2.2	4.3	>4	>4	13.8	13.8	>4	>4	0.0	0.0
Meropenem	0.06	0.06	100.0	100.0	0.06	0.12	99.0	100.0	0.06	0.12	97.8	100.0	0.06	0.12	100.0	100.0	>4	>4	3.9	100.0
Piperacillin/tazobactam (4 mg/L)	16	64	35.3	-	64	>128	19.2	-	64	>128	10.9	-	32	>128	13.8	-	>128	>128	0.0	-

$MIC_{50/90}$, concentration required to inhibit 50%/90% of isolates; Sus, susceptible; Sus (IE), susceptible increased exposure. 50 out of 51 KPC isolates were *K. pneumoniae.*

TABLE 3: Summary of activity of cefepime/enmetazobactam and comparators against ESBL+OXA- and MBL-positive Enterobacterales

Antimicrobial	ESBL+OXA Enterobacterales (n=13)				ESBL+OXA *K. pneumoniae* (n=10)				MBL Enterobacterales (n=15)			
	MIC_{50}	MIC_{90}	%SUS	%SIE	MIC_{50}	MIC_{90}	%SUS	%SIE	MIC_{50}	MIC_{90}	%SUS	%SIE
Cefepime	>16	>16	0.0	0.0	>16	>16	0.0	0.0	>16	>16	0.0	0.0
Cefepime/enmetazobactam (8 mg/L)	**0.5**	**16**	**76.9**	**84.6**	**0.5**	**4**	**80.0**	**90.0**	**64**	**>64**	**0.0**	**0.0**
Ceftazidime	>16	>16	0.0	7.7	>16	>16	0.0	0.0	>16	>16	0.0	0.0
Ceftazidime/avibactam (4 mg/L)	0.5	2	100.0	-	0.5	2	100.0	-	>16	>16	0.0	-
Ceftriaxone	>4	>4	0.0	0.0	>4	>4	0.0	0.0	>4	>4	0.0	0.0
Meropenem	2	>4	69.2	100.0	2	>4	60.0	100.0	>4	>4	13.3	100.0
Piperacillin/tazobactam (4 mg/L)	>128	>128	0.0	-	>128	>128	0.0	-	>128	>128	0.0	-

$MIC_{50/90}$, concentration required to inhibit 50%/90% of isolates; Sus, susceptible; Sus (IE), susceptible increased exposure.

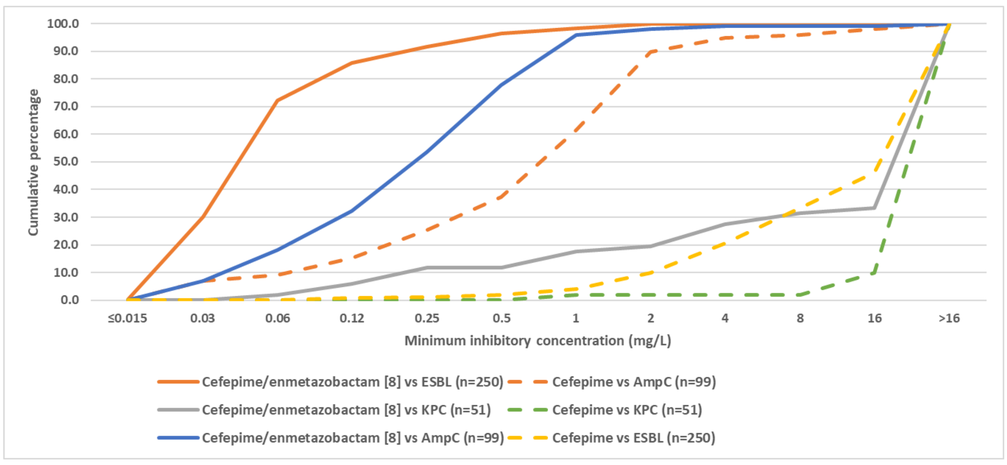

FIGURE 3: cumulative percentage susceptibility of cefepime/enmetazobactam and cefepime against ESBL-, AmpC- and KPC-positive Enterobacterales isolates

RESULTS SUMMARY

- The most common beta-lactamases identified were ESBLs (252 isolates), followed by AmpCs (99 isolates) and KPCs (51 isolates).
- The addition of enmetazobactam restored cefepime activity against ESBL-positive isolates to 98.4% susceptibility (100% at increased exposure).
- Similarly, enmetazobactam greatly enhanced the activity of cefepime against isolates encoding AmpC, AmpC+ESBL and ESBL+OXA genes.
- Expectedly, enmetazobactam only slightly restored the activity of cefepime against isolates with a KPC and has no effect on isolates carrying a metallo-beta-lactamase.

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CONCLUSIONS

- In this study, the most common beta-lactamases found to be currently circulating in Europe are ESBLs and AmpCs.
- The addition of enmetazobactam restored the activity of cefepime against these isolates and indicate the potential utility of cefepime/enmetazobactam against ESBL-producing Enterobacterales.

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