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Antimicrobial Spectrum and Potency of Cefepime Combined with Sulbactam when Tested with Four Candidate Ratio or Fixed Concentration Formulations

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ABSTRACT

Background: We evaluated the in vitro activity of sulbactam (SUL) when tested alone and in combination with cefepime (CPM) against recent representative clinical isolates producing hydrolytic enzymes.
Methods: CPM/SUL activity was determined by the broth microdilution method against 319 selected clinical pathogens, including 83 Gram-positive (GP) cocci, 133 Enterobacteriaceae (ENT), 66 non-fermentative (NF) Gram-negative (GN) bacilli and 37 anaerobes selected according to resistance (R) phenotypes. CPM/SUL was tested by reference CLSI methods at 1:1 and 2:1 ratios and at fixed SUL concentrations of 2 and 4 µg/ml. Results were compared with those of each drug tested alone and with piperacillin/tazobactam (P/T; fixed conc. of 4 µg/ml).
Results: Against GP strains CPM activity remained the same or it was slightly reduced (antagonistic) when SUL was added, but these adverse interactions did not reduce CPM spectrum against these species (streptococci). Against GN aerobes, the addition of SUL to CPM improved the potency and/or the number of susceptible (S) strains. The most striking synergy was observed among ESBL-producing strains. S to CPM increased from 50.0 to 83.3-91.7% among ESBL-producing *E. coli*, while among ESBL-producing *Klebsiella* spp. the MIC_{90} decreased from 32 to 8 µg/ml. SUL markedly expanded CPM activity against *Acinetobacter* spp. (20 to 80% S) and *S. maltophilia* (6 strains tested), but against *P. aeruginosa* the expansion of CPM spectrum was limited. CPM/SUL was generally more potent than P/T against GN aerobic strains. SUL also improved CPM spectrum against anaerobes (from 16 to 96% S). The various formulations used produced similar results, but 2:1 and fixed 4 µg/ml seem preferred.
Conclusions: CPM/SUL combination has increased activity over CPM against several groups of clinical important organisms, including ESBL-producing ENT, some NF-GN and anaerobes. This combination seems worthy of continued clinical development as a needed broad-spectrum agent against GN bacilli.

INTRODUCTION

Cefepime is a broad spectrum "fourth-generation" cephalosporin. It is highly active against Gram-negative bacteria due to rapid penetration into the periplasmic space (zwitterion) and high stability against ß-lactamases, especially AmpC and some carbapenemases, such as NmcA.

Sulbactam is a ß-lactamase-inhibitor extensively used in combination with other ß-lactams, such as ampicillin and cefoperazone outside of North America. Sulbactam's spectrum of ß-lactamase inhibition is similar to that of tazobactam and slightly greater than clavulanic acid. In addition, sulbactam exhibits direct antimicrobial activity against *Acinetobacter* spp. Its mechanism of antimicrobial activity against *Acinetobacter* spp. may be related to its ability to bind essential PBPs or to alter the permeability of outer membrane of Gram-negative bacilli, which results in the leakage of ß-lactamases and thus better penetration by other antimicrobial agents.

In the present study, we evaluate the in vitro activity of sulbactam when alone and in various combinations with cefepime tested against a selected collection of clinical bacterial isolates producing hydrolytic enzymes.

MATERIALS AND METHODS

Antimicrobial combinations.

- Antimicrobial agents tested against Gram-negative aerobic bacteria, enterococci and staphylococci (range):
  - Cefepime (0.03 - 64 µg/ml)
  - Sulbactam (0.03 - 64 µg/ml)
  - Cefepime/sulbactam (fixed concentration, 0.03/2 - 64/2 µg/ml)
  - Cefepime/sulbactam (fixed concentration, 0.03/4 - 64/4 µg/ml)
  - Cefepime/sulbactam (1:1 ratio, 0.03/0.03 - 64/64 µg/ml)
  - Cefepime/sulbactam (2:1 ratio, 0.03/0.016 - 64/32 µg/ml)
  - Piperacillin/tazobactam (fixed concentration, 0.12/4 - 256/4 µg/ml)
  - Piperacillin (0.25 - 256 µg/ml)
- Antimicrobial agents tested against *Streptococcus* spp. (range):
  - Cefepime (0.004 - 8 µg/ml)
  - Sulbactam (0.004 - 8 µg/ml)
  - Cefepime/sulbactam (fixed concentration, 0.004/2 - 8/2 µg/ml)
  - Cefepime/sulbactam (fixed concentration, 0.004/4 - 8/4 µg/ml)
  - Cefepime/sulbactam (1:1 ratio, 0.004/0.004 - 8/8 µg/ml)
  - Cefepime/sulbactam (2:1 ratio, 0.004/0.002 - 8/4 µg/ml)
  - Piperacillin/tazobactam (fixed concentration, 0.016/4 - 32/4 µg/ml)
  - Piperacillin (0.03 - 32 µg/ml)
- Antimicrobial agents tested against anaerobic bacteria (ranges):
  - Cefepime (0.03 - 64 µg/ml)
  - Sulbactam (0.03 - 64 µg/ml)
  - Cefepime/sulbactam (fixed concentration, 0.03/4 - 64/4 µg/ml)
  - Cefepime/sulbactam (2:1 ratio, 0.03/0.016 - 64/32 µg/ml)
  - Piperacillin/tazobactam (fixed concentration, 0.03/4 - 64/4 µg/ml)

Susceptibility testing. Aerobic bacteria were tested by reference broth microdilution methods while anaerobic bacteria were tested by the agar dilution method. All tests were performed according to the Clinical and Laboratory Standards Institute (CLSI) guidelines.

Organisms. A total of 319 organism were tested:

- Gram-positive bacteria (number of strains)
  - *S. aureus* (23; penicillinase-positive [13] and penicillinase-negative [10])
  - Coagulase-negative staphylococci (10)
  - *Enterococcus* spp. (10)
  - ß-haemolytic streptococci (10)
  - viridans group streptococci (10)
  - *S. pneumoniae* (20)
- Gram-negative enteric bacilli (number of strains)
  - *E. coli* (32; wild-type [10], ESBL-positive [12] and ESBL-negative [10])
  - *Klebsiella* spp. (30; wild-type [10], ESBL-positive [10] and ESBL-negative [10])
  - *C. freundii* (10)
  - *Enterobacter* spp. (20; wild-type [10] and AmpC-producers [10])
  - *P. mirabilis* (10)
  - *M. morganii* (10)
  - Indole-positive Proteae (11)
  - *S. marcescens* (10)
- Gram-negative non-enteric bacteria (number of strains)
  - *P. aeruginosa* (40; wild-type [20] and piperacillin/tazobactam or ceftazidime-resistant [20])
  - *Acinetobacter* spp. (20; wild-type [10] and multidrug-resistant isolates [10])
  - *S. maltophilia* (six)
- Gram-negative anaerobic bacteria (25 strains)
- Gram-positive anaerobic bacteria (12 strains)

RESULTS

- Sulbactam did not alter cefepime activity against staphylococcal strains, independent of ß-lactamase production. Cefepime + sulbactam showed potency and spectrum most similar to piperacillin/tazobactam.
- Against enterococcal species (10 strains tested), piperacillin ± tazobactam was four-fold more active than cefepime ± sulbactam ($MIC_{50/90}$, 16 µg/ml; intermediate susceptibility). All strains were ampicillin, penicillin and piperacillin-susceptible, but resistant to sulbactam.
- Against ß-haemolytic streptococci the MIC_{50} of cefepime (0.06 µg/ml) increased four-fold in the presence of sulbactam (0.25 µg/ml). Similarly, piperacillin alone had an MIC_{90} of 0.06 µg/ml, but with piperacillin/tazobactam the MIC_{90} increased to 0.25 µg/ml e.g. equal to cefepime with sulbactam at all formulations tested. These unusual findings were considered "antagonism" for both inhibitor combinations.
- Like ß-haemolytic streptococci, viridans group streptococci isolates showed an antagonistic interaction of cefepime + sulbactam. Cefepime MIC_{90} results (0.5 µg/ml) were elevated to 4 µg/ml by sulbactam. A four-fold increase in the piperacillin MIC was noted when tazobactam was added (8 to 32 µg/ml); antagonistic interaction.
- *S. pneumoniae* were best inhibited by cefepime alone while antagonism was observed with cefepime + sulbactam and piperacillin + tazobactam (two- to four-fold MIC increases for both). However, all cefepime + sulbactam MIC results remained at ≤ 2 µg/ml, indicating susceptibility or intermediate categorization.
- "Wild-type" *E. coli* and *Klebsiella* strains showed a modest decrease (two-fold) in the cefepime MIC with sulbactam, but only with the fixed concentration tests (Table 1). Cefepime ± sulbactam was 100.0% effective by all tests utilized. Synergy between cefepime and sulbactam was noted for the ESBL-producing *E. coli* and *Klebsiella* spp. strains (Table 1). All sulbactam tests with cefepime lowered MIC_{90} values to the susceptible or intermediate category (≤ 16 µg/ml).
- The ESBL phenotypes having a AmpC mechanism were generally cefepime-susceptible (90.0%) and the potency of cefepime was not increased by the addition of sulbactam (Table 1). Piperacillin/tazobactam activity was poor against these organisms.
- Cefepime activity against *C. freundii, Enterobacter* spp., *P. mirabilis, M. morganii*, Indole-positive Proteae and *Serratia* spp. was slightly enhanced by sulbactam (Table 1). In general, cefepime alone was more active than piperacillin/tazobactam against these pathogens.
- For the piperacillin/tazobactam- and/or ceftazidime-resistant *P. aeruginosa* (Table 2), the addition of sulbactam slightly expanded cefepime susceptibility from 0.0% to 15.0 - 50.0% depending on the test used.
- Sulbactam significantly expanded cefepime activity against MDR *Acinetobacter* spp. (20.0 to 80.0% susceptible), but only 10.0% of these strains were susceptible to piperacillin/tazobactam at ≤ 16/4 µg/ml (Table 2).
- A synergistic or additive effect was noted between cefepime and sulbactam for the limited sample of *S. maltophilia* isolates tested. Cefepime resistance rates were reduced by one-half by the addition of sulbactam, a level comparable to piperacillin/tazobactam.
- Against anaerobic bacteria, two combination formulation tests for cefepime + sulbactam were tested and with the 2:1 ratio MIC results, the cefepime susceptibility rate was increased from only 16.0 to 96.0%. Piperacillin was excellent versus these Gram-negative (*B. fragilis* group) anaerobes, having a susceptibility rate of 100.0% and a 16/4 µg/ml MIC_{90} (Table 3).

Table 1. Activity of antimicrobial agents tested against Enterobacteriaceae.

Organism/antimicrobial agent (no. tested)	MIC (µg/ml) 50%	90%	Range	%susceptible/resistant[a]
Wild-type *E. coli* (10)				
Cefepime	0.12	0.5	≤0.03-0.5	100.0/0.0
Sulbactam	32	64	16->64	-/-
Cefepime/sulbactam (fixed 2 µg/ml)	0.12	0.25	≤0.03-0.25	100.0/0.0
Cefepime/sulbactam (fixed 4 µg/ml)	0.06	0.25	≤0.03-0.25	100.0/0.0
Cefepime/sulbactam (1:1 ratio)	0.12	0.5	≤0.03-0.5	100.0/0.0
Cefepime/sulbactam (2:1 ratio)	0.12	0.5	≤0.03-0.5	100.0/0.0
Piperacillin/tazobactam	4	128	2->256	70.0/20.0
Piperacillin	256	>256	2->256	10.0/80.0
ESBL-confirmed *E. coli* (12)				
Cefepime	8	>64	0.12->64	50.0/33.3
Sulbactam	32	>64	32->64	-/-
Cefepime/sulbactam (fixed 2 µg/ml)	2	8	0.06-64	91.7/8.3
Cefepime/sulbactam (fixed 4 µg/ml)	1	8	≤0.03-64	91.7/8.3
Cefepime/sulbactam (1:1 ratio)	2	8	0.06-32	91.7/8.3
Cefepime/sulbactam (2:1 ratio)	4	16	0.12-32	83.3/8.3
Piperacillin/tazobactam	16	>256	4->256	58.3/41.7
Piperacillin	>256	>256	32->256	0.0/91.7
ESBL-unconfirmed *E. coli* (10)				
Cefepime	0.5	1	0.12-2	100.0/0.0
Sulbactam	64	64	32->64	-/-
Cefepime/sulbactam (fixed 2 µg/ml)	0.25	2	0.06-2	100.0/0.0
Cefepime/sulbactam (fixed 4 µg/ml)	0.25	1	0.06-2	100.0/0.0
Cefepime/sulbactam (1:1 ratio)	0.5	1	0.12-2	100.0/0.0
Cefepime/sulbactam (2:1 ratio)	0.5	2	0.12-2	100.0/0.0
Piperacillin/tazobactam	16	128	8->256	70.0/20.0
Piperacillin	256	>256	32->256	0.0/70.0
Wild-type *Klebsiella* spp. (10)				
Cefepime	0.06	0.25	≤0.03-0.25	100.0/0.0
Sulbactam	32	64	>64	-/-
Cefepime/sulbactam (fixed 2 µg/ml)	0.06	0.12	≤0.03-0.25	100.0/0.0
Cefepime/sulbactam (fixed 4 µg/ml)	0.06	0.12	≤0.03-0.25	100.0/0.0
Cefepime/sulbactam (1:1 ratio)	0.12	0.25	≤0.03-0.5	100.0/0.0
Cefepime/sulbactam (2:1 ratio)	0.12	0.12	≤0.03-0.25	100.0/0.0
Piperacillin/tazobactam	8	32	4->256	80.0/10.0
Piperacillin	32	>256	4->256	40.0/20.0
ESBL-confirmed *Klebsiella* spp. (10)				
Cefepime	2	32	0.5-32	70.0/20.0
Sulbactam	64	>64	32->64	-/-
Cefepime/sulbactam (fixed 2 µg/ml)	2	8	≤0.03-8	100.0/0.0
Cefepime/sulbactam (fixed 4 µg/ml)	2	8	≤0.03-8	100.0/0.0
Cefepime/sulbactam (1:1 ratio)	2	8	0.5-8	100.0/0.0
Cefepime/sulbactam (2:1 ratio)	2	8	0.5-8	100.0/0.0
Piperacillin/tazobactam	256	>256	4->256	30.0/60.0
Piperacillin	>256	>256	128->256	0.0/100.0
ESBL-unconfirmed *Klebsiella* spp. (10)				
Cefepime	0.5	2	0.12-32	90.0/10.0
Sulbactam	64	>64	32->64	-/-
Cefepime/sulbactam (fixed 2 µg/ml)	0.25	2	0.12-16	90.0/0.0
Cefepime/sulbactam (fixed 4 µg/ml)	0.25	2	0.12-16	90.0/0.0
Cefepime/sulbactam (1:1 ratio)	0.5	4	0.12-8	90.0/0.0
Cefepime/sulbactam (2:1 ratio)	0.5	2	0.06-16	90.0/0.0
Piperacillin/tazobactam	32	>256	16->256	10.0/30.0
Piperacillin	>256	>256	32->256	0.0/70.0
C. freundii (10)				
Cefepime	0.06	1	≤0.03-1	100.0/0.0
Sulbactam	32	64	32-64	-/-
Cefepime/sulbactam (fixed 2 µg/ml)	0.12	0.5	≤0.03-0.5	100.0/0.0
Cefepime/sulbactam (fixed 4 µg/ml)	0.12	0.25	≤0.03-0.5	100.0/0.0
Cefepime/sulbactam (1:1 ratio)	0.25	0.5	≤0.03-0.5	100.0/0.0
Cefepime/sulbactam (2:1 ratio)	0.25	1	≤0.03-1	100.0/0.0
Piperacillin/tazobactam	16	64	2-128	60.0/10.0
Piperacillin	128	>256	2->256	40.0/60.0
Enterobacter spp. (10)				
Cefepime	0.12	0.5	≤0.03-0.5	100.0/0.0
Sulbactam	64	>64	32->64	-/-
Cefepime/sulbactam (fixed 2 µg/ml)	0.12	0.25	≤0.03-1	100.0/0.0
Cefepime/sulbactam (fixed 4 µg/ml)	0.12	0.5	≤0.03-0.5	100.0/0.0
Cefepime/sulbactam (1:1 ratio)	0.12	0.25	≤0.03-0.5	100.0/0.0
Cefepime/sulbactam (2:1 ratio)	0.12	0.5	≤0.03-0.5	100.0/0.0
Piperacillin/tazobactam	8	16	2-16	100.0/0.0
Piperacillin	8	16	4-32	90.0/0.0
Ceftazidime-resistant *Enterobacter* spp. (10)				
Cefepime	2	16	0.25-16	80.0/0.0
Sulbactam	64	>64	32->64	-/-
Cefepime/sulbactam (fixed 2 µg/ml)	2	16	0.25-16	80.0/0.0
Cefepime/sulbactam (fixed 4 µg/ml)	1	8	0.06-16	90.0/0.0
Cefepime/sulbactam (1:1 ratio)	1	8	0.25-8	100.0/0.0
Cefepime/sulbactam (2:1 ratio)	2	16	0.25-16	80.0/0.0
Piperacillin/tazobactam	64	>256	4->256	10.0/50.0
Piperacillin	256	>256	64->256	0.0/90.0
P. mirabilis (10)				
Cefepime	≤0.03	0.06	≤0.03-2	100.0/0.0
Sulbactam	64	64	64->64	-/-
Cefepime/sulbactam (fixed 2 µg/ml)	≤0.03	0.06	≤0.03-1	100.0/0.0
Cefepime/sulbactam (fixed 4 µg/ml)	≤0.03	0.06	≤0.03-0.5	100.0/0.0
Cefepime/sulbactam (1:1 ratio)	≤0.03	0.06	≤0.03-1	100.0/0.0
Cefepime/sulbactam (2:1 ratio)	≤0.06	0.06	≤0.03-2	100.0/0.0
Piperacillin/tazobactam	0.5	1	≤0.12-16	100.0/0.0
Piperacillin	0.5	>256	≤0.25->256	70.0/30.0
M. morganii (10)				
Cefepime	≤0.03	0.06	≤0.03-0.25	100.0/0.0
Sulbactam	>64	>64	64->64	-/-
Cefepime/sulbactam (fixed 2 µg/ml)	≤0.03	≤0.03	≤0.03-0.12	100.0/0.0
Cefepime/sulbactam (fixed 4 µg/ml)	≤0.03	≤0.03	≤0.03-0.12	100.0/0.0
Cefepime/sulbactam (1:1 ratio)	≤0.03	0.06	≤0.03-0.25	100.0/0.0
Cefepime/sulbactam (2:1 ratio)	≤0.03	≤0.03	≤0.03-0.25	100.0/0.0
Piperacillin/tazobactam	0.5	1	0.25-8	100.0/0.0
Piperacillin	2	8	1-64	90.0/0.0
Indole-positive Proteae (11)				
Cefepime	≤0.03	0.12	≤0.03-0.12	100.0/0.0
Sulbactam	64	>64	32->64	-/-
Cefepime/sulbactam (fixed 2 µg/ml)	≤0.03	0.12	≤0.03-0.25	100.0/0.0
Cefepime/sulbactam (fixed 4 µg/ml)	≤0.03	0.12	≤0.03-0.12	100.0/0.0
Cefepime/sulbactam (1:1 ratio)	≤0.03	0.12	≤0.03-0.12	100.0/0.0
Cefepime/sulbactam (2:1 ratio)	≤0.03	0.12	≤0.03-0.12	100.0/0.0
Piperacillin/tazobactam	1	4	0.5-16	100.0/0.0
Piperacillin	2	16	0.5-32	90.9/0.0
S. marcescens (10)				
Cefepime	1	4	≤0.03-32	90.0/10.0
Sulbactam	>64	>64	64->64	-/-
Cefepime/sulbactam (fixed 2 µg/ml)	0.25	1	≤0.03-32	90.0/10.0
Cefepime/sulbactam (fixed 4 µg/ml)	0.12	0.5	≤0.03-32	90.0/10.0
Cefepime/sulbactam (1:1 ratio)	0.5	2	≤0.03-16	90.0/0.0
Cefepime/sulbactam (2:1 ratio)	0.5	2	≤0.03-32	90.0/10.0
Piperacillin/tazobactam	2	8	1-256	90.0/10.0
Piperacillin	128	>256	2->256	40.0/60.0

a. Criteria as published by the CLSI (2005).

Table 2. Activity of antimicrobial agents tested against non-fermentative Gram-negative bacilli.

Organism/antimicrobial agent (no. tested)	MIC (µg/ml) 50%	90%	Range	%susceptible/resistant[a]
Wild-type *P. aeruginosa* (20)				
Cefepime	2	8	1-8	100.0/0.0
Sulbactam	>64	>64	>64	-/-
Cefepime/sulbactam (fixed 2 µg/ml)	2	8	1-32	95.0/5.0
Cefepime/sulbactam (fixed 4 µg/ml)	2	8	1-8	100.0/0.0
Cefepime/sulbactam (1:1 ratio)	2	8	1-8	100.0/0.0
Cefepime/sulbactam (2:1 ratio)	2	8	1-8	100.0/0.0
Piperacillin/tazobactam	8	16	2-64	100.0/0.0
Piperacillin	8	8	2-64	100.0/0.0
Pip/tazo- and/or ceftazidime-resist. *P. aeruginosa* (20)				
Cefepime	16	64	16->64	0.0/30.0
Sulbactam	>64	>64	64->64	-/-
Cefepime/sulbactam (fixed 2 µg/ml)	16	64	8->64	15.0/25.0
Cefepime/sulbactam (fixed 4 µg/ml)	16	64	8->64	20.0/25.0
Cefepime/sulbactam (1:1 ratio)	8	32	8-64	50.0/20.0
Cefepime/sulbactam (2:1 ratio)	16	32	8->64	25.0/20.0
Piperacillin/tazobactam	256	>256	128->256	0.0/100.0
Piperacillin	>256	>256	256->256	0.0/100.0
Wild-type *Acinetobacter* spp. (10)				
Cefepime	2	16	1-16	80.0/0.0
Sulbactam	1	2	0.5-16	-/-
Cefepime/sulbactam (fixed 2 µg/ml)	≤0.03	≤0.03	≤0.03-16	90.0/0.0
Cefepime/sulbactam (fixed 4 µg/ml)	≤0.03	≤0.03	≤0.03-16	90.0/0.0
Cefepime/sulbactam (1:1 ratio)	0.5	1	0.5-8	100.0/0.0
Cefepime/sulbactam (2:1 ratio)	1	1	0.5-16	90.0/0.0
Piperacillin/tazobactam	4	16	≤0.12-64	90.0/0.0
Piperacillin	32	64	16-128	40.0/10.0
MDR *Acinetobacter* spp. (10)				
Cefepime	32	>64	2->64	20.0/70.0
Sulbactam	16	64	2->64	-/-
Cefepime/sulbactam (fixed 2 µg/ml)	4	32	≤0.03->64	60.0/40.0
Cefepime/sulbactam (fixed 4 µg/ml)	0.5	32	≤0.03->64	60.0/40.0
Cefepime/sulbactam (1:1 ratio)	4	16	1-64	80.0/10.0
Cefepime/sulbactam (2:1 ratio)	4	16	1-64	60.0/10.0
Piperacillin/tazobactam	256	>256	16->256	10.0/70.0
Piperacillin	>256	>256	256->256	0.0/100.0
S. maltophilia (6)				
Cefepime	32	-	16-64	0.0/66.7
Sulbactam	>64	-	>64	-/-
Cefepime/sulbactam (fixed 2 µg/ml)	16	-	8-64	16.7/50.0
Cefepime/sulbactam (fixed 4 µg/ml)	16	-	8-32	16.7/33.3
Cefepime/sulbactam (1:1 ratio)	8	-	8-32	50.0/33.3
Cefepime/sulbactam (2:1 ratio)	16	-	8-32	33.3/33.3
Piperacillin/tazobactam	32	-	16->256	16.7/33.3
Piperacillin	128	-	64->256	0.0/83.3

a. Criteria as published by the CLSI (2005).

Table 3. Activity of antimicrobial agents tested against anaerobes.

Organism/antimicrobial agent (no. tested)	MIC (µg/ml) 50%	90%	Range	%susceptible/resistant[a]
Gram-negative (25)[d]				
Cefepime	>64	>64	0.25->64	16.0/68.0
Sulbactam	16	32	0.5-32	-/-
Cefepime/sulbactam (fixed 2 µg/ml)	NT[c]	NT	NT	-/-
Cefepime/sulbactam (fixed 4 µg/ml)	2	64	≤0.03->64	72.0/12.0
Cefepime/sulbactam (1:1 ratio)	NT	NT	NT	-/-
Cefepime/sulbactam (2:1 ratio)	4	16	0.06-32	96.0/0.0
Piperacillin/tazobactam	0.5	16	≤0.03-32	100.0/0.0
Piperacillin	NT	NT	NT	-/-
Gram-positive (25)[d]				
Cefepime	1	2	0.12-8	100.0/0.0
Sulbactam	8	>64	4->64	-/-
Cefepime/sulbactam (fixed 2 µg/ml)	NT[c]	NT	NT	-/-
Cefepime/sulbactam (fixed 4 µg/ml)	0.25	1	≤0.03-4	100.0/0.0
Cefepime/sulbactam (1:1 ratio)	NT	NT	NT	-/-
Cefepime/sulbactam (2:1 ratio)	1	4	0.25-4	100.0/0.0
Piperacillin/tazobactam	0.12	0.25	≤0.03-2	100.0/0.0
Piperacillin	NT	NT	NT	-/-

a. Criteria as published by the CLSI (2005).
b. Includes: *Bacteroides caccae* (one strain), *B. eggerthii* (one strain), *B. fragilis* (12 strains), *B. thetaiotaomicron* (three strains), *B. uniformis* (one strain), *Fusobacterium necrophorum* (one strain), *Fusobacterium* spp. (one strain), *Prevotella bivia* (two strains), *P. melaninogenica* (one strain) and *P. oralis* (two strains).
c. NT = not tested.
d. Includes: *Clostridium innocuum* (one strain), *C. perfringens* (four strains), *C. ramosum* (one strain), *Peptostreptococcus micros* (one strain), *Peptostreptococcus* spp. (two strains), *Propionibacterium acnes* (one strain) and *Propionibacterium* spp. (two strains).

CONCLUSIONS

- Generally, the addition of sulbactam to cefepime improved either the potency or the number of susceptible strains using the current CLSI cefepime breakpoint concentrations. Interactions varied from antagonism (streptococci) to synergy, but adverse interactions did not reduce the overall cefepime spectrum of activity.
- The various formulation tests (fixed concentrations [2 and 4 µg/ml] or ratios [1:1 and 2:1]) produced similar results. The fixed 4 µg/ml and 2:1 ratio tests would be preferred.
- The greatest advantages of cefepime + sulbactam were:
  - Greater activity against ESBL-producing Enterobacteriaceae;
  - Greater activity against MDR non-fermentative Gram-negative bacilli (*P. aeruginosa* and *S. maltophilia*);
  - Direct antimicrobial effects of sulbactam versus *Acinetobacter* spp.; and
  - Expanded spectrum against anaerobic Gram-negative species.
- This combination seems worthy of continued investigations at dosages of cefepime + sulbactam of 2 + 1 gram BID or TID. PK/PD analyses and Monte Carlo simulations should further focus the dosing directed by the target attainment for this promising combination.

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