

Sulbactam Enhances in vitro Activity of β -Lactam Antibiotics Against *Acinetobacter baumannii*

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Purpose: To evaluate in vitro activities of β -lactam antibiotics alone and in combination with sulbactam at different ratios against *Acinetobacter baumannii* clinical strains from China.

Methods: A total of 300 clinical isolates of *A. baumannii* were collected from 29 hospitals across China in 2018. Susceptibility to common antibiotics was assessed, and β -lactamase genes were detected. In vitro activity of ampicillin, cefoperazone and imipenem was tested alone and in combination with sulbactam at the ratios of 2:1, 1:1, 1:1.5, 1:2, 1:2.5 and 1:3.

Results: High resistant rates for common antibiotics were observed except tigecycline and polymyxin B. Among carbapenem-resistant *A. baumannii*, 97.3% isolates harbored *bla*_{OXA-23}. MIC₅₀ and MIC₉₀ values for sulbactam were 32 mg/L and 64 mg/L, respectively. High resistant rates for ampicillin, cefoperazone and imipenem were observed (92.3%, 93% and 85.3%, respectively). A stepwise increase in the ratio of sulbactam to partner β -lactam antibiotics led to a stepwise decrease in the MICs and a stepwise increase in the susceptible rates. The susceptible rates for imipenem-sulbactam 1:3, ampicillin-sulbactam 1:3 and cefoperazone-sulbactam 1:3 reached 16.3%, 58.3% and 91%, respectively.

Conclusion: The increasing proportion of sulbactam could enhance antimicrobial activities of imipenem-sulbactam, ampicillin-sulbactam and cefoperazone-sulbactam combinations against *A. baumannii* clinical strains in China, with cefoperazone-sulbactam as the most potent compound.

Keywords: sulbactam, ampicillin, cefoperazone, imipenem, *Acinetobacter baumannii*

Introduction

Acinetobacter baumannii is one of the most troublesome pathogens among health-care-associated infections, and it could evolve into multidrug-resistance (MDR) clones, even extensively-drug resistance (XDR) clones, which are often associated with prolonged length and increased cost of hospital stay as well as high mortality.¹ Apparently, intrinsic resistance and acquired resistance due to inappropriate administration of antimicrobial agents could be the critical reasons for the development of MDR bacteria.^{2,3}

Carbapenem-resistant *A. baumannii* (CRAB), as a matter of great concern, has been labelled as “critical pathogen” by World Health Organization (WHO) and as “urgent threat” by Centers for Disease Control and Prevention (<https://www.cdc.gov/drugresistance/biggest-threats.html>).⁴ In the China Antimicrobial Surveillance Network (www.chinets.com/Chinet), clinical isolates of *Acinetobacter* in 2019 displayed resistance rates to cefoperazone-sulbactam 2:1, ampicillin-sulbactam, imipenem and meropenem of 46.5%, 69.3%, 73.6% and 75.1%, respectively.

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Additionally, resistance rates to cefoperazone-sulbactam 1:1 and meropenem were 40.4% and 75.3%, respectively, for *Acinetobacter* isolates collected from China in 2013–2014.⁵ Despite potent in vitro antimicrobial activities, tigecycline and polymyxin demonstrate conspicuous disadvantages, such as poor distribution in tissue, low plasma concentration and obvious adverse reactions, which could preclude their clinical use.⁶ Hence, few treatment options are available against MDR *A. baumannii*.

Sulbactam, a semisynthetic penicillanic acid sulfone, acts as an inhibitor of β -lactamase and has intrinsic activity against the *Acinetobacter* genus.⁷ Previous study has found excellent antimicrobial activity of cefoperazone-sulbactam, ampicillin-sulbactam and carbapenem-sulbactam combinations against MDR *Acinetobacter* in vitro and in vivo.^{8–11} In China, commercially available are sulbactam alone, ampicillin-sulbactam in proportion of 2:1 as well as cefoperazone-sulbactam in proportion of 2:1 and 1:1. As indicated by above resistance data, the current combinations could be insufficiently effective yet. Notably, adding more sulbactam to cefoperazone-sulbactam combinations enhanced the in vitro antimicrobial activity against *Acinetobacter*.¹² Consequently, sulbactam-based combinations, as one of alternative therapeutics, are attracting attention.

Therefore, we evaluated in vitro activity of ampicillin-sulbactam, cefoperazone-sulbactam and imipenem-sulbactam at different ratios against *A. baumannii* clinical isolates in China so as to find better antimicrobial regimens.

Materials and Methods

Bacterial Strains

A total of 300 clinical isolates of *A. baumannii* were collected from 29 hospitals in 26 cities across China in 2018, including carbapenem-susceptible *A. baumannii* (CSAB) and CRAB. They were isolated from respiratory tract (199, 66.3%), skin and skin structure (21, 7.0%), blood (12, 4.0%), urine tract (8, 2.7%), cerebrospinal fluid (4, 1.3%), bile (3, 1.0%) and others (53, 17.7%). Bacteria were preliminarily identified in the isolated hospitals, and confirmed by Matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) Vitek mass spectrometry (VMS) in our hospital. The study protocol was approved by the Institutional Review Board of Huashan Hospital, Fudan University (No. 2018-408).

Antimicrobial Susceptibility Testing

The minimum inhibitory concentrations (MICs) of antimicrobial agents were determined using broth microdilution method and interpreted on the basis of the Clinical and Laboratory Standards Institute (CLSI) criteria.¹³ Sulbactam, β -lactam antibiotics, fluoroquinolones, amikacin, trimethoprim-sulfamethoxazole, tigecycline and polymyxin B were tested for comparison. Ampicillin, cefoperazone and imipenem were tested alone and in combination with sulbactam at the ratios of 2:1, 1:1, 1:1.5, 1:2, 1:2.5 and 1:3, respectively.

Given that neither CLSI nor European Committee on Antimicrobial Susceptibility Testing (EUCAST) provides the breakpoints for sulbactam-based combinations against *A. baumannii*, breakpoints for partner β -lactam antibiotics were referred carefully.¹² Specifically, the MIC breakpoints for ampicillin and ampicillin-sulbactam were as follows: S, ≤ 8 mg/L; I, 16 mg/L; R, ≥ 32 mg/L. The MIC breakpoints for cefoperazone and cefoperazone-sulbactam were those for *Enterobacteriaceae*: S, ≤ 16 mg/L; I, 32 mg/L; R, ≥ 64 mg/L. The MIC breakpoints for imipenem and imipenem-sulbactam were as follows: S, ≤ 2 mg/L; I, 4 mg/L; R, ≥ 8 mg/L.

Detection of β -Lactamase

β -lactamase genes (*bla*_{TEM}, *bla*_{SHV}, *bla*_{VEB}, *bla*_{PER}, *bla*_{GES}, *bla*_{IMP}, *bla*_{VIM}, *bla*_{KPC}, *bla*_{OXA-23} and *bla*_{OXA-58}) were detected by PCR.¹⁴ Primers sequences were obtained as previously described.¹³ Amplification was performed as follows: initial denaturation at 94°C for 5 min; 30 cycles of denaturation at 94°C for 30 s, annealing at 55°C for 30 s and elongation at 72°C for 1 min; and a final elongation step at 72°C for 5 min.

Results

Antimicrobial Susceptibility Testing for Common Antibiotics and Identification of β -Lactamase

Susceptibility rates of 300 *A. baumannii* isolates to most comparator agents were less than 30%, including β -lactams, fluoroquinolones, amikacin and trimethoprim-sulfamethoxazole, while those to tigecycline and polymyxin B were 98.7% and 99.3%, respectively (Table 1).

Among CRAB, 97.3% (256/263) isolates harbored *bla*_{OXA-23}, and *bla*_{TEM} was present in 51.7% (136/263) isolates. Neither *bla*_{TEM} nor *bla*_{OXA-23} was detected in the CSAB isolates. None of the isolates carried *bla*_{SHV},

Table I Antimicrobial Susceptibilities of *A. baumannii* Determined by the Broth Microdilution Method

Antimicrobial Agents	MIC (mg/L)			Susceptible Rate (%)	Intermediate Rate (%)	Resistant Rate (%)
	Range	MIC ₅₀	MIC ₉₀			
Ceftazidime	1→32	>32	>32	11.7	0.7	87.7
Cefepime	0.5→128	128	>128	12.0	1.7	86.3
Aztreonam	4→128	64	128	3.3	7.7	89.0
Piperacillin-tazobactam ^a	≤2→256	>256	>256	10.7	0.7	85.3
Meropenem	0.12→64	64	>64	12.0	0.7	87.3
Ciprofloxacin	≤0.06→8	>8	>8	12.0	0.0	88.0
Levofloxacin	≤0.12→16	8	>64	12.3	3.3	84.3
Amikacin	≤1→128	>128	>128	17.7	0.7	81.7
Trimethoprim-sulfamethoxazole ^b	≤0.25–32	>32	>32	28.3	/	71.7
Tigecycline	≤0.06–16	1	2	98.7	1.0	0.3
Polymyxin B	0.25–4	1	2	99.3	/	0.7

Notes: ^aFor piperacillin-tazobactam, only concentration of piperacillin is listed. ^bFor trimethoprim-sulfamethoxazole, only concentration of trimethoprim is listed.

*bla*_{VEB}, *bla*_{PER}, *bla*_{GES}, *bla*_{IMP}, *bla*_{VIM}, *bla*_{KPC} or *bla*_{OXA-58}.

Antimicrobial Susceptibility Testing for Sulbactam-Based Combinations

In vitro activities of sulbactam, ampicillin, cefoperazone, imipenem and corresponding combinations are shown in Table 2. MIC₅₀ and MIC₉₀ values for sulbactam were 32 mg/L and 64 mg/L, respectively. High resistant rates for ampicillin, cefoperazone and imipenem were observed (92.3%, 93% and 85.3%, respectively). Overall, a stepwise increase in the ratio of sulbactam to β -lactams led to a stepwise decrease in the β -lactams MIC. Small-scale increase was observed in the susceptibility for imipenem-sulbactam from 13.7% to 16.3%, while remarkable elevations were evidenced in the susceptibility for ampicillin-sulbactam and cefoperazone-sulbactam with the increasing proportion of sulbactam (from 12.3% to 58.3%, from 15% to 91%, respectively). Notably, susceptibility overtly increased from 29.3% for cefoperazone-sulbactam 1:1 to 66.3% for cefoperazone-sulbactam 1:1.5. Among all combinations, cefoperazone-sulbactam 1:3 demonstrated the most effective antibacterial activity with MIC₉₀ of 16 mg/L.

Although susceptibility rates of CSAB to ampicillin and cefoperazone were fairly low (only 10.8% and 18.9%, respectively), all CSAB isolates were susceptible to ampicillin-sulbactam combinations and cefoperazone-sulbactam combinations at all ratios (Table 3). For CRAB strains, escalating addition of sulbactam enhanced the in vitro antimicrobial activities of imipenem-sulbactam, ampicillin-sulbactam and cefoperazone-

sulbactam combinations gradually, with the susceptibility rate rising from 1.5% to 4.6%, from 0% to 52.5%, from 3.0% to 89.7%, respectively.

Discussion

A. baumannii displayed high resistance rate to imipenem (85.3%) in this study. Meanwhile, *Acinetobacter spp.* in the China Antimicrobial Surveillance Network in 2018 (www.chinets.com/Chinet) also depicted similar resistance rate to imipenem (73.2%). A 10-year-spanning study in Hungary observed an increase in resistance levels of *Acinetobacter spp.* originating from urine samples.¹⁵ Although there are emerging novel antimicrobial agents for gram-negative bacteria, few of them are effective for *A. baumannii* yet. Hence, nowadays combination therapeutics based on existing drugs could be a practical approach to treating infections caused by *A. baumannii*.

This study demonstrated again that the higher ratio of sulbactam, the more potent in vitro antimicrobial activity of imipenem-sulbactam, ampicillin-sulbactam and cefoperazone-sulbactam combinations against *A. baumannii*. Higher susceptibility rate for cefoperazone-sulbactam was also observed compared with those of imipenem-sulbactam and ampicillin-sulbactam. Cefoperazone-sulbactam 1:3 displayed best in vitro activity among all sulbactam-based combinations and showed superior activity to most comparator agents, including other β -lactams, fluoroquinolones, aminoglycosides and trimethoprim-sulfamethoxazole.

Previous study revealed that cefoperazone-sulbactam 1:1 exhibited greatest in vitro activity against CRAB,

Table 2 In vitro Activities of Imipenem-Sulbactam, Ampicillin-Sulbactam and Cefoperazone-Sulbactam Against *A. baumannii*

Drugs	MIC (mg/L) ^a			Susceptible Rate (%)	Intermediate Rate (%)	Resistant Rate (%)
	Range	MIC ₅₀	MIC ₉₀			
SUL	0.5–256	32	64	/	/	/
IPM	0.12–128	32	64	13.7	1.0	85.3
IPM-SUL 2:1	0.12–256	32	64	13.7	1.0	85.3
IPM-SUL 1:1	0.12–64	16	32	14.3	1.0	84.7
IPM-SUL 1:1.5	0.12–64	16	32	14.3	1.3	84.3
IPM-SUL 1:2	0.12–64	8	16	15.0	3.7	81.3
IPM-SUL 1:2.5	0.12–64	8	16	15.7	9.0	75.3
IPM-SUL 1:3	0.12–32	8	16	16.3	18.3	65.3
AMP	8–>256	>256	>256	1.3	6.3	92.3
AMP-SUL 2:1	1–>256	64	128	12.3	2.0	85.7
AMP-SUL 1:1	0.5–256	32	64	14.3	16.3	69.3
AMP-SUL 1:1.5	0.25–256	16	64	20.3	35.0	44.7
AMP-SUL 1:2	0.25–256	16	32	28.3	46.0	25.7
AMP-SUL 1:2.5	0.12–128	8	32	51.3	35.3	13.3
AMP-SUL 1:3	0.25–128	8	16	58.3	32.7	9.0
CFP	16–>256	>256	>256	2.3	4.7	93.0
CFP-SUL 2:1	1–>256	64	128	15.0	12.7	72.3
CFP-SUL 1:1	0.5–>256	32	64	29.3	47.3	23.3
CFP-SUL 1:1.5	0.5–256	16	32	66.3	24.0	9.7
CFP-SUL 1:2	0.25–256	16	32	78.7	14.0	7.3
CFP-SUL 1:2.5	0.25–256	16	32	86.3	8.0	5.7
CFP-SUL 1:3	0.25–128	8	16	91.0	4.3	4.7

Notes: ^aFor MIC of IPM-SUL, AMP-SUL and CFP-SUL combinations, only the concentrations of imipenem, ampicillin and cefoperazone are listed respectively.

Abbreviations: SUL, sulbactam; IPM, imipenem; IPM-SUL, imipenem-sulbactam; AMP, ampicillin; AMP-SUL, ampicillin-sulbactam; CFP, cefoperazone; CFP-SUL, cefoperazone-sulbactam.

Table 3 In vitro Activities of Ampicillin-Sulbactam and Cefoperazone-Sulbactam Against Carbapenem-Susceptible *A. baumannii* and Carbapenem-Resistant *A. baumannii*

Drugs	MIC (mg/L)		Susceptible Rate (%)	Drugs	MIC (mg/L)		Susceptible Rate (%)
	MIC ₅₀	MIC ₉₀			MIC ₅₀	MIC ₉₀	
CSAB (n=37)				CRAB (n=263)			
SUL	1	2	/	SUL	32	64	/
AMP	16	32	10.8	AMP	>256	>256	0.0
AMP-SUL 2:1	2	4	100.0	AMP-SUL 2:1	64	128	0.0
AMP-SUL 1:1	1	2	100.0	AMP-SUL 1:1	32	64	2.3
AMP-SUL 1:1.5	0.5	1	100.0	AMP-SUL 1:1.5	32	64	9.1
AMP-SUL 1:2	0.5	1	100.0	AMP-SUL 1:2	16	32	18.3
AMP-SUL 1:2.5	0.5	0.5	100.0	AMP-SUL 1:2.5	16	32	44.5
AMP-SUL 1:3	0.25	0.5	100.0	AMP-SUL 1:3	8	32	52.5
CFP	32	128	18.9	CFP	>256	>256	0.0
CFP-SUL 2:1	2	4	100.0	CFP-SUL 2:1	64	128	3.0
CFP-SUL 1:1	1	2	100.0	CFP-SUL 1:1	32	64	19.4
CFP-SUL 1:1.5	1	1	100.0	CFP-SUL 1:1.5	16	64	61.6
CFP-SUL 1:2	0.5	1	100.0	CFP-SUL 1:2	16	32	75.7
CFP-SUL 1:2.5	0.5	1	100.0	CFP-SUL 1:2.5	16	32	84.4
CFP-SUL 1:3	0.5	0.5	100.0	CFP-SUL 1:3	8	32	89.7

Abbreviations: SUL, sulbactam; IPM, imipenem; IPM-SUL, imipenem-sulbactam; AMP, ampicillin; AMP-SUL, ampicillin-sulbactam; CFP, cefoperazone; CFP-SUL, cefoperazone-sulbactam; CSAB, carbapenem-susceptible *A. baumannii*; CRAB, carbapenem-resistant *A. baumannii*.

followed by cefoperazone-sulbactam 2:1 and cefoperazone (susceptibility rate, 80.0% vs 40.0% and 0%).¹⁶ Additionally, cefoperazone-sulbactam 1:2 demonstrated antimicrobial benefit, with the susceptibility rates for cefoperazone-sulbactam 1:2, 1:1 and 2:1 of 92.6%, 76.2% and 41.0%, respectively.¹² Similarly, imipenem-sulbactam at a 1:1 ratio was slightly superior to that at a 2:1 ratio (resistance rate, 23.3% vs 26.7%) in inhibiting CRAB isolates.¹⁷ Our findings were basically consistent with these data, which revealed the importance of the ratio of sulbactam. However, there were scarce reports about in vitro activities of imipenem-sulbactam, ampicillin-sulbactam combinations at higher ratios against *A. baumannii* clinical strains.

Growing clinical evidence has suggested sulbactam as a promising treatment option in the management of *Acinetobacter* infections. For the bloodstream infections caused by carbapenem-non-susceptible *Acinetobacter* spp., sulbactam-based regimens demonstrated similar clinical efficacy rates as carbapenem-based regimens (50.0% vs 45.8%).¹⁸ In term of the treatment of XDR *Acinetobacter* infections, sulbactam-based regimens displayed higher clinical efficacy rate instead of carbapenem-based regimens (62.5% vs 47.4%).¹⁹ A significant reduction in the 28-day mortality was observed for those receiving cefoperazone-sulbactam compared with those receiving tigecycline (29.3% vs 51.9%).²⁰ In a network meta-analysis, combination therapy of colistin with sulbactam was superior to that of colistin with tigecycline and colistin monotherapy in microbiological eradication while no significant differences were noted in all-cause mortality for MDR and XDR *A. baumannii* infections.²¹ Early study also reported lower incidence rate of adverse events of high-dose ampicillin-sulbactam (30.7%, including 15.3% nephrotoxicity) than that of colistin (39.6%, including 33% nephrotoxicity) in patients with MDR *A. baumannii* ventilator-associated pneumonia.²² Additionally, compared with tigecycline and colistin, sulbactam is also characterized by advantages of tissue distribution, tolerability and cost.

CSAB displayed susceptibility to sulbactam alone, ampicillin-sulbactam combinations and cefoperazone-sulbactam combinations, and either *bla*_{OXA23} or *bla*_{TEM} gene was undetected among them in this study. Sulbactam possesses the intrinsic activity against *A. baumannii*. It binds to penicillin-binding proteins (PBPs), hinders the synthesis of bacterial cell wall and kills bacteria.²³ Moreover, sulbactam rendered the bacteria more susceptible to phagocytosis as well as to killing by polymorphonuclear leukocytes.²⁴

Nevertheless, as indicated by in vitro activity, sulbactam alone was insufficient to fight against CRAB, which could be primarily due to hydrolysis of β -lactamases, including class A β -lactamase TEM-1 and Class D β -lactamase OXA-23.^{25–27} In fact, sulbactam activity could be potentiated by durlobactam (formerly ETX2514),²⁸ a novel inhibitor for class A, C and D β -lactamases, with the combination sulbactam/durlobactam currently being assessed in a Phase III clinical trial in patients with *A. baumannii* infections (<https://clinicaltrials.gov/ct2/results?cond=&term=ETX2514&cntry=&state=&city=&dist=>).

There are few studies on the actual mechanism underpinning enhanced antibacterial activity of β -lactam-sulbactam combinations. The complementary and saturated PBP binding could be one of the mechanisms since β -lactams and sulbactam exhibit different binding affinities for PBPs.^{29,30} Another possible explanation could be the alternative shielding hypothesis.³¹ Sulbactam binds to the active site of the β -lactamases and acts as a better substrate for β -lactamases, thus preventing the hydrolysis of the partner β -lactam antibiotics and allowing the partner to reach its target PBPs more effectively.^{25–27,32} High turnover numbers of sulbactam for TEM-1 and OXA-23 enzyme (sulbactam/enzyme molar ratio required for complete inhibition of each enzyme) as well as the coexistence of other β -lactamases may rationalize high-ratio sulbactam in combinations.³³ In addition, compounds could damage biofilm architecture significantly and exerted superior killing effects against CRAB.³⁴ Overall, above hypotheses need further confirmations. However, it remains to explain why cefoperazone-sulbactam exhibited superior activity over imipenem-sulbactam and ampicillin-sulbactam.

Nevertheless, this study had some limitations. Firstly, numbers of clinical isolates were relatively small though these isolates were from multiple centers. Secondly, the β -lactamase type is relatively simple, focusing on TEM-1 and OXA-23. Further large-scale studies are warranted to verify our research.

Conclusion

In conclusion, the increasing proportion of sulbactam could enhance antimicrobial activity of imipenem-sulbactam, ampicillin-sulbactam and cefoperazone-sulbactam compound against *A. baumannii* strains, with cefoperazone-sulbactam as the most potent. Our study suggests that high-ratio cefoperazone-sulbactam compound could be a promising antimicrobial regimen for *A. baumannii* infection in China.

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Disclosure

The authors report no conflicts of interest in this work.

References

- Douzandeh-Mobarrez B, Alizade H, Kafil HS, Karmostaji A. Antimicrobial categories in describing multidrug resistance, extensive drug resistance and pan-drug resistance in *Pseudomonas aeruginosa* and *Acinetobacter baumannii*: a systematic review. *Rev Med Microbiol*. 2021;32:6–11.
- Aslam A, Gajdacs M, Zin CS, Binti ARN, Ahmed SI, Jamshed SQ. Public awareness and practices towards self-medication with antibiotics among the Malaysian Population. A development of questionnaire and pilot-testing. *Antibiotics*. 2020;9:97.
- Gajdacs M, Urbán E. Epidemiological trends and resistance associated with *Stenotrophomonas maltophilia* bacteremia: a 10-year Retrospective Cohort Study in a tertiary-care hospital in Hungary. *Diseases*. 2019;7:41.
- Shlaes DM, Bradford PA. Antibiotics-from there to where?: how the antibiotic miracle is threatened by resistance and a broken market and what we can do about it. *Pathog Immun*. 2018;3(1):19–43. doi:10.20411/pai.v3i1.231
- Pfaller MA, Flamm RK, Duncan LR, Mendes RE, Jones RN, Sader HS. Antimicrobial activity of tigecycline and cefoperazone/sulbactam tested against 18,386 gram-negative organisms from Europe and the Asia-Pacific region (2013–2014). *Diagn Microbiol Infect Dis*. 2017;88(2):177–183. doi:10.1016/j.diagmicrobio.2017.02.020
- Gajdacs M. The concept of an ideal antibiotic: implications for drug design. *Molecules*. 2019;24:892. doi:10.3390/molecules24050892
- Williams JD. Beta-lactamase inhibition and in vitro activity of sulbactam and sulbactam/cefoperazone. *Clin Infect Dis*. 1997;24:494–497. doi:10.1093/clinids/24.3.494
- Higgins PG, Wisplinghoff H, Stefanik D, Seifert H. In vitro activities of the beta-lactamase inhibitors clavulanic acid, sulbactam, and tazobactam alone or in combination with beta-lactams against epidemiologically characterized multidrug-resistant *Acinetobacter baumannii* strains. *Antimicrob Agents Chemother*. 2004;48(5):1586–1592. doi:10.1128/AAC.48.5.1586-1592.2004
- Ji J, Du X, Chen Y, Fu Y, Wang H, Yu Y. In vitro activity of sulbactam in combination with imipenem, meropenem, panipenem or cefoperazone against clinical isolates of *Acinetobacter baumannii*. *Int J Antimicrob Agents*. 2013;41(4):400–401. doi:10.1016/j.ijantimicag.2012.12.014
- Choi JY, Park YS, Cho CH, et al. Synergic in-vitro activity of imipenem and sulbactam against *Acinetobacter baumannii*. *Clin Microbiol Infect*. 2004;10(12):1098–1101. doi:10.1111/j.1469-0691.2004.00987.x
- Lee NY, Wang CL, Chuang YC, et al. Combination carbapenem-sulbactam therapy for critically ill patients with multidrug-resistant *Acinetobacter baumannii* bacteremia: four case reports and an in vitro combination synergy study. *Pharmacotherapy*. 2007;27(11):1506–1511. doi:10.1592/phco.27.11.1506
- Lai CC, Chen CC, Lu YC, Lin TP, Chuang YC, Tang HJ. Appropriate composites of cefoperazone-sulbactam against multidrug-resistant organisms. *Infect Drug Resist*. 2018;11:1441–1445. doi:10.2147/IDR.S175257
- CLSI. *Performance Standards for Antimicrobial Susceptibility Testing*. 30th ed. Wayne, PA: Clinical and Laboratory Standards Institute; 2020. CLSI supplement M100.
- Dallenne C, Da CA, Decr D, Favier C, Arlet G. Development of a set of multiplex PCR assays for the detection of genes encoding important beta-lactamases in *Enterobacteriaceae*. *J Antimicrob Chemother*. 2010;65(3):490–495. doi:10.1093/jac/dkp498
- Gajdacs M, Burián K, Terhes G. Resistance levels and Epidemiology of Non-Fermenting Gram-Negative Bacteria in Urinary Tract Infections of inpatients and outpatients (RENFUTI): a 10-year epidemiological snapshot. *Antibiotics*. 2019;8:143.
- Lai CC, Chen CC, Lu YC, Chuang YC, Tang HJ. In vitro activity of cefoperazone and cefoperazone-sulbactam against carbapenem-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. *Infect Drug Resist*. 2019;12:25–29. doi:10.2147/IDR.S181201
- Wang FD, Lin ML, Lee WS, Liu CY. In vitro activities of beta-lactam antibiotics alone and in combination with sulbactam against gram-negative bacteria. *Int J Antimicrob Agents*. 2004;23(6):590–595. doi:10.1016/j.ijantimicag.2003.10.008
- Xu S, Li Y, Xu X, et al. A case-control study: clinical characteristics of nosocomial bloodstream infections versus non-bloodstream infections of *Acinetobacter* spp. *Clin Infect Dis*. 2018;67(suppl_2):S189–S195. doi:10.1093/cid/ciy671
- Li Y, Guo Q, Wang P, et al. Clonal dissemination of extensively drug-resistant *Acinetobacter baumannii* producing an OXA-23 β -lactamase at a teaching hospital in Shanghai, China. *J Microbiol Immunol Infect*. 2015;48(1):101–108. doi:10.1016/j.jmii.2014.04.005
- Niu T, Luo Q, Li Y, Zhou Y, Yu W, Xiao Y. Comparison of tigecycline or cefoperazone/sulbactam therapy for bloodstream infection due to carbapenem-resistant *Acinetobacter baumannii*. *Antimicrob Resist Infect Control*. 2019;8:52. doi:10.1186/s13756-019-0502-x
- Kengkla K, Kongpakwattana K, Saokaew S, Apisarnthanarak A, Chaiyakunapruk N. Comparative efficacy and safety of treatment options for MDR and XDR *Acinetobacter baumannii* infections: a systematic review and network meta-analysis. *J Antimicrob Chemother*. 2018;73(1):22–32. doi:10.1093/jac/dkx368
- Betrosian AP, Frantzeskaki F, Xanthaki A, Douzinas EE. Efficacy and safety of high-dose ampicillin/sulbactam vs. colistin as monotherapy for the treatment of multidrug resistant *Acinetobacter baumannii* ventilator-associated pneumonia. *J Infect*. 2008;56(6):432–436. doi:10.1016/j.jinf.2008.04.002
- Penwell WF, Shapiro AB, Giacobbe RA, et al. Molecular mechanisms of sulbactam antibacterial activity and resistance determinants in *Acinetobacter baumannii*. *Antimicrob Agents Chemother*. 2015;59(3):1680–1689. doi:10.1128/AAC.04808-14
- Kazmierczak A, Pechinot A, Siebor E, Cordin X, Labia R. Sulbactam: secondary mechanisms of action. *Diagn Microbiol Infect Dis*. 1989;12(4 Suppl):139S–146S. doi:10.1016/0732-8893(89)90126-0
- Krizova L, Poirel L, Nordmann P, Nemec A. TEM-1 beta-lactamase as a source of resistance to sulbactam in clinical strains of *Acinetobacter baumannii*. *J Antimicrob Chemother*. 2013;68(12):2786–2791. doi:10.1093/jac/dkt275
- Yang Y, Xu Q, Li T, et al. OXA-23 is a prevalent mechanism contributing to sulbactam resistance in diverse *Acinetobacter baumannii* clinical strains. *Antimicrob Agents Chemother*. 2019;63(1). doi:10.1128/AAC.01676-18
- Kuo SC, Lee YT, Yang LT, et al. Contribution of *Acinetobacter*-derived cephalosporinase-30 to sulbactam resistance in *Acinetobacter baumannii*. *Front Microbiol*. 2015;6:231. doi:10.3389/fmicb.2015.00231

28. Durand-Reville TF, Guler S, Comita-Prevoir J, et al. ETX2514 is a broad-spectrum beta-lactamase inhibitor for the treatment of drug-resistant gram-negative bacteria including *Acinetobacter baumannii*. *Nat Microbiol.* **2017**;2:17104. doi:10.1038/nmicrobiol.2017.104
29. Moya B, Barcelo IM, Bhagwat S, et al. Potent beta-lactam enhancer activity of zidebactam and WCK 5153 against *Acinetobacter baumannii*, including carbapenemase-producing clinical isolates. *Antimicrob Agents Chemother.* **2017**;61(11). doi:10.1128/AAC.01238-17
30. Papp-Wallace KM, Senkfor B, Gatta J, et al. Early insights into the interactions of different beta-lactam antibiotics and beta-lactamase inhibitors against soluble forms of *Acinetobacter baumannii* PBP1a and *Acinetobacter* sp. PBP3. *Antimicrob Agents Chemother.* **2012**;56(11):5687–5692. doi:10.1128/AAC.01027-12
31. Sutaria DS, Moya B, Green KB, et al. First penicillin-binding protein occupancy patterns of beta-lactams and beta-lactamase inhibitors in *Klebsiella pneumoniae*. *Antimicrob Agents Chemother.* **2018**;62(6). doi:10.1128/AAC.00282-18
32. Wong D, Nielsen TB, Bonomo RA, Pantapalangkoor P, Luna B, Spellberg B. Clinical and pathophysiological overview of *Acinetobacter* infections: a century of challenges. *Clin Microbiol Rev.* **2017**;30(1):409–447. doi:10.1128/CMR.00058-16
33. Shapiro AB. Kinetics of sulbactam hydrolysis by beta-lactamases, and kinetics of beta-lactamase inhibition by sulbactam. *Antimicrob Agents Chemother.* **2017**;61(12). doi:10.1128/AAC.01612-17
34. Wang YC, Kuo SC, Yang YS, et al. Individual or combined effects of meropenem, imipenem, sulbactam, colistin, and tigecycline on biofilm-embedded *Acinetobacter baumannii* and biofilm architecture. *Antimicrob Agents Chemother.* **2016**;60(8):4670–4676. doi:10.1128/AAC.00551-16

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