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Short Communication

Comparative activity of newer β-lactam/β-lactamase inhibitor combinations against *Pseudomonas aeruginosa* isolates from US medical centres (2020–2021)

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ABSTRACT

Objectives: To evaluate the in-vitro activity of ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam, imipenem-relebactam and comparator agents against contemporary *Pseudomonas aeruginosa* isolates from US hospitals.

Methods: In total, 3184 isolates were collected consecutively from 71 US medical centres in 2020–2021, and susceptibility tested by reference broth microdilution. Clinical Laboratory Standard Institute breakpoints were applied.

Results: Ceftazidime-avibactam [97.0% susceptible (S)], ceftolozane-tazobactam (98.0%S), imipenem-relebactam (97.3%S) and tobramycin (96.4%S) were the most active agents against the aggregate *P. aeruginosa* isolate collection, and retained good activity against piperacillin-tazobactam-non-susceptible, meropenem-non-susceptible and multi-drug-resistant (MDR) isolates. All other antimicrobials tested showed limited activity against piperacillin-tazobactam-non-susceptible, meropenem-non-susceptible and MDR isolates. The most common infections were pneumonia (45.9%), skin and skin structure infections (19.0%), urinary tract infections (17.0%) and bloodstream infections (11.7%); ceftazidime-avibactam, ceftolozane-tazobactam and imipenem-relebactam showed consistent activity against isolates from these infection types. Susceptibility to piperacillin-tazobactam and meropenem was lower among isolates from pneumonia compared with other infection types.

Conclusions: Ceftazidime-avibactam, ceftolozane-tazobactam and imipenem-relebactam were highly active, and exhibited similar coverage against a large contemporary collection of *P. aeruginosa* isolates from US hospitals. Cross-resistance among the newer β-lactams/β-lactam inhibitors (BL/BLIs) varied markedly; ≥72.1% of isolates resistant to one of the three newer BL/BLIs approved for *P. aeruginosa* treatment remained susceptible to at least one of the other two BL/BLIs, indicating that all three should be tested in the clinical laboratory. These three BL/BLIs represent valuable therapeutic options for *P. aeruginosa* infection.

1. Introduction

Pseudomonas aeruginosa is a common cause of healthcare-associated infections, including pneumonia, skin and skin structure infections (SSSIs), bloodstream infections (BSIs) and complicated urinary tract infections (cUTIs). It is estimated that *P. aeruginosa* is responsible for 8% of all healthcare-associated infections [1]. The most common type of *P. aeruginosa* infection is pneumonia; *P. aeruginosa* and *Staphylococcus aureus* are the most commonly isolated bacteria from patients with healthcare-associated pneumonia and ventilator-associated pneumonia in US medical centres [1,2]. It is also estimated that *P. aeruginosa* is responsible for 16.2% of infections in intensive care units (ICUs), including 23% of all ICU-acquired respiratory infections [2,3].

Independent of clinical presentation or infection source, β-lactams (BLs) remain the backbone therapy for treatment of serious *P. aeruginosa* infections, potentially in combination with a second agent such as an aminoglycoside. Moreover, for difficult-

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to-treat *P. aeruginosa*, defined as isolates that exhibit non-susceptibility to piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem-cilastatin, ciprofloxacin and levofloxacin, guidelines currently recommend the use of newer BL/β-lactamase inhibitor (BLI) combinations, such as ceftazidime-avibactam, ceftolozane-tazobactam and imipenem-relebactam [4]. Several studies have shown that these three BL/BLI combinations are highly active against *P. aeruginosa*, including multidrug-resistant (MDR) isolates, but studies comparing the antipseudomonal activity of these compounds are scarce. This study evaluated the in-vitro activity of ceftazidime-avibactam, ceftolozane-tazobactam, imipenem-relebactam and many comparators, including meropenem-vaborbactam, against a large collection of contemporary *P. aeruginosa* isolates from US hospitals.

2. Methods

Participating medical centres were invited to collect a specific number (30–100, depending on infection type) of consecutive isolates (one per patient) per infection type per year. Only bacterial isolates determined to be significant by local criteria as the reported probable cause of an infection were included in this investigation. The organism collection included 3184 *P. aeruginosa* isolates, which were evaluated in the present study. *P. aeruginosa* isolates were from 71 medical centres across 36 states from all nine US census divisions.

Antimicrobial susceptibility was evaluated by reference broth microdilution in a monitoring laboratory (JMI Laboratories, North Liberty, IA, USA), and conducted according to Clinical and Laboratory Standards Institute (CLSI) procedures (Document M07) [5]. Ceftazidime-avibactam, ceftolozane-tazobactam, imipenem-relebactam and piperacillin-tazobactam were tested with the BLI at a fixed concentration of 4 mg/L, whereas meropenem-vaborbactam was tested with vaborbactam at a fixed concentration of 8 mg/L [5]. Minimum inhibitory concentration (MIC) values were interpreted according to CLSI and/or US Food and Drug Administration (FDA) breakpoints when available [6,7]. Meropenem-vaborbactam is not approved for *P. aeruginosa* treatment in the USA; thus, meropenem-vaborbactam breakpoints published for Enterobacterales ($\leq$4/8/$\geq$16 mg/L for susceptible/intermediate/resistant) were applied for comparison.

Isolates were categorized as MDR or extensively-drug-resistant (XDR) according to criteria defined in 2012 by the joint European and US Centers for Disease Control [8]. These criteria define MDR as non-susceptible to at least one agent in at least three antimicrobial classes, and XDR as susceptible to two classes or fewer. The following antimicrobial class representative agents and CLSI interpretive criteria were applied: ceftazidime ($\geq$16 mg/L), cefepime ($\geq$16 mg/L), meropenem ($\geq$4 mg/L), imipenem ($\geq$4 mg/L), piperacillin/tazobactam ($\geq$32/4 mg/L), levofloxacin ($\geq$2 mg/L), ciprofloxacin ($\geq$1 mg/L), gentamicin ($\geq$8 mg/L), amikacin ($\geq$32 mg/L), tobramycin ($\geq$8 mg/L) and colistin ($\geq$4 mg/L).

3. Results

Overall, ceftazidime-avibactam [$MIC_{50/90}$ 2/4 mg/L; 97.0% susceptible (S)], ceftolozane-tazobactam ($MIC_{50/90}$ 0.5/2 mg/L; 98.0%S) and imipenem-relebactam ($MIC_{50/90}$ 0.25/1 mg/L; 97.3%S) were the most active compounds against *P. aeruginosa* isolates (Table 1). Meropenem-vaborbactam inhibited 87.5% of isolates at $\leq$4 mg/L (CLSI/US FDA susceptible breakpoint for Enterobacterales) and 92.3% at $\leq$8 mg/L (EUCAST susceptible breakpoint for *P. aeruginosa*) [9]. Tobramycin was the most active comparator agent ($MIC_{50/90}$ 0.5/1 mg/L; 96.4%S; Table 1). It is important to note that the higher 'susceptibility' rates of meropenem-vaborbactam in comparison with meropenem are a result of the different breakpoints applied to the two compounds ($\leq$2 mg/L for meropenem and $\leq$4 mg/L for meropenem-vaborbactam) rather than a substantial improvement in activity, as evidenced by the identical $MIC_{50/90}$ values obtained for these two compounds (Table 1). Overall susceptibility rates for piperacillin-tazobactam, ceftazidime and meropenem were 81.1%, 84.9% and 82.4% (Table 1).

Ceftazidime-avibactam, ceftolozane-tazobactam and imipenem-relebactam retained potent activity against piperacillin-tazobactam-non-susceptible isolates (susceptibility rates of 85.6%, 91.0% and 89.9%, respectively) and meropenem-non-susceptible isolates (susceptibility rates of 84.8%, 90.2%, 86.3% respectively; Table 1). Besides ceftazidime-avibactam, ceftolozane-tazobactam and imipenem-relebactam, only tobramycin exhibited good activity against these resistant subsets (Table 1).

Ceftazidime-avibactam ($MIC_{50/90}$ 4/16 mg/L; 81.1%S), ceftolozane-tazobactam ($MIC_{50/90}$ 2/8 mg/L; 88.2%S), imipenem-relebactam ($MIC_{50/90}$ 1/4 mg/L; 85.3%S) and tobramycin ($MIC_{50/90}$ 1/>16 mg/L; 82.2%S) were the only compounds with good activity against MDR *P. aeruginosa* isolates (Table 1). Meropenem-vaborbactam inhibited 35.7% of MDR isolates at $\leq$4 mg/L (56.2% at $\leq$8 mg/L), and showed $MIC_{50/90}$ values identical to meropenem (8/32 mg/L; Table 1). Ceftazidime-avibactam, ceftolozane-tazobactam, imipenem-relebactam and tobramycin were also the only compounds active against XDR isolates, with susceptibility rates varying from 71.5% to 81.2%, whereas all other agents tested were active against <25% of isolates (Table 1).

The activities of the BL/BLIs and selected comparators stratified by infection type are displayed in Table 2. *P. aeruginosa* was the second most common organism isolated from patients hospitalized with pneumonia (23.1% of cases) and SSSIs (7.1%), the fourth most common organism isolated from patients with cUTIs (5.6%), and the fifth most common organism isolated from patients with BSIs (5.1%; data not shown). Ceftazidime-avibactam, ceftolozane-tazobactam, imipenem-relebactam and tobramycin showed more consistent activity across infection types compared with other agents. The lowest susceptibility rates were observed among isolates from pneumonia, except for imipenem-relebactam (SSSIs) and ciprofloxacin (UTIs), whereas the highest susceptibility rates were usually among isolates from UTIs, except for meropenem (other infections), ciprofloxacin (other infections) and tobramycin (SSSIs; Table 2).

Cross-resistance among the three most recently approved BL/BLIs for *P. aeruginosa* treatment in the USA was also evaluated (Table 3). Ceftazidime-avibactam remained active against 31.7% and 52.5% of ceftolozane-tazobactam-non-susceptible and imipenem-relebactam-non-susceptible isolates, respectively. Ceftolozane-tazobactam remained active against 54.7% and 68.9% of ceftazidime-avibactam-non-susceptible and imipenem-relebactam-non-susceptible isolates, respectively. Imipenem-relebactam remained active against 64.2% and 64.8% of isolates non-susceptible to ceftazidime-avibactam and ceftolozane-tazobactam, respectively. Most importantly, 72.1–82.1% of isolates resistant to one of the three newer BL/BLIs approved for *P. aeruginosa* treatment remained susceptible to at least one of the other two BL/BLIs (Table 3).

4. Discussion

Systemic *P. aeruginosa* infections are difficult to treat. This organism is intrinsically resistant to many antimicrobial agents, and can acquire a diverse array of resistance mechanisms [10,11]. Prompt initiation of effective antimicrobial therapy is crucial to improve outcomes; however, a limited number of antimicrobials have a satisfactory spectrum of activity to be used for empiric therapy [4,12,13].

Table 1
Activity of amikacin and comparator antimicrobial agents tested against *Pseudomonas aeruginosa* isolates from US medical centres.

Antimicrobial agent	MIC (mg/L)		Susceptibility per CLSI[a]		
	50%	90%	%S	%I	%R
P. aeruginosa (*n*=3184)					
Ceftazidime-avibactam	2	4	97.0		3.0
Ceftolozane-tazobactam	0.5	2	98.0	0.9	1.0
Imipenem-relebactam	0.25	1	97.3	1.8	0.9
Meropenem-vaborbactam[b]	0.5	8	87.5[b]	4.8[b]	7.7[b]
Piperacillin-tazobactam	4	64	81.1	9.3	9.6
Cefepime	2	16	86.6	8.9	4.5
Ceftazidime	2	32	84.9	3.5	11.6
Meropenem	0.5	8	82.4	5.0	12.6
Imipenem	1	8	80.9	4.3	14.8
Levofloxacin	0.5	8	72.2	8.9	18.9
Ciprofloxacin	0.12	2	80.0	5.7	14.3
Tobramycin	0.5	1	96.4	0.8	2.7
Piperacillin-tazobactam-non-susceptible (*n*=603)					
Ceftazidime-avibactam	4	16	85.6		14.4
Ceftolozane-tazobactam	2	4	91.0	4.5	4.5
Imipenem-relebactam	0.5	4	89.9	6.6	3.4
Meropenem-vaborbactam[b]	4	32	54.1[b]	14.9[b]	31.0[b]
Piperacillin-tazobactam	128	>128	0.0	49.1	50.9
Cefepime	16	32	39.6	39.1	21.2
Ceftazidime	32	>32	25.4	16.1	58.5
Meropenem	4	32	45.9	7.5	46.6
Imipenem	4	>8	48.1	7.5	44.4
Levofloxacin	2	32	43.1	14.1	42.8
Ciprofloxacin	0.5	>4	58.0	10.0	32.0
Tobramycin	0.5	4	91.0	3.2	5.8
Meropenem-non-susceptible (*n*=559)					
Ceftazidime-avibactam	4	16	84.8		15.2
Ceftolozane-tazobactam	1	4	90.2	4.5	5.4
Imipenem-relebactam	1	4	86.3	9.2	4.5
Meropenem-vaborbactam[b]	8	32	29.2[b]	26.8[b]	44.0[b]
Piperacillin-tazobactam	32	>128	41.7	25.0	33.3
Cefepime	8	32	51.5	27.2	21.3
Ceftazidime	8	>32	54.9	7.7	37.4
Meropenem	8	32	0.0	28.3	71.7
Imipenem	8	>8	12.3	10.7	76.9
Levofloxacin	4	32	29.7	16.5	53.8
Ciprofloxacin	1	>4	47.8	9.8	42.4
Tobramycin	0.5	16	87.3	2.7	10.0
Multi-drug-resistant (*n*=482)					
Ceftazidime-avibactam	4	16	81.1		18.9
Ceftolozane-tazobactam	2	8	88.2	5.4	6.4
Imipenem-relebactam	1	4	85.3	10.0	4.7
Meropenem-vaborbactam[b]	8	32	35.7[b]	20.5[b]	43.8[b]
Piperacillin-tazobactam	64	>128	16.4	36.9	46.7
Cefepime	16	32	30.5	42.3	27.2
Ceftazidime	32	>32	34.0	13.3	52.7
Meropenem	8	32	21.6	13.3	65.1
Imipenem	8	>8	24.3	10.8	64.9
Levofloxacin	4	32	17.6	17.2	65.1
Ciprofloxacin	2	>4	34.6	14.7	50.6
Tobramycin	1	>16	82.2	5.0	12.9
Extensively-drug-resistant (*n*=256)					
Ceftazidime-avibactam	8	32	71.5		28.5
Ceftolozane-tazobactam	2	16	81.2	8.2	10.5
Imipenem-relebactam	2	4	79.6	13.7	6.6
Meropenem-vaborbactam[b]	16	32	20.3[b]	19.9[b]	59.8[b]
Piperacillin-tazobactam	128	>128	5.9	37.1	57.0
Cefepime	16	>32	13.7	48.0	38.3
Ceftazidime	32	>32	23.4	15.2	61.3
Meropenem	16	32	9.4	10.5	80.1
Imipenem	8	>8	14.5	10.9	74.6
Levofloxacin	8	>32	2.3	18.0	79.7
Ciprofloxacin	2	>4	20.3	14.1	65.6
Tobramycin	1	>16	76.2	7.4	16.4

MIC, minimum inhibitory concentration; CLSI, Clinical and Laboratory Standards Institute; S, susceptible; I, intermediate; R, resistant.
[a] Criteria as published by CLSI (2022).
[b] Not approved to treat *P. aeruginosa* infections in the USA; Enterobacterales breakpoints of ≤4/8/≥16 mg/L (S/I/R) were applied for comparison.

Table 2
Antimicrobial susceptibility of *Pseudomonas aeruginosa* stratified by infection type.

Antimicrobial	% Susceptible (no. of isolates)[a]				
	Pneumonia (*n*=1462)	SSSI (*n*=606)	UTI (*n*=542)	BSI (*n*=372)	Others (*n*=202)
Ceftazidime-avibactam	95.7	97.4	99.4	97.6	98.0
Ceftolozane-tazobactam	97.0	98.8	99.6	97.6	99.5
Imipenem-relebactam	96.8	96.4	99.1	98.7	99.0
Meropenem-vaborbactam[b]	83.5[b]	90.2[b]	92.4[b]	89.5[b]	92.0[b]
Piperacillin-tazobactam	76.4	82.2	88.4	84.1	86.1
Ceftazidime	80.8	86.6	91.5	87.4	87.6
Meropenem	77.2	85.5	87.6	87.4	88.6
Ciprofloxacin	79.1	81.4	77.1	83.6	83.7
Tobramycin	95.4	97.9	96.5	97.8	97.0

SSSI, skin and skin structure infection; UTI, urinary tract infection; BSI, bloodstream infection; CLSI, Clinical and Laboratory Standards Institute; S, susceptible; I, intermediate; R, resistant.
[a] Criteria as published by CLSI (2022).
[b] Not approved to treat *P. aeruginosa* infections in the USA; Enterobacterales breakpoints of ≤4/8/≥16 mg/L (S/I/R) were applied for comparison.

Table 3
Cross-resistance among newer β-lactamase inhibitor combinations.

Resistance phenotype (*n*)	% Susceptible[a]			
	CAZ-AVI	C-T	IMI-REL	CAZ-AVI or C-T or IMI-REL[b]
CAZ-AVI-NS (95)	–	54.7	64.2	82.1
C-T-NS (63)	31.7	–	64.8	73.0
IMI-REL-NS (61)	52.5	68.9	–	72.1

CAZ-AVI, ceftazidime-avibactam; NS, non-susceptible; C-T, ceftolozane-tazobactam; IMI-REL, imipenem-relebactam.
[a] Criteria as published by Clinical and Laboratory Standards Institute (2022).
[b] Percentages of isolates susceptible to at least one of the other two β-lactams/β-lactamase inhibitors.

Novel BL/BLIs represent valuable therapeutic options for *P. aeruginosa* infections, especially in medical centres with high resistance rates for the traditional antipseudomonal BLs, such as piperacillin-tazobactam, ceftazidime, cefepime, meropenem and imipenem [4]. The results of this study corroborate those of other investigators by showing that the BL/BLIs approved most recently for *P. aeruginosa* treatment (i.e., ceftazidime-avibactam, ceftolozane-tazobactam and imipenem-relebactam) provide a broad coverage of *P. aeruginosa* causing infections in US medical centres, with 97.0–98.0% susceptibility rates. Notably, these three BL/BLIs retained good activity against isolates resistant to traditional antipseudomonal BLs, as well as against MDR and XDR isolates.

It is also important to note that the activities of these new BL/BLIs against *P. aeruginosa* from US medical centres are similar to those reported for other geographic regions. The present authors recently evaluated the activities of all four new BL/BLIs against 360 *P. aeruginosa* isolates collected in 2020 from patients with skin and soft tissue infections from Western Europe, Eastern Europe, the Asia-Pacific region and Latin America, and observed susceptibility rates of 96.8–100.0% for ceftazidime-avibactam, 95.2–100.0% for ceftolozane-tazobactam, 95.2–99.5% for imipenem-relebactam and 84.1–96.6% for meropenem-vaborbactam based on European Committee on Antimicrobial Susceptibility Testing criteria; the lowest susceptibility rates were found in Eastern Europe and the Asia-Pacific region [14].

Moreover, the present results complement the findings of other investigators by providing the comparative activity of the three BL/BLIs approved for *P. aeruginosa* treatment in the USA against a large collection of contemporary *P. aeruginosa* isolates from US medical centres. The results clearly showed that rates of cross-resistance among the newer BL/BLIs varied markedly, and ≥72.1% of isolates resistant to one of the three newer BL/BLIs approved for *P. aeruginosa* treatment remained susceptible to at least one of the other two BL/BLIs. These results reflect the variety of resistance mechanisms expressed by *P. aeruginosa*, and illustrate how these mechanisms may have different impacts on each of these compounds. Mechanisms of resistance to these new BL/BLIs are usually very complex, and caused by the presence and interaction of multiple mutation-driven resistance mechanisms [11,15,16]. Therefore, the activity of these compounds, and especially the rates of cross-resistance between them, may vary widely depending on selective pressure due to previous antibiotic usage. These results also emphasize the importance of routine susceptibility testing of all three BL/BLIs against *P. aeruginosa* isolates, especially in medical centres with high rates of resistance.

One limitation of this study was that cefiderocol was not tested; this novel cephalosporin was approved recently by the US FDA for treatment of infections caused by *P. aeruginosa* and other Gram-negative organisms [17]. Unfortunately, the authors were not able to obtain cefiderocol powder at the time the study was performed.

In conclusion, the BL/BLIs approved most recently by the US FDA for treatment of *P. aeruginosa* infections represent valuable therapeutic options. Large surveillance programmes are crucial to monitor the activity and guide the clinical use of new antipseudomonal agents in US medical centres.

Competing interests

JMI Laboratories were contracted to perform services in 2019–2021 for Affinity Biosensors, Allecra Therapeutics, Allergan, Amicrobe Advanced Biomaterials, Inc., AmpliPhi Biosciences Corp., Amplyx Pharma, Antabio, Arietis Corp., Arixa Pharmaceuticals, Inc., Artugen Therapeutics USA, Inc., Astellas Pharma Inc., Athelas, Becton, Basilea Pharmaceutica Ltd., Bayer AG, Becton, Beth Israel Deaconess Medical Center, BIDMC, bioMerieux, Inc., bioMerieux SA, BioVersys Ag, Boston Pharmaceuticals, Bugworks Research Inc., Cidara Therapeutics, Inc., Cipla, Contrafect, Cormedix Inc., Crestone, Inc., Curza, CXC7, DePuy Synthes, Destiny Pharma, Dickinson and Company, Discuva Ltd., Dr. Falk Pharma GmbH, Emery Pharma, Entasis Therapeutics, Fedora Pharmaceutical, F. Hoffmann-La Roche Ltd., Fimbrion Therapeutics, US Food and Drug Administration, Fox Chase Chemical Diversity Center, Inc., Gateway Pharmaceutical LLC, GenePOC Inc., GlaxoSmithKline plc, Guardian Therapeutics, Harvard University, Helperby, HiMedia Laboratories, ICON plc, Idorsia

Pharmaceuticals Ltd., IHMA, Iterum Therapeutics plc, Janssen Research & Development, Johnson & Johnson, Kaleido Biosciences, KBP Biosciences, Laboratory Specialists, Inc., Luminex, Matrivax, Mayo Clinic, Medpace, Meiji Seika Pharma Co., Ltd., Melinta Therapeutics, Inc., Menarini, Merck & Co., Inc., Meridian Bioscience Inc., Micromyx, Microchem Laboratory, MicuRx Pharmaceutics, Inc., Mutabilis Co., N8 Medical, Nabriva Therapeutics plc, National Institutes of Health, NAEJA-RGM, National University of Singapore, North Bristol NHS Trust, Novartis AG, Novome Biotechnologies, Oxoid Ltd., Paratek Pharmaceuticals, Inc., Pfizer, Inc., Pharmaceutical Product Development, LLC, Polyphor Ltd., Prokaryotics Inc., QPEX Biopharma, Inc., Ra Pharmaceuticals, Inc., Rhode Island Hospital, RIHML, Roche, Roivant Sciences, Ltd., Safeguard Biosystems, Salvat, Scynexis, Inc., SeLux Diagnostics, Inc., Shionogi and Co., Ltd., SinSa Labs, Specific Diagnostics, Spero Therapeutics, Summit Pharmaceuticals International Corp., SuperTrans Medical LT, Synlogic, T2 Biosystems, Taisho Pharmaceutical Co., Ltd., TenNor Therapeutics Ltd., Tetraphase Pharmaceuticals, The Medicines Company, The University of Queensland, Theravance Biopharma, Thermo Fisher Scientific, Tufts Medical Center, Universite de Sherbrooke, University of Colorado, University of Southern California-San Diego, University of Iowa, University of Iowa Hospitals and Clinics, University of North Texas Health Science Center, University of Wisconsin, UNT System College of Pharmacy, URMC, UT Southwestern, VenatoRx, Viosera Therapeutics, Vyome Therapeutics Inc., Wayne State University, Wockhardt, Yukon Pharmaceuticals, Inc., Zai Lab, and Zavante Therapeutics, Inc. There are no speakers' bureaus or stock options to declare.

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Ethical approval

Not required.

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