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Letter to the Editor

Potent *in vitro* activity of sulbactam-durlobactam against NDM-producing *Escherichia coli* including cefiderocol and aztreonam-avibactam-resistant isolates

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To the Editor,

The global dissemination of NDM-producing *Escherichia coli* represents a significant challenge, as it leaves very few effective antimicrobial options available. The two current guidelines published by the European Society of Clinical Microbiology and Infectious Diseases and the Infectious Diseases Society of America suggest the combination of ceftazidime-avibactam with aztreonam or the use of cefiderocol as a first-line treatment for infections associated with NDM-producing *E. coli* [1,2]. Tigecycline and eravacycline are also proposed as alternative therapeutic options [1,2]. However, the increasing report of NDM-producing *E. coli* isolates that are resistant to either aztreonam-avibactam or cefiderocol is a major source of concern [3]. A recent study has suggested that the novel β-lactamase inhibitor durlobactam, commercialized as a combo with sulbactam to treat infections caused by *Acinetobacter baumannii*, might be interesting to consider when dealing with infections caused by NDM-producing *E. coli* [4]. Actually, durlobactam is effective against *Enterobacterales* as a single agent by targeting PBP-2 (despite being only marketed as a β-lactamase inhibitor). In addition, this molecule exhibits a significant inhibitory activity against most β-lactamases belonging to Ambler classes A, C, and D, but not against the metallo-β-lactamases (Ambler class B) [5]. The objective of this study was to assess the *in vitro* efficacy of the commercially available combination, sulbactam-durlobactam, against a recent collection of NDM-producing *E. coli* clinical isolates in comparison with the activities of other therapeutic options proposed in the current guidelines by the European Society of Clinical Microbiology and Infectious Diseases and the Infectious Diseases Society of America [1,2].

For that purpose, all consecutive and nonduplicate NDM-producing *E. coli* clinical isolates collected at the Swiss National Reference Center for Emerging Antibiotic Resistance (NARA) from January 2023 to May 2024 and recovered across all parts of Switzerland were included in the study. The initial identification of the resistance pattern was made phenotypically (solid antibiogram), then by confirmation of the bla_{NDM} gene positivity, and finally identification of the NDM variant by sequencing of the corresponding amplicon. To gain further insight into the genetic composition of the isolates, additional PCRs were performed to detect the potential co-production of CTX-M or CMY enzymes. MICs were determined by broth microdilution in triplicate for aztreonam, aztreonam-avibactam, sulbactam-durlobactam, tigecycline, eravacycline, and cefiderocol. Durlobactam was also evaluated alone because of its strong direct antibacterial activity against *Enterobacterales*. The concentrations of avibactam and durlobactam, as β-lactamase inhibitors, were fixed at 4 mg/L, in accordance with the CLSI guidelines. MIC values of cefiderocol were evaluated using the UMIC® Cefiderocol test. The interpretation was based on the EUCAST susceptible breakpoints for aztreonam, aztreonam-avibactam, cefiderocol, tigecycline, and eravacycline. The 50% and 90% MIC values, MIC_{50}, and MIC_{90}, were also determined for all antibiotics and combinations included in the study.

The tested collection included a total of 110 NDM-producing *E. coli* clinical isolates, with the majority (n = 87) producing

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Table 1
Cumulative MIC distribution of aztreonam, aztreonam-avibactam, cefiderocol, tigecycline, eravacycline, and sulbactam-durlobactam against a collection of 110 NDM-producing *Escherichia coli* clinical isolates

Antimicrobial agents	Cumulative % of isolate at MIC (mg/L)											% Of susceptible isolates[a]	MIC_{50}	MIC_{90}
	≤0.06	0.125	0.25	0.5	1	2	4	8	16	32	≥64			
Aztreonam	—	—	6.4	6.4	7.3	10	11.8	14.6	16.4	20.9	100	12	256	256
Aztreonam-avibactam[b]	—	30	31.8	37.3	50	66.4	80	83.6	89.1	95.5	100	80	1	32
Cefiderocol	0.9	0.9	2.7	9.1	20	33.6	62.7	83.6	93.6	100	—	34	4	16
Tigecycline	—	3.6	39.1	89.1	99.1	100	—	—	—	—	—	89	0.5	1
Eravacycline	95.5	99	100	—	—	—	—	—	—	—	—	100	0.015	0.06
Sulbactam-durlobactam[b]	100	—	—	—	—	—	—	—	—	—	—	NA	≤0.06	≤0.06
Durlobactam	—	15.5	55.5	85.5	92.7	100	—	—	—	—	—	NA	0.25	1

NA, not applicable due to the lack of breakpoints available from CLSI or EUCAST.
[a] Susceptible isolate was defined according to the following breakpoints: ≤4 mg/L for aztreonam and aztreonam-avibactam, ≤2 mg/L for cefiderocol, and ≤0.5 mg/L for tigecycline and eravacycline.
[b] Those β-lactamase inhibitors were used at fixed concentration of 4 mg/L.

NDM-5, 20 producing NDM-1, two producing NDM-7, and a single isolate producing NDM-19. Noteworthy, the majority of the isolates co-produced an AmpC-type CMY-like enzyme ($n = 94$). With regard to the susceptibility testing results as presented in Table 1, the aztreonam-avibactam combination demonstrated activity against 80% of the collection, with an MIC_{50} and MIC_{90} being, respectively, at 1 and 32 mg/L. According to EUCAST breakpoints, only 34% of the isolates remained susceptible to cefiderocol, nonetheless a large proportion of them showed MIC values ranging between 2 mg/mL and 16 mg/L, that corresponds to a susceptibility rate of 63% when considering CLSI guidelines. High susceptibility rates were found for tigecycline and eravacycline, being respectively at 89% and 100%. When testing the novel commercially available combination sulbactam-durlobactam, including a fixed concentration of durlobactam at 4 mg/L, very low MIC values were found, being ≤0.06 mg/L for all tested isolates. Interestingly, the MIC_{50} and MIC_{90} values found for durlobactam alone were 0.25 mg/L and 1 mg/L, respectively. Even though sulbactam either acts as a β-lactam antibiotic or as a β-lactamase inhibitor, its direct antibacterial activity against *E. coli* isolates is relatively weak. Conversely, durlobactam exhibits strong direct antibacterial activity against *E. coli* by targeting only PBP-2 [5]. This explains why this molecule is not affected by the PBP-3 modifications observed in aztreonam-avibactam or cefiderocol-resistant *E. coli* isolates. Durlobactam, belonging to the diazabicyclooctane family, is stable against β-lactamase hydrolysis, such as CMY and NDM. Given that the combination of sulbactam and durlobactam contains a fixed concentration of 4 mg/L of durlobactam, and all MIC values of durlobactam were found to be below 4 mg/L in this study, we may consider that durlobactam was the primary effective agent in the sulbactam-durlobactam combination.

Therefore, our results showed that the combination sulbactam-durlobactam might also be considered as an effective alternative therapeutic option for various infections caused by NDM-producing *E. coli* isolates, especially when dealing with aztreonam-avibactam and cefiderocol-resistant isolates. Furthermore, evaluation of PK/PD and clinical outcomes for sulbactam-durlobactam against NDM-producing *Enterobacterales* is required. However, the information presented here may be of relevance to the medical community.

Author contributions

C.L.T. and L.P. participated in conceptualization and design of the study. C.L.T. and A.D. participated in acquisition of data. C.L.T., P.N., and L.P. participated in interpretation of data. C.L.T. participated in drafting of the initial manuscript. P.N. and L.P. participated in critical revision of the manuscript for important intellectual content, supervision, and obtained funding. C.L.T. and L.P. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors critically revised the manuscript for important intellectual content and gave approval for the final version to be published.

Transparency declaration

Potential conflict of interest

The authors declare that they have no conflicts of interest.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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