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A Novel β-lactam/β-lactamase Inhibitor: Ceftolozane/tazobactam

Yeni Bir β-laktam/β-laktamaz İnhibitörü: Seftolozan/tazobaktam

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Abstract

Ceftolozane/tazobactam is a novel generation cephalosporin and β-lactamase inhibitor combination antibiotic. It was approved for the treatment of adults (18 years and older) with complicated intraabdominal infections used in combination with metronidazole and complicated urinary tract infections by the United States Food and Drug Administration. Its primary activity is against multidrug-resistant *Pseudomonas aeruginosa* and other aerobic Gram-negative bacteria. The main characteristic features of the antibiotic include: (1) a greater affinity for penicillin-binding proteins produced by *P. aeruginosa*; (2) better outer membrane permeability that displays resistance mechanisms against upregulation of efflux pumps, and (3) effectiveness against pathogens producing AmpC β-lactamases, primitive β-lactamases (TEM-1, TEM-2, SHV-1, and OXA-1), and extended spectrum β-lactamases. However, it is not effective against pathogens producing metallo-β-lactamases and *Klebsiella pneumoniae* carbapenemases. Ceftolozane/tazobactam is promising for difficult-to-treat infections caused by multidrug-resistant Gram-negative bacteria. Herein, the features of ceftolozane/tazobactam, including its pharmacokinetics, antimicrobial spectrum, and data from recent clinical studies are reviewed.
Keywords: CRE, ESBL, hemodialysis, chronic kidney disease, complicated intra-abdominal infections

Öz

Seftolozan/tazobaktam yeni kuşak sefalosporin ve β-laktamaz inhibitörü kombinasyonu olan bir antibiyotiktir. On sekiz yaş ve üzerindeki erişkinlerde meydana gelen komplike üriner sistem enfeksiyonları ve metronidazol ile kombine edilerek komplike intraabdominal enfeksiyonların tedavisinde Amerikan Gıda ve İlaç Dairesi onayı almıştır. Başlıca etki spektrumu çoklu ilaç dirençli (ÇİD) *Pseudomonas aeruginosa* ve diğer aerobik Gram-olumsuz bakterilerdir (GNB). Başlıca karakteristik özellikleri: (1) *P. aeruginosa*'nın penisilin bağlayan proteinlerine yüksek afinitesi olması, (2) dış membran penetrasyonunun yüksek olması ve bu nedenle efluks pompası aktivitesinden daha az etkilenmesi, (3) AmpC β-laktamaz, primitif β-laktamazlar (TEM-1, TEM-2, SHV-1 ve OXA-1) ve genişlemiş spektrumlu β-laktamaz olumlu bakterilere etkili olmasıdır. Buna karşın, metallo-β-laktamaz ve *Klebsiella pneumoniae* karbapenemazları enzimleri üreten patojenlere etkisizdir. Seftolozan/tazobaktamın özellikle tedavi seçeneğinin kısıtlı olduğu ÇİD GNB'nin neden olduğu enfeksiyonların tedavisinde faydalı olacağı düşünülmektedir. Bu yazıda, henüz ülkemizde kullanıma girmemiş olan bu antibiyotiğin farmakokinetik özellikleri, antimikrobiyal spektrumu ve güncel çalışmalardaki verileri derlenmiştir.
Anahtar Kelimeler: CRE, GSBL, hemodiyaliz, kronik böbrek yetmezliği, komplike intra-abdominal enfeksiyonlar

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Introduction

Antibiotic resistance in clinically important Gram-negative bacteria (GNB) is one of the most serious global health concerns. The rate of infection-related mortality due to multidrug-resistant (MDR) bacteria has been reported as 33-38%[1,2]. Treatment options are limited for difficult-to-treat infections caused by MDR *Pseudomonas aeruginosa*, especially strains that produce carbapenemases (KPC) and/or extended-spectrum β-lactamases (ESBL)[3].

Ceftolozane/tazobactam is a new antibiotic that is effective against *P. aeruginosa* and other common Gram-negative pathogens, including those with antibiotic resistance[2]. In this paper, the pharmacological properties, antimicrobial spectrum, and data from current studies of this antibiotic, which is not yet available in Turkey are reviewed.

Clinical Pharmacology

Ceftolozane/tazobactam is a new-generation cephalosporin/β-lactamase inhibitor that combines a new semi-synthetic cephalosporin, ceftolozane, and the β-lactamase inhibitor tazobactam, at a ratio of 2:1 (2 units ceftolozane, 1 unit tazobactam)[4]. Ceftolozane is an oximino-aminothiazolyl cephalosporin in which the pyridium at position 3 in ceftazidime is replaced by the heavier pyrazole[5]. It binds to penicillin-binding proteins and inhibits cell wall synthesis.

Ceftolozane has several characteristic properties: (1) it has higher affinity than ceftazidime to various penicillin-binding proteins in *P. aeruginosa;* (2) it has more efficient outer membrane permeability and is therefore less affected by efflux pump activity; (3) it shows greater resistance to AmpC β-lactamase than ceftazidime; (4) it is not affected by primitive β-lactamases (TEM-1, TEM-2, SHV-1 and OXA-1); and (5) it is hydrolyzed by ESBLs, but is resistant to these enzymes when combined with tazobactam[4-6]. These properties enhance its effectiveness against GNB, including *P. aeruginosa* strains[5]. However, ceftolozane/tazobactam is hydrolyzed by metallo-β-lactamases and *Klebsiella pneumoniae* KPC enzymes[7].

Maximum plasma concentration is reached approximately one hour after initiating antibiotic infusion. Its plasma half-life is short at 2.7 hours on average. Therefore, a repeat dose is required every eight hours. Ceftolozane is minimally metabolized in the kidneys and excreted unaltered in the urine[8]. The steady-state volume of distribution of ceftolozane is 12.9 l, which is close to the mean extracellular volume. Volume of distribution was found to increase in obese patients and patients with infection[9]. These properties indicate that the antibiotic will reach an adequate therapeutic concentration in areas of extracellular infection. No antagonism has been observed when used *in vitro* with other antibiotics. Ceftolozane/tazobactam is contraindicated in patients with history of severe hypersensitivity reactions to any β-lactam antibiotic, especially piperacillin/tazobactam. Ceftolozane/tazobactam is classified as pregnancy category B. The drug is excreted unaltered in the urine, and dosage adjustment is required for patients with kidney disease. The recommended dose based on creatinine clearance of 30-50 ml/min is ceftolozane 500 mg/tazobactam 250 mg every 8 hours; for 15-29 ml/min, ceftolozane 250 mg/tazobactam 125 mg every 8 hours. In end-stage kidney disease requiring hemodialysis, the initial dose is ceftolozane 500 mg/tazobactam 250 mg, followed by a maintenance dose of ceftolozane 100 mg/tazobactam 50 mg every eight hours. Dose adjustment is not needed for liver disease. The recommended dose and duration of the antibiotic is 1 g administered intravenously every eight hours for seven days for complicated urinary system infections (UTI), while a duration of 4-14 days is recommended for complicated intra-

Table 1. Studies that led to United States Food and Drug Administration approval of ceftolozane/tazobactam[10]

Indication	Antibiotics compared	Results
Complicated urinary tract infections	Ceftolozane/tazobactam: 1 g/0.5 g i.v. every 8 h, 7 days vs. levofloxacin 750 mg i.v. every 24 h, 7 days	Ceftolozane/tazobactam Total cure: 76.9% (306/398) Microbiological cure: 83.3% (284/341) vs. levofloxacin Total cure: 68.4% (275/402) Microbiological cure: 75.4% (266/353) **Primary and secondary outcomes: Noninferior**
Complicated intra-abdominal infections	Ceftolozane/tazobactam: 1 g/0.5 g i.v. every 8 h + metronidazole 500 mg i.v. every 8 h vs. meropenem 1 g i.v. every 8 h + placebo every 8 h	Ceftolozane/tazobactam + metronidazole Clinical cure: 83% Microbiological cure: 94.2% vs. meropenem + placebo Clinical cure: 87.3% **Primary and secondary outcomes: Noninferior**

i.v.: Intravenous

abdominal infections depending on their severity. Its safety and effectiveness have not been determined in pediatric patients[10].

Antibacterial Activity

Ceftolozane/tazobactam is primarily effective against aerobic GNB. Major pathogens that it affects are *P. aeruginosa*, ESBL-positive *Enterobacteriaceae*, MDR Gram-negative bacilli, and various antibiotic-resistant phenotypes (e.g., certain carbapenem-resistant isolates, piperacillin-tazobactam and ceftazidime-resistant isolates)[10]. Ceftolozane is resistant to AmpC β-lactamase and unaffected by efflux pump activity and loss of OprD porin, making it a very effective antipseudomonal agent. However, it is not effective against *Acinetobacter* or

Table 2. *In vitro* efficacy of ceftolozane/tazobactam against *E. coli*, *K. pneumoniae*, and *P. aeruginosa*

Isolate	Infection site	Number of isolates	% S	Reference
Enterobacteriaceae	Bloodstream, pneumonia, skin and soft tissue	1474	89.2	17
ESBL-positive	Bloodstream, pneumonia, skin and soft tissue	378	79.1	17
Escherichia coli	Bloodstream, pneumonia, skin and soft tissue	375	100	4
Escherichia coli	Bloodstream, pneumonia, skin and soft tissue	568	94.5	17
ESBL-positive	Clinical samples*	76-715	93.4-95.7	4
CTX-M-15-positive	Bloodstream, other	219	100	4
CTX-M-15-positive	Bloodstream, other	233	97.9	16
AmpC-positive	Bloodstream	29	96.6	16
MBL-positive	Bloodstream	95	0	16
Klebsiella pneumoniae	Clinical samples*	126-1408	82.7-89.1	4
ESBL-positive	Clinical samples*	132-493	41.8-78.7	4
CTX-M-positive	Bloodstream	82	86.6	16
MBL-positive	Bloodstream	169	0	16
Meropenem-resistant	Bloodstream, skin and soft tissue, pneumonia, urinary tract	140	1.4	4
Meropenem-resistant	Bloodstream, skin and soft tissue, pneumonia, urinary tract	100	0	18
KPC+	Bloodstream	138	1.4	16
Pseudomonas aeruginosa	Bloodstream	212	93.4	4
Pseudomonas aeruginosa	Bloodstream	243	99	16
Ceftazidime-resistant	Bloodstream, skin and soft tissue, pneumonia, urinary tract	398	94.5	4
Ceftazidime-resistant	Bloodstream, skin and soft tissue, pneumonia, urinary tract	83	41.9	16
Ceftazidime-resistant	Bloodstream, skin and soft tissue, pneumonia, urinary tract	551	90.7	19
Meropenem-resistant	Bloodstream, skin and soft tissue, pneumonia, urinary tract	401	96.5	4
Meropenem-resistant	Bloodstream, skin and soft tissue, pneumonia, urinary tract	614	94.8	19
Meropenem-resistant	Bloodstream	20	75	20
AmpC-positive	Bloodstream	149	96.6	16
ESBL-positive	Bloodstream	31	3.2	16
MBL-positive	Bloodstream	125	0	16
Resistant to all β-lactam antibiotics	Bloodstream	422	51.9	16
Colistin-resistant	Bloodstream, skin and soft tissue, pneumonia, urinary tract	154	93.5	19
Colistin-resistant	Bloodstream, skin and soft tissue, pneumonia, urinary tract	143	93.5	21

*No data on infection site, KPC: *Klebsiella pneumoniae* Carbapenemase, ESBL: Extended-spectrum β-lactamase, MBL: Metallo-β-lactamase, CTX-M: Cefotaximase, Amp-C: Ampicillinase C

Table 3. Comparison of activity against various isolates between ceftolozane/tazobactam and other antibiotics

	CTZ		FEP		CAZ		TZP		MEM		CST		
Isolates (number)	MIC_{50}	% S	MIC_{50}	% S	MIC_{50}	% S	MIC_{50}	% S	MIC_{50}	% S	MIC_{50}	% S	Reference
P. aeruginosa (489)	0.5	90.8	2	79.1	2	74.2	4	72.1	0.5	71.7	1	98.4	17
P. aeruginosa (1971)	0.5	90.4	4	82.4	2	82.9	8	76.8	0.5	8.3	1	99.1	18
P. aeruginosa (3229)	0.5	98.3	-	-	4	83	4	84.1	0.5	81	1	95.2	19
P. aeruginosa (935)	1	90.9	4	71.1	4	70.4	16	59.9	1	65.3	2	84.7	21
P. aeruginosa (497)	0.5	95.6	2	88.3	2	87.9	8	83.7	0.5	74.8	1	99.8	22
P. aeruginosa, PDR (175)	4	50	>16	10.9	32	9.1	>64	2.3	8	7.4	1	97.7	18
P. aeruginosa, PDR (84)	2	78.6	-	-	>32	0	128	0	16	0	1	89.3	19
Enterobacteriaceae (3249)	≤1	32.3	≤1	29.1	≤1	15.5	≤8	16.3	≤2	70.8	≤2	90.8	16
Enterobacteriaceae, ESBL-positive (378)	0.5	79.1	16	19.1	16	22.8	8	70.8	≤0.06	99.5	≤0.5	96.3	17
E. coli (568)	0.25	94.5	≤0.5	69.6	0.25	74.1	2	92.8	≤0.06	98.8	≤0.5	98.4	17
E. coli (202)	0.25	96	<0.06	83.7	0.25	83.2	2	91.6	≤0.06	100	0.5	100	22
E. coli, ESBL-positive (198)	0.5	87.9	16	17.3	16	29.3	4	86.9	≤0.06	100	≤0.5	98	17
E. coli, ESBL-positive (327)	0.5	79.8	16	44.5	16	31.8	8	77.4	≤0.06	97.6	≤0.25	98	18
E. coli, ESBL-positive (32)	0.5	81.3	16	6.3	8	0	4	75	≤0.06	100	≤0.5	100	22
K. pneumoniae (570)	0.25	84.2	≤0.5	69.3	0.25	67.2	4	78.4	≤0.06	93	≤0.5	97.2	17
K. pneumoniae (233)	0.25	93.1	≤0.06	85	0.12	82.8	2	83.3	≤0.06	100	0.5	97.9	22
K. pneumoniae, ESBL+ (173)	1	69.4	>16	20.2	16	13.9	16	52.3	≤0.06	98.8	≤0.5	97.1	17
K. pneumoniae, ESBL+ (244)	1	22.1	>16	27.9	>32	5.3	>64	25.4	≤0.06	59	0.5	92.5	18
E. aerogenes (58)	0.25	82.8	≤0.5	86.2	0.5	67.2	4	77.6	≤0.06	98.4	≤0.5	98.2	17
E. aerogenes (14)	0.5	57.1	0.25	78.6	2	42.9	8	50	≤0.06	92.9	0.5	100	22

CTZ: Ceftolozane/tazobactam, FEP: Cefepime, CAZ: Ceftazidime, TZP: Piperacillin/tazobactam, MEM: Meropenem, CST: Colistin, MIC: Minimum inhibitory concentration, PDR: Susceptible to only one or two classes of antibiotics

Stenotrophomonas spp.[2,11,12]. It has activity against certain streptococci, minimal activity against staphylococci, and it is not effective against enterococci. Its effect against anaerobic bacteria is limited: it is effective against *Fusobacterium* and *Propionibacterium* spp., activity against *Bacteroides* spp. has not been documented, and it is ineffective against *Clostridium* spp.[13,14].

Indications

Ceftolozane/tazobactam was introduced to the market in 2014 by Cubist Pharmaceuticals under the name Zerbaxa®. It was approved by the United States Food and Drug Administration (FDA) for use in the treatment of complicated UTI (pyelonephritis) and for the treatment of complicated intra-abdominal infections in adults aged 18 or older (in combination with metronidazole)[15]. Randomized studies that led to gaining FDA approval are presented in Table 1[10]. Studies performed during the licensing process for ceftolozane/tazobactam demonstrated efficacy against complicated UTI (pyelonephritis) caused by *Escherichia coli, K. pneumoniae*, *Proteus mirabilis*, and *P. aeruginosa* and complicated intra-abdominal infections caused by *Enterobacter cloacae, E. coli, Klebsiella oxytoca, K. pneumoniae, P. mirabilis, P. aeruginosa, Bacteroides fragilis, Streptococcus anginosus, Streptococcus constellatus*, and *Streptococcus salivarius*[15].

In Vitro Efficacy

Enterobacteriaceae isolates with minimum inhibitory concentration (MIC) ≤1 mg/l are sensitive and those with >1 mg/l are resistant according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria, while strains with MIC ≤2 mg/l are sensitive and >2 mg/l are resistant according to the Clinical and Laboratory Standards Institute (CLSI) criteria. For *P. aeruginosa* isolates, the EUCAST and CLSI criteria are the same: those with MIC ≤4 mg/l are sensitive and >4 mg/l are resistant[16,17]. The major *in vitro* studies evaluating the efficacy of ceftolozane/tazobactam against *E. coli, K. pneumoniae*, and *P. aeruginosa* are presented in Table 2[5,16-21]. The antibiotic showed high activity, especially against *P. aeruginosa*, with a microbiological eradication rate of 84.4-99%. Among more resistant *P. aeruginosa* strains, the microbiological eradication rate was 77.7-94.5% for ceftazidime-resistant isolates, 70.3-92.8% for meropenem-resistant isolates, and 89.5-93.5% for colistin-resistant isolates.

The efficacy of ceftolozane/tazobactam against *Enterobacteriaceae* isolates varies depending on bacterium's resistance patterns, and it is generally less effective than with *P. aeruginosa* isolates (Table 2). Its microbiological eradication rate in *Enterobacteriaceae* isolates was 89.2% overall and 79.1% in ESBL-positive isolates. Its microbiological eradication rate in *E. coli* isolates was 94.5-99.3% overall and 93.4-95.7% and 97.9-100% in ESBL- and CTX-M-15-positive isolates, respectively. It appears that ceftolozane/tazobactam efficacy is the least against *K. pneumoniae*. The microbiological eradication rate in *K. pneumoniae* isolates was 82.7-89.1% overall and 41.8-78.7% in ESBL-positive isolates. Its microbiological eradication rate in meropenem-resistant isolates is negligible (1.4-4%), which is mainly due to its ineffectiveness against KPC[16].

The results of various studies of the *in vitro* efficacy of ceftolozane/tazobactam against Gram-negative isolates compared to that of cefepime, ceftazidime, piperacillin/tazobactam, meropenem, and colistin are shown in Table 3. Its efficacy against *P. aeruginosa* isolates was found to be similar to colistin and higher than the other antibiotics. Although it was vastly superior to all of the other antibiotics except colistin against *P. aeruginosa* and PDR *P. aeruginosa* isolates in particular, it was slightly less effective compared to colistin. For *Enterobacteriaceae* isolates, it was superior to cefepime and ceftazidime, equivalent or superior to piperacillin/tazobactam, and far inferior to meropenem and colistin.

Ceftolozane/tazobactam was found to be much more effective than cefepime and ceftazidime and slightly more effective than piperacillin/tazobactam, while it was found less effective than meropenem and colistin against ESBL-positive *Enterobacteriaceae* isolates. At the species level, ceftolozane/tazobactam was superior to cefepime and ceftazidime and equivalent or superior compared to piperacillin/tazobactam for *E. coli* and *K. pneumoniae* isolates. In particular, its efficacy was found to be much higher than cefepime and ceftazidime against ESBL-positive isolates of these species. It was inferior to cefepime and superior to ceftazidime and piperacillin/tazobactam against *Enterobacter* strains. Ceftolozane/tazobactam was found to be less effective than meropenem and colistin against all *Enterobacteriaceae*.

Clinical Studies

There are no clinical studies from Turkey on ceftolozane/tazobactam. Although clinical studies are in progress, it is believed that ceftolozane/tazobactam will be especially useful in the treatment of infections caused by MDR *Pseudomonas* spp. and MDR *Enterobacteriaceae* isolates[6,23]. Small case series reported in the literature support the effectiveness of ceftolozane/tazobactam against *P. aeruginosa* infections, including MDR isolates (Table 4). In these case series, ceftolozane/tazobactam was mostly used in the treatment of severe PDR and MDR *P. aeruginosa* infections in patients who had malignancy, organ transplantation, serious underlying diseases such as HIV, and in immunosuppressed patients either alone or in combination with other antibiotics (mostly colistin and amikacin) and had relatively high success rate (54/74, 72.97%). It was effective even in the presence of bacteremia and septic shock (8/12, 66.6%). Ceftolozane/tazobactam was also found to be effective in off-label use such as pneumonia, bone and joint infections, meningitis, and skin and soft tissue infections caused by MDR *P. aeruginosa* (Table 4).

Studies evaluating the efficacy of ceftolozane/tazobactam against infections caused by enteric bacteria are ongoing. In a meta-analysis of phase 3 studies investigating its efficacy against infections caused by ESBL-positive *E. coli* and *K. pneumoniae*, it was compared with levofloxacin (750 mg/day) in UTIs, and combined with metronidazole (1500 mg/day) for comparison with meropenem (3 g/day) in intra-abdominal infections[29]. According to US FDA/EUCAST threshold values, 81.8% / 72.3% of 150 ESBL-positive isolates (95% / 88.1% *E. coli*, 56.7% / 36.7% *K. pneumoniae*) were sensitive to ceftolozane/tazobactam, while 25.3% / 24.1% were sensitive to levofloxacin and 98.3% / 98.3% were sensitive to meropenem. Clinical cure rates were found to be 97.4% (76/78) in the ceftolozane/tazobactam group [98% (49/50) for *E. coli*, 94.4% (17/18) for *K. pneumoniae*], 82.6% (38/46) in the levofloxacin group, and 88.5% (23/26) in the meropenem group. These results indicate that ceftolozane/tazobactam is effective against UTI and intra-abdominal infections caused by ESBL-positive enteric bacteria. A double-blind, randomized phase 2 study performed at 35 centers in five countries by Lucasti et al.[30] compared ceftolozane/tazobactam (1.5 g every eight hours, 4-7 days) (alone or in combination with metronidazole) with meropenem (3 g/day) for complicated intra-abdominal infections. Ceftolozane/tazobactam was administered to 82 patients and meropenem to 39 patients. The clinical cure rates were 83.6% and 96%, respectively. The most commonly isolated pathogen in both groups was *E. coli* [67.2% (41/61) in the ceftolozane/tazobactam group and 76% (19/25) in the meropenem group]. Success rates for infections caused by *E. coli* were 89.5% (34/38) in the ceftolozane/tazobactam group and 94.7% (18/19) in the meropenem group. In another phase 3 study comparing meropenem with ceftolozane/tazobactam (1.5 g/day) combined with metronidazole (500 mg every eight hours) for complicated intra-abdominal infections, similar clinical cure rates were reported in both groups (83% for ceftolozane/tazobactam and 87.3% for meropenem)[31]. In patients with infections caused by ESBL-positive *Enterobacteriaceae* isolates, clinical cure rates were 95.8% (23/24) in the ceftolozane/tazobactam group and 88.5% (23/26) in the meropenem group. In patients with CTX-M-ESBL-producer bacterial infections, the clinical cure rate was 100% (13/13) in the ceftolozane/tazobactam group and 88.5% (23/26) in the meropenem group.

Table 4. Characteristics and treatment outcomes of patients with resistant *P. aeruginosa* infections treated with ceftolozane/tazobactam

Patient	Sex/age (years)	Comorbidities	Primary infection site	Bacteremia	Agent
1	M/61	Lymphoma, peripheral stem cell transplantation	Pneumonia		PDR *P. aeruginosa*
2	F/70	-	Pneumonia		PDR *P. aeruginosa*
3	F/48	Pancreatic cancer	Intra-abdominal infection		PDR *P. aeruginosa*
4	M/60	-	Pneumonia		PDR *P. aeruginosa*
5	M/3	Liver transplantation	Vascular graft		PDR *P. aeruginosa*
6	M/64	Kidney transplantation	Urinary tract infection		PDR *P. aeruginosa*
7	F/73	Neutropenia, leukemia	Pneumonia		PDR *P. aeruginosa*
8	F/38	HIV, kidney transplantation	Urinary tract infection		PDR *P. aeruginosa*
9	M/73	Lymphoma, kidney transplantation	Pneumonia		PDR *P. aeruginosa*
10	E/22	Neurologic disease	Meningitis		PDR *P. aeruginosa*
11	M/49	Neurologic disease	Pneumonia		PDR *P. aeruginosa*
12	M/38	Lung transplantation	Pneumonia		PDR *P. aeruginosa*
13	F/53	Autoimmune hepatitis	Intra-abdominal infection		PDR *P. aeruginosa*
14	F/41	Lupus	Bone and joint infection		PDR *P. aeruginosa*
15	M/35	Multiple sclerosis	Urinary tract infection		PDR *P. aeruginosa*
16	F/65	DM	Intra-abdominal, septic shock	Yes	MDR *P. aeruginosa*
17	F/75	-	Pneumonia, septic shock	Yes	MDR *P. aeruginosa*
18	M/37	Bronchomalacia	Pneumonia, severe sepsis	No	MDR *P. aeruginosa*
19	M/70	-	Intra-abdominal	No	MDR *P. aeruginosa*
20	M/45	Burkitt lymphoma, deep neutropenia	Otitis and mastoiditis, sepsis	No	MDR *P. aeruginosa*
21	M/74	Lung cancer, DM, COPD, acute kidney disease	Pneumonia, septic shock	Yes	MDR *P. aeruginosa*
22	M/53	Hepatitis C infection	Intra-abdominal infection, septic shock	No	MDR *P. aeruginosa*
23	F/76	DM, COPD	Biliary, septic shock	No	MDR *P. aeruginosa*
24	M/79	DM, COPD, kidney disease, chronic heart disease	Septic shock	Yes	MDR *P. aeruginosa*
25	M/79	-	Pneumonia	Yes	MDR *P. aeruginosa*
26	M/61	Immunosuppression	Pneumonia, septic shock	Yes	MDR *P. aeruginosa*
27	M/58	Lung transplantation, acute kidney disease, immunosuppression, mediastinitis	Pneumonia, septic shock	No	MDR *P. aeruginosa*
28-63 (35 patients)[1]	No data	No data	Pneumonia (n=18)[2]	Yes in 6 patients	Carbapenem-resistant *P. aeruginosa*
64-70 (7 patients)	No data	No data	Skin and soft tissue infection, osteomyelitis		PDR *P. aeruginosa*
71	M/69	Esophageal cancer	Pneumonia		*P. aeruginosa*
72	M/63	Polyneuropathy, chronic steroid use	Pneumonia		*P. aeruginosa*
73	M/52	AIDS (CD4: 59 cells/µl), colon perforation and intra-abdominal abscess	Pneumonia		*P. aeruginosa*

PDR: Susceptible to only one or two classes of antibiotics. F: Female, M: Male, COPD: Chronic obstructive pulmonary disease, DM: Diabetes mellitus, MDR: Multidrug-resistant, PDR: Susceptible to only one or two classes of antibiotics. [1]Multicentre study evaluating 35 patients, [2]Diagnosis uncertain in other patients; [3]Ceftolozane/tazobactam was combined with another antibiotic in eight patients and used as monotherapy in 27 patients, 4Favorable in four bacteremic patients

Table 4. Contiuned

Antibiotic used in combination	Treatment duration (days)	Clinical success at the end of treatment	Outcome at 28 days post-treatment	Other-cause mortality	Reference
Levofloxacin	15	Favorable	Favorable	No	24
Colistin	10	Favorable	Favorable	No	24
Metronidazole	16	Favorable	Favorable	No	24
Colistin	15	Favorable	Not evaluated	Yes	24
Colistin	57	Unfavorable	Not evaluated	No	24
-	19	Favorable	Favorable	No	24
Amikacin	18	Unfavorable	Not evaluated	Yes	24
-	22	Favorable	Favorable	No	24
Colistin	4	Unfavorable	Not evaluated	No	24
-	11	Favorable	Unfavorable, recurrence	No	24
-	11	Favorable	Favorable	No	24
Colistin	5	Favorable	Favorable	No	24
-	15	Unfavorable, death	Not evaluated	No	24
Colistin	63	Unfavorable	Not evaluated	Yes	24
Amikacin	11	Favorable	Favorable	No	24
Colistin	14	Favorable	Favorable	No	25
Colistin	10	Favorable	Favorable	No	25
Colistin	10	Favorable	No	No	25
Colistin	21	Favorable	No	No	25
Colistin	21	Unfavorable			25
Colistin	15	Unfavorable, death			25
-	11	Favorable			25
-	9	Favorable			25
Meropenem + amikacin	14	Favorable			25
-	14	Favorable			25
Colistin	3	Death			25
Colistin	21	Favorable			25
8[3]	-	26 (74%) favorable[4]			26
-	-	6 (86%)			27
-	14	Favorable			28
-	14	Favorable			28
-	10	Favorable			28

These results indicate that ceftolozane/tazobactam is effective against intra-abdominal and UTI caused by *Enterobacteriaceae* species including ESBL-positive isolates.

Studies evaluating the efficacy of ceftolozane/tazobactam in nosocomial pneumonia caused by *P. aeruginosa* are ongoing, and initial results are promising[23]. Favorable outcomes have been reported in pneumonia caused by PDR and MDR *P. aeruginosa* in patients with severe underlying conditions such as kidney disease, malignancy, neutropenia, and solid organ transplantation (Table 4).

Conclusion

In summary, the cephalosporin/β-lactamase combination ceftolozane/tazobactam shows remarkable efficacy against GNB. Although it is not effective against carbapenemase-positive pathogens, it is effective against *Enterobacteriaceae* isolates, including those that are ESBL-positive. Its efficacy against *P. aeruginosa* isolates, especially MDR and PDR isolates, is noteworthy. With these properties, ceftolozane/tazobactam has the potential to improve treatment success in patients with infections caused by difficult-to-treat MDR and PDR GNB. The antibiotic is FDA-approved for the treatment of complicated UTI and intra-abdominal infections, and was also found to be effective in the treatment of other off-label infections. Determining the efficacy of this antibiotic in Turkey against MDR and PDR Gram-negative isolates in particular may give an idea of its role in the treatment of our patients.

Ethics

Peer-review: Externally and internally peer-reviewed.

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