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# Activity of Ceftolozane/Tazobactam Against Gram-Negative Rods of the Family *Enterobacteriaceae* and *Pseudomonas Spp.* Isolated from Onco-Hematological Patients Hospitalized in a Clinical Hospital in Poland

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Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
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**Background:** The most common etiological agents of infections in onco-hematological patients are Gram-negative rods resistant to many antimicrobials, including carbapenems. Recently, ceftolozane combined with tazobactam became a novel therapeutic option. The aim of the present study was to analyze the susceptibility to ceftolozane/tazobactam of the clinical strains of these bacteria.





**Material/Methods:** Material comprised rectal swabs, urine, and bronchoalveolar lavage fluid obtained from onco-hematological patients hospitalized in a clinical hospital (1050 beds) in Poland. Identification of the isolated bacteria was done by matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) using the MALDI Biotyper (Bruker). Ceftolozane/tazobactam susceptibility of the isolates was assessed using antimicrobial gradient strips (E-test, BioMérieux). Antimicrobial susceptibility testing and interpretation of the results was done according to the current recommendations of the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

**Results:** In total, 281 rectal swabs and 116 urine samples were tested for the presence of Gram-negative rods producing ESBL, and 531 rectal swabs and 8 bronchoalveolar lavage fluid samples were tested for the presence of Gram-negative rods resistant to carbapenems. In the analyzed period, 69 non-repetitive strains of bacteria were isolated that were in the spectrum of activity of ceftolozane/tazobactam. Among 44 clinical strains of ESBL(+) *Enterobacteriaceae* rods, 76% were susceptible to ceftolozane/tazobactam. All 9 strains of non-carbapenemase-producing *P. aeruginosa* resistant or with decreased susceptibility to carbapenems were susceptible to ceftolozane/tazobactam.

**Conclusions:** Ceftolozane/tazobactam may be an option in the therapy of infections caused by ESBL(+) strains of *Enterobacteriaceae* as well as non-carbapenemase-producing carbapenem-resistant strains of *P. aeruginosa*.

**MeSH Keywords:** **Carbapenems • Enterobacteriaceae • Pseudomonas aeruginosa**

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## Background

Onco-hematological patients comprise a very important group particularly prone to infections caused by exogenous and endogenous microflora because of the course of their primary malignancy and prolonged and repetitive use of antibiotics. Among bacteria causing colonization or infection of these patients, the most common are Gram-negative rods classified in the family *Enterobacteriaceae* (as well as other Gram-negative rods at present classified in the order *Enterobacterales*). Apart from enteric rods, Gram-negative nonfermenting bacilli such as *Pseudomonas aeruginosa* also play a significant role in the etiology of healthcare-associated infections (HAIs) in this group of patients. In healthcare institutions, multidrug-resistant (MDR) or extensively drug-resistant (XDR) strains of Gram-positive and Gram-negative bacteria are cultured from clinical samples, often posing a significant therapeutic challenge in the management of the infections they cause [1,2].

Worldwide, the most commonly isolated strains of Gram-negative rods of the family *Enterobacteriaceae* are ESBL (extended-spectrum  $\beta$ -lactamases) – producers, particularly *Klebsiella pneumoniae*. Therefore, in recent years carbapenems have been increasingly used in the treatment of infections caused by ESBL-positive strains, as so called “life-saving drugs” or “last-line agents”. This has certainly contributed to the selection of bacterial strains resistant to even this group of antibiotics by production of carbapenemases and/or changes in cell wall permeability, as well as activation of efflux pumps [3].

According to the data of the European Antimicrobial Resistance Surveillance System (EARS-Net), in 2016 the highest percentage of *K. pneumoniae* CPE (carbapenemase-producing *Enterobacteriaceae*) strains was reported in Italy (33.9%) and Romania (31.4%). In Portugal it amounted to 5.2%. In contrast to these data, in the United Kingdom, Germany, France, and the Scandinavian countries, the strains of *K. pneumoniae* CPE comprised <1%. In Poland, the percentage of *K. pneumoniae* CPE strains increased from 0.5% in 2015 to 2.1% in 2016, while the percentage of *E. coli* CPE strains isolated from blood samples rose from 0.1% to 0.2%, respectively.

Recently, a novel therapeutic option became available in the form of a new cephalosporin – ceftolozane (representing the third-generation cephalosporins) – combined with tazobactam (an inhibitor of many  $\beta$ -lactamases) in the ratio of 2: 1. The ceftolozane molecule binds to the penicillin-binding proteins (PBPs) localized in the bacterial cell membrane, thus causing inhibition of synthesis of the bacterial cell wall.

## Extended-spectrum $\beta$ -lactamases (ESBL)

Extended-spectrum  $\beta$ -lactamases (ESBL) are the enzymes which are able to hydrolyze all penicillins, cephalosporins (except cephamycin), and monobactams. According to the classification based on the chemical structure, they belong to class A (subgroup 2be) and class D (subgroup 2de) of these enzymes [4]. In the literature, the rate of infections caused by ESBL-producing bacterial strains vary from 25% to even >90%, depending on the type of ward/hospital and geographical location [5,6]. The genes encoding ESBL enzymes are often located on conjugative plasmids and within the specific mobile genetic elements (e.g., transposons, integrons, and resistance islands), which contribute to their rapid spread and high rate of expression. At present, an increase in the number of infections caused by ST13 strain of *E. coli* producing a  $\beta$ -lactamase type CTX-M is observed (mainly urinary tract infections and complicated infections within the abdominal cavity) [7]. The presence of CTX-M  $\beta$ -lactamases means resistance to cephalosporins, and – in case of hyperproduction of this enzyme or the inoculum effect – resistance to  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combinations such as amoxicillin/clavulanate, ampicillin/sulbactam, ticarcillin/clavulanate, or piperacillin/tazobactam. However, in most cases CTX-M  $\beta$ -lactamase is fully inhibited by tazobactam [8].

## Ceftolozane/tazobactam

The chemical structure of the ceftolozane molecule was described for the first time in 2014 by Zhanel et al. [9]. It consists of 2 side-chains: R1 and R2. Chain R1 contains a molecule similar to ceftazidime, while the chain R2 is responsible for resistance of ceftolozane to hydrolytic activity of AmpC  $\beta$ -lactamase of *P. aeruginosa* [9]. The mechanism of antibacterial activity of ceftolozane depends on its binding to the penicillin-binding proteins (PBPs) of the cell membrane (mainly PBP1b and PBP3), which leads to the inhibition of the cell wall synthesis, and subsequently to the death of the bacterial cell.

Tazobactam is an inhibitor of all  $\beta$ -lactamases classified in class A and also several enzymes in class C. By its binding to the active center of the  $\beta$ -lactamase, it blocks hydrolysis of ceftolozane [10,11].

Ceftolozane/tazobactam is registered for use in the therapy of complicated urinary tract infections and acute pyelonephritis caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Pseudomonas aeruginosa*. Combined with metronidazole, this drug may also be used in the therapy of complicated infections within the abdominal cavity caused by both Gram-negative bacteria (*Enterobacter cloacae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Proteus mirabilis*, *Pseudomonas aeruginosa*), Gram-positive bacteria (*Streptococcus*

*anginosus*, *Streptococcus constellatus*, *Streptococcus salivarius*), and strict anaerobes (*Bacteroides fragilis*) [12,13]. Ceftolozane/tazobactam is active against strains of the *Enterobacteriaceae* family, producing  $\beta$ -lactamases of the ESBL type (and several class A  $\beta$ -lactamases, including TEM-1, TEM-2, SHV-1, SHV-2, and CTX-M 14/15), and against *Pseudomonas aeruginosa*, including the strains which are multidrug-resistant due to the loss of porin proteins in cell membrane, overproduction of the chromosomal AmpC enzymes (mutation in PBP4), or overexpression of the efflux pumps [14–17]. However, ceftolozane/tazobactam has limited activity against *Acinetobacter* spp., *Stenotrophomonas maltophilia*, Gram-positive cocci, and Gram-negative rods of the family *Enterobacteriaceae* which produce  $\beta$ -lactamases type AmpC, carbapenemases, or metallo- $\beta$ -lactamases [18].

The excellent activity of ceftolozane/tazobactam against *P. aeruginosa* strains is due to the fact that this combined drug is not a substrate for AmpC  $\beta$ -lactamases and it is not removed from the bacterial cells by the efflux pumps. Ceftolozane/tazobactam also has a higher affinity to PBPs in comparison to other antibiotics such as ceftazidime. Furthermore, the activity of ceftolozane is not diminished by a decreased permeability of the cell membranes resulting from the loss of OprD porin proteins (specific for carbapenems), which are present in *P. aeruginosa* [19,20].

### Aim of the study

The aim of the study was to analyze the susceptibility to ceftolozane/tazobactam of the clinical strains of bacteria isolated from rectal swabs, urine, and bronchoalveolar lavage fluid (BALF) samples obtained from onco-hematological patients hospitalized in a tertiary care university-affiliated hospital.

## Material and Methods

Material used included rectal swabs, urine, and bronchoalveolar lavage fluid (BALF) samples (total n=936) obtained from the hematological patients hospitalized in the Department of Internal Medicine, Hematology and Oncology (Central Clinical Hospital in Warsaw, Poland) from 01.07.2017 to 21.09.2017. The study group comprised mainly patients with acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), or multiple myeloma (MM). In total, 281 rectal swabs and 116 urine samples were tested for the presence of Gram-negative rods producing ESBL, as well as 531 rectal swabs and 8 BALF samples, for the presence of Gram-negative rods resistant to carbapenems (Figure 1).

The clinical samples were inoculated on the selective chromogenic media for preliminary isolation and identification

of ESBL-producing strains (BioMaxima) and strains resistant to carbapenems due to non-enzymatic mechanism (Graso). Identification of the isolated bacteria was done by matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) using the MALDI Biotyper Microflex LT (Bruker) analyzer.

Thereafter, each of the isolated strains was tested for ESBL production by the phenotypic method – the DDST (double-disk synergy test), using the following disks: ceftazidime (30  $\mu$ g), cefotaxime (30  $\mu$ g), and amoxicillin/clavulanic acid (20/10  $\mu$ g). To increase the sensitivity of the test, disks containing aztreonam (30  $\mu$ g) and cefepime (30  $\mu$ g) were added.

Ceftolozane/tazobactam susceptibility of the isolates was assessed using antimicrobial gradient strips (E-test, BioMérieux). Antimicrobial susceptibility testing and interpretation of the results was done according to the current recommendations of EUCAST (the European Committee on Antimicrobial Susceptibility Testing) and KORLD (the National Reference Center for Antibiotic Resistance and Surveillance).

## Results

In the analyzed period, a total of 69 non-repetitive strains of bacteria were isolated, which were in the spectrum of activity of ceftolozane/tazobactam (Figure 1). Gram-negative rods of the family *Enterobacteriaceae* were dominant, comprising almost 87% (n=60) of all isolates. The remaining 9 strains (13%) were identified as *P. aeruginosa* with resistance or decreased susceptibility to carbapenems, cultured mainly from rectal swabs (n=8) and 1 strain was isolated from the bronchoalveolar lavage fluid; all these strains were susceptible to ceftolozane/tazobactam. Among *Enterobacteriaceae*, ESBL production was detected in 57 strains. Among them, 33 strains (55%) were *E. coli* (31 strains from rectal swabs and 2 from urine) and 21 strains (35%) were *K. pneumoniae*, out of which 20 isolates were cultured from rectal swabs and 1 strain from urine, 1 strain (1.67%) of *K. oxytoca* from a rectal swab, 1 strain (1.67%) of *K. ascorbata* from a rectal swab, and 1 strain (1.67%) of *E. cloacae* from a urine sample. Regarding susceptibility to ceftolozane/tazobactam of the strains classified in the family *Enterobacteriaceae*, isolated from urine, 2 strains of *E. coli* were susceptible, while 1 strain of *K. pneumoniae* and 1 strain of *E. cloacae* were resistant to this combined formulation. Furthermore, 3 strains (5%) of *K. pneumoniae* were cultured from rectal swabs, which were characterized by resistance or decreased susceptibility to carbapenems. All these strains were resistant to ceftolozane/tazobactam. Among the ESBL(+) strains of *Enterobacteriaceae*, susceptible strains comprised 81% (n=46/57 strains), while resistance was detected in 19% (n=11/57 strains) of all isolates. Among ESBL(+) strains of *E. coli*, susceptibility was detected in

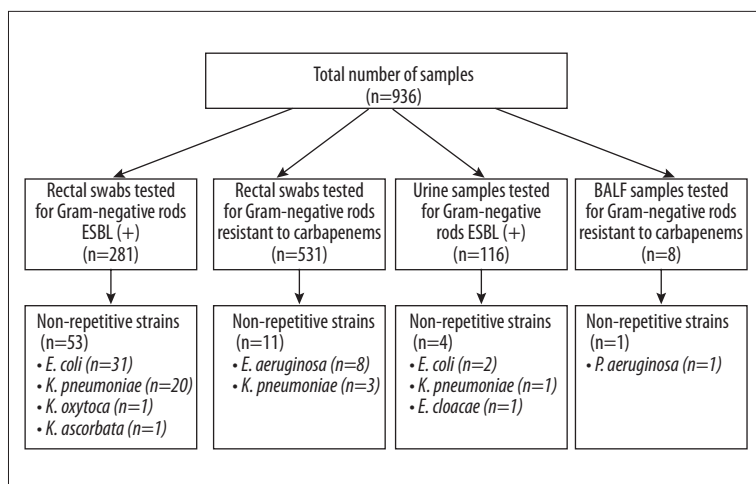


Figure 1. Study design.

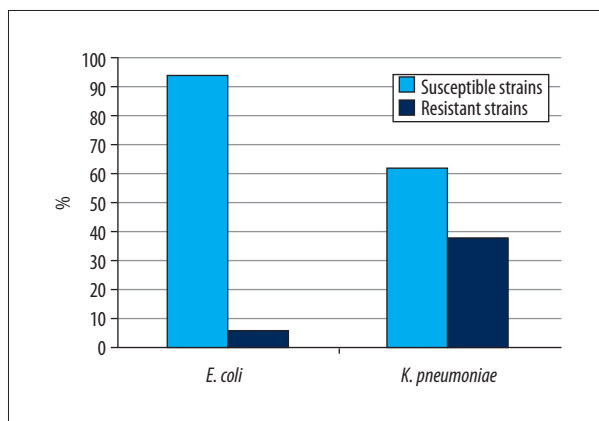


Figure 2. Profile of susceptibility to ceftolozane/tazobactam (%) of ESBL(+) strains of *E. coli* (n=33) and *K. pneumoniae* (n=21).

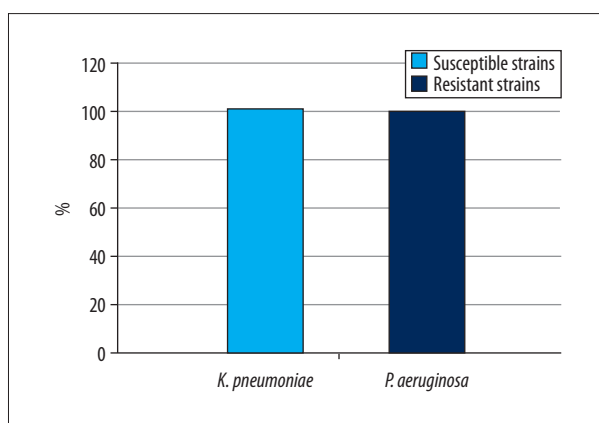


Figure 3. Profile of susceptibility to ceftolozane/tazobactam (%) of carbapenem-resistant (non-enzymatic mechanism) clinical strains of *K. pneumoniae* (n=3) and *P. aeruginosa* (n=9).

Table 1. Profile of susceptibility to ceftolozane/tazobactam of strains of the family *Enterobacteriaceae* and *Pseudomonas aeruginosa* isolated from rectal swabs.

	Susceptible strains (S)	Resistant strains (R)
<i>E. coli</i> ESBL(+)	29 (93.5%)	2 (6.5%)
<i>K. pneumoniae</i> ESBL(+)	13 (65.0%)	7 (35.0%)
<i>K. oxytoca</i> ESBL(+)	1	0
<i>K. pneumoniae</i> (resistance or decreased susceptibility to carbapenems)	0	3 (100.0%)
<i>Kluyvera ascorbata</i> ESBL(+)	1	0
<i>P. aeruginosa</i> (resistance or decreased susceptibility to carbapenems)	8 (100.0%)	0

94% (31/33 strains), while ESBL(+) strains of *K. pneumoniae* were detected in 62% (13/21 strains) (Figure 2). Of note, all strains of *Pseudomonas aeruginosa* (n=9) that were resistant or with decreased susceptibility to carbapenems were susceptible to ceftolozane/tazobactam (Figure 3). The profile of susceptibility to ceftolozane/tazobactam of strains of the family *Enterobacteriaceae* and *Pseudomonas aeruginosa* isolated from rectal swabs is shown in Table 1.

### Discussion

The high frequency of multidrug-resistance of Gram-negative rods to antibiotics, which spreads mainly in the hospital environment, endangers patients and may lead to many

complications during the therapy of infections, including even death. Onco-hematological patients are at particularly high risk of infections, including those caused by endogenous microflora. This group comprises mainly patients with acute myeloid leukemia (AML), myelodysplastic syndrome (MDS) or multiple myeloma (MM), chronic myelomonocytic leukemia (CMML), and acute lymphoblastic leukemia (ALL), as well as different types of lymphomas. In the course of hospitalization these patients are subjected to many risk factors predisposing them to infections, including chemotherapy, hematopoietic stem cell transplantation (HSCT) and retransplantation, the use of broad-spectrum antibiotics and glucocorticoids, prolonged neutropenia, the use of central venous catheters, and graft-versus-host disease (GVHD).

Availability on the market of new antimicrobials opens new possibilities in combating microorganisms, including MDR strains. New antimicrobials that are a combination of a  $\beta$ -lactam antibiotic with a  $\beta$ -lactamase inhibitor, including ceftolozane/tazobactam, may be an option in the therapy of infections caused by ESBL(+) strains. Their use will also enable protection of carbapenems as "last-line" antimicrobials.

There are many reports in the literature indicating the effectiveness of ceftolozane/tazobactam against Gram-negative rods of the family *Enterobacteriaceae*. Sorbera et al. showed that ceftolozane/tazobactam has higher activity than piperacillin/tazobactam and cefepime against the strains of *Enterobacteriaceae* resistant to ceftazidime, while its activity against ESBL(+) strains of *P. mirabilis* is similar to the activity of piperacillin/tazobactam [21].

Skalweit reported that ceftolozane/tazobactam combined with metronidazole is a comparable alternative therapy in the empiric treatment of complicated infections within the abdominal cavity, similar to carbapenems, and therefore should be used as first-line therapy [12]. It was also documented that the rate of cure was higher in patients with infections caused by ESBL-producing *Enterobacteriaceae* treated with ceftolozane/tazobactam combined with metronidazole (95.8%) compared to meropenem (88.5%).

Titelman et al. also analyzed the activity of ceftolozane/tazobactam against ESBL-producing strains of *E. coli* i *K. pneumoniae* [22]. They showed that only 58% of tested strains were susceptible to piperacillin/tazobactam, while up to 96% of these strains were susceptible to ceftolozane/tazobactam, with an MIC value of  $\leq 1$   $\mu\text{g/ml}$ . Similar results were reported by Shortridge et al. [18], who analyzed 966 isolates of *E. coli* and 369 strains of *K. pneumoniae*, in which susceptibility to ceftolozane/tazobactam was 92.2% and 5.1%, respectively. In the present study, we confirmed other published reports that *in vitro* activity of ceftolozane/tazobactam is higher against *E. coli* ESBL(+) strains than against *K. pneumoniae* ESBL(+)

isolates [23]. Despite *in vitro* susceptibility of many other enteric rods to ceftolozane/tazobactam, there are no recommendations as to the clinical effectiveness of this combined formulation against *Citrobacter freundii*, *Citrobacter koseri*, *Enterobacter aerogenes*, *Morganella morganii*, *Proteus vulgaris*, *Serratia liquefaciens*, or *Serratia marcescens*.

In another study, Alatoon et al. compared the activity of ceftolozane/tazobactam and ceftazidime/avibactam. They reported that both these antibacterial formulations have comparable activity against Gram-negative rods of the family *Enterobacteriaceae* producing ESBL (97% vs. 100%, respectively) and *P. aeruginosa* (97% vs. 94%, respectively) [24]. Ceftolozane has excellent activity against *P. aeruginosa*, both alone and combined with tazobactam. This activity is at least 8-fold higher than that of ceftazidime, cefepime, or doripenem [25].

In a multicenter study performed in the USA, Shortridge et al. found that activity of ceftolozane/tazobactam against 3737 non-repetitive strains of *P. aeruginosa* was excellent, with 97.3% strains susceptible to this combined formulation [18]. Analysis of *P. aeruginosa* strains resistant to meropenem revealed that up to 88.6% of them are susceptible to ceftolozane/tazobactam. Among the MDR strains resistant to 4 groups of antibiotics (piperacillin/tazobactam, ceftazidime, cefepime and meropenem), 70.5% remained susceptible to ceftolozane/tazobactam.

Walkty et al. examined 2435 strains of *P. aeruginosa* isolated from patients hospitalized in different hospitals in Canada, and reported an excellent *in vitro* activity of ceftolozane/tazobactam against this bacterial species, with the MIC<sub>90</sub> value of ceftolozane/tazobactam 32-fold lower than that of ceftazidime [26]. This suggests that ceftolozane/tazobactam is useful in therapy of infections caused by *P. aeruginosa*, including the MDR and XDR strains, resistant to piperacillin/tazobactam, antipseudomonal cephalosporins, and carbapenems [26,27].

These findings were also confirmed by Sorbera et al., who showed that ceftolozane/tazobactam is more active than piperacillin/tazobactam or imipenem against the strains of *P. aeruginosa* susceptible to imipenem and ceftazidime, and comparable to the activity of doripenem [23]. At the same time, ceftolozane/tazobactam maintained its activity against ceftazidime-resistant (but susceptible to imipenem) strains of *P. aeruginosa*. Sorbera et al. also reported that ceftolozane/tazobactam inhibited the growth of strictly anaerobic bacteria, mainly *Bacteroides* spp. and *Prevotella* spp. [21].

There are recent reports suggesting that ceftolozane/tazobactam should be considered as an alternative antibacterial agent in the empiric combined therapy of infections caused by resistant strains of *P. aeruginosa*, particularly in patients from the risk group who cannot be treated with aminoglycosides [28].

We found that ceftolozane/tazobactam shows activity against the clinical isolates of *P. aeruginosa*, including the carbapenem-resistant strains (non-carbapenemase-producing). Pfaller et al. [29] also documented that this combination is the most active  $\beta$ -lactam antibiotic against *P. aeruginosa*, and the second most powerful (after meropenem) against Gram-negative rods of the family *Enterobacteriaceae*. However, it was inactive or only slightly active against carbapenem-resistant strains of *Enterobacteriaceae* rods, which was also confirmed in our study. The limitations of the present study were lack of no analysis of the duration of the malignant disease in our patients or their prior exposure to antibiotics, which may have influenced the rate of multidrug-resistant bacteria isolated from these patients. However, we have confirmed that ceftolozane/tazobactam is highly active against the ESBL(+) clinical isolates of *Enterobacteriaceae* rods, particularly *E. coli*, as well as against the clinical strains of non-carbapenemase-producing strains of *P. aeruginosa*.

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## Conclusions

- In total, 76% of ESBL(+) clinical strains of *Enterobacteriaceae* rods were susceptible to ceftolozane/tazobactam.
- Among the ESBL(+) clinical isolates of *Enterobacteriaceae* rods, 94% of *E. coli* strains and 61.9% of *K. pneumoniae* strains were susceptible to ceftolozane/tazobactam.
- Strains of *K. pneumoniae* showing resistance or decreased susceptibility to carbapenems (non-carbapenemase-producing) comprised 5% of all isolates and were totally resistant to ceftolozane/tazobactam.
- In the present study, all clinical strains of non-carbapenemase-producing *P. aeruginosa* (13%), characterized by resistance or decreased susceptibility to carbapenems, were susceptible to ceftolozane/tazobactam.

## Conflict of interests

Beata Sulik-Tyszka, Grzegorz W. Basak, and Marta M. Wróblewska participated in the lectures and conferences sponsored by MSD Poland.

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