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## **Effectiveness of Ceftazidime/Avibactam treatment for infections caused by *Klebsiella pneumoniae* Carbapenemase (KPC), a 30-day mortality perspective. Comparison of results with control groups treated with other antibiotics**

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### **Abstract:**

**Introduction:** Infections caused by *Klebsiella pneumoniae* carbapenemase (KPC) pose a significant clinical challenge due to increasing antibiotic resistance. This study analyzes the effectiveness of ceftazidime/avibactam treatment for KPC infections, focusing on 30-day mortality and comparing results with control groups treated with different antibiotics.

**Material and methods:** We conducted a retrospective analysis of six cohort studies, comparing thirty-day mortality in patients treated with ceftazidime/avibactam with control groups using other antibiotics. The studies included patients infected with KPC, and the analysis focused on therapeutic effectiveness.

**Aim of the study:** The aim of the study is to compare the results in terms of 30-day mortality in groups treated with ceftazidime/avibactam compared to control groups using different antibiotics.

**Conclusions:** Data analysis from various studies revealed varied 30-day mortality outcomes in groups treated with ceftazidime/avibactam compared to control groups using different antibiotics. Ceftazidime/avibactam proved to be more effective in all studies, reducing mortality rates compared to other treatment regimens. We emphasize that emerging antibiotic resistance, especially in the case of KPC, requires a comprehensive therapeutic approach. Despite promising ceftazidime/avibactam results, factors such as overall patient health and treatment delays may influence final therapy outcomes. We also highlight controversies regarding combination therapy vs. monotherapy, necessitating further research. Our work underscores the importance of monitoring the effectiveness of KPC infection treatment and exploring new therapeutic strategies. Further clinical studies are essential to

develop a fuller understanding and optimal therapeutic protocols in the face of the growing antibiotic resistance problem.

**Key words :ceftazidime/avibactam; Klebsiella pneumoniae Carbapenemase; 30-day mortality**

## **Introduction:**

*Klebsiella pneumoniae* is a Gram-negative bacterium, part of the natural human gastrointestinal flora [1]. It is also commonly found in nature, including in soil, other animals, and medical devices [2]. Unfortunately, this bacterium can cause serious infections, especially in patients with weakened immune systems. It is one of the pathogens causing the highest mortality due to antibiotic resistance [3], and mortality for carbapenem-resistant strains is two to three times higher than for other infections [4]. Currently, strains producing both KPC and NDM resistance are described [5], posing a huge clinical challenge that requires ongoing attention and further research.

This study focuses on demonstrating the effects of ceftazidime/avibactam therapy in KPC infections. One of the main causes of resistance in this pathogen is the production of enzymes from the  $\beta$ -lactamase group [6]. KPC genes encode the ability to produce carbapenemases, which can deactivate key antibiotics such as carbapenems [7]. This phenomenon presents unique therapeutic challenges, complicating the effective treatment of infections.

Ceftazidime is a third-generation cephalosporin belonging to beta-lactams [20] [8], while avibactam is a  $\beta$ -lactamase inhibitor. Structurally, avibactam has a different composition than classical  $\beta$ -lactamase inhibitors such as clavulanic acid, sulbactam, and tazobactam [9], lacking a  $\beta$ -lactam core [10]. The binding of avibactam to  $\beta$ -lactamase prevents the regeneration of  $\beta$ -lactamase, unlike other enzyme inhibitors [9]. Published data have shown that CAZ-AVI inhibits Ambler class A, C, and D  $\beta$ -lactamases, including AmpC, *K. pneumoniae* carbapenemase (KPC), and OXA-48 [9]. In this way, avibactam prevents the hydrolysis of ceftazidime by these enzymes [11]. Unfortunately, it has been demonstrated that avibactam is not active, especially against Ambler class B metallo- $\beta$ -lactamases (e.g., New Delhi metallo- $\beta$ -lactamases, NDM) [9][12].

Ceftazidime/avibactam is considered a last resort in the treatment of carbapenem-resistant *Klebsiella pneumoniae* infections [13] and is recognized as one of the most effective drugs in treating infections caused by this pathogen [12]. Unfortunately, since its approval by the United States in 2015, the European Union in 2016, and China in 2019, there are increasing reports of resistance worldwide [14][9][15][16].

### **Materials and Methods:**

In our study, we analyzed six retrospective cohort studies, focusing on the effectiveness of CAZ/AVI treatment. All patients were infected with *Klebsiella pneumoniae* KPC, as confirmed by microbiological tests. We assessed thirty-day mortality in populations treated with CAZ/AVI and compared treatment effects to those of patients treated with other antibiotics. Our goal was to investigate whether adding CAZ/AVI to the treatment regimen would impact 30-day mortality. Inclusion criteria were age >18 years, the presence of a control group and a test group, and infections with *Klebsiella pneumoniae* KPC. The study group was always treated with CAZ/AVI, while the control group received standard regimens. In this study, we use abbreviations: KPC - *Klebsiella pneumoniae* carbapenemase - a type of  $\beta$ -lactamase enzyme [4] [14], NDM-1 - New Delhi metallo- $\beta$ -lactamase-1 - an enzyme  $\beta$ -lactamase [4] [14], CAZ/AVI - ceftazidime/avibactam. Study limitations: demographic limitation - a small study population, potential impact on health of other factors such as age, comorbidities, quality of medical care, which may have slightly differed between the test group and the control group, random allocation of patients to control and test groups.

## Results:

Table 1.

Nr. rej.	References	Year of publication	Number of people treated CAZ/AVI	Mortality 30 days	Control group* Number of people treated	Mortality 30 days	Applied treatment
[17]	David van Duin et al.	2018	37	5,4%-8,1%	96	31,3%-34,4%	Colistin
[18]	Ryan K Shields et.al	2017	13	8%	96	31%	Combination of other antibiotics
[11]	Fei Zhang	2021	22	13,6%	32	43,8%	Combination of other antibiotics
[19]	Guanhao Zhenga	2022	82	35,4%	82	69,5%	Polymyxin and other antibiotics
[20]	Mario Tumbarello	2018	104	36,5%	104	55,8%	Kombinacje innych antybiotyków
[21]	Courtney L Luterbach	2022	20	5%	29	51,7%	Combination of other antibiotics
[22]	Jie Gu	2021	42	19%	48	45,8%	Combination of other antibiotics

\*The patients from the control group have never been treated with CAZ/AVI.

[17]

A prospective observational study from September 2017 included 137 patients. Out of the population, 38 patients treated with CAZ/AVI had only one not infected with *Klebsiella Pneumoniae* KPC. Therefore, the 30-day in-hospital mortality for any cause ranges from 5.4% to 8.1% (Table 1). In comparison, among the 99 infected patients, 96 were infected with the same bacteria, and three others were infected with different Enterobacteriaceae. These individuals were treated with colistin, and within 30 days, 33 patients died, resulting in a 30-day in-hospital mortality of 31.3% to 34.4%. It was also demonstrated that the likelihood of better treatment outcomes with CAZ/AVI compared to colistin, adjusted by IPTV\*, is 64%. Treatment with CAZ/AVI also showed a more favorable benefit-to-risk ratio compared to colistin. An important limitation of this study is the lack of detailed information on colistin dosage.

[18]

In another retrospective cohort study involving 109 patients, treatment regimens included CAZ/AVI (n=13), Carbapenem+Aminoglycoside (n=25), Carbapenem+Colistin (n=30), and others. The study showed that clinical success was achieved more frequently in patients treated with a regimen containing CAZ/AVI than in other regimens, even those containing 2 or more active substances in vitro. Treatment with CAZ/AVI also had a significantly lower rate of acute kidney injury until the end of treatment. The values were 18% for CAZ/AVI, 44% for carbapenem plus aminoglycoside, and 57% for carbapenem plus colistin.

[11]

In a published retrospective study from 2021, cases of individuals infected with *Klebsiella Pneumoniae* KPC after kidney transplant were analyzed. It was shown that the 30-day mortality in the group using monotherapy with CAZ/AVI (n=16) is significantly lower than in the comparative group using other drug combinations, primarily tigecycline and colistin. The analysis of a broader group of 22 individuals, 16 in monotherapy with CAZ/AVI and 6 receiving an additional carbapenem, also indicated lower 30-day mortality rates in this group compared to the comparative group: 13.6% vs. 43.8%. It was also shown that in favor of the group receiving CAZ/AVI compared to the comparative group using other antibiotics (n=32), the following outcomes were observed: 14-day microbiological cure rates of 86.4% vs. 46.9%, and 14-day clinical cure rates of 81.8% vs. 53.1%. Additionally, infection recurrence was less frequent in the CAZ/AVI-treated group compared to the comparative group, 9.1% vs. 21.9%. No adverse events related to CAZ/AVI were observed during the therapy.

[19]

In a cohort retrospective study from 2022, the treatment history of 164 individuals was analyzed. Among the 82 individuals receiving CAZ/AVI-based regimens, 33 were in monotherapy, with a 30-day mortality rate of 51.5%. Forty-nine percent of patients also received other antibiotics, resulting in better 30-day mortality outcomes in the CAZ/AVI-treated group compared to those in monotherapy: 24.5% vs. 51.5%. The group receiving CAZ/AVI in monotherapy or combination therapy, compared to the control group treated with polymyxin B-based regimens, achieved a better 30-day mortality rate than the control group: 35.4% vs. 69.5%. The CAZ/AVI-treated group also significantly achieved a better microbiological eradication rate within 30 days, 80.5% vs. 32.9%, in the control group.

[20]

In 2019, the results of another retrospective study were published. A population of 208 individuals was treated for bacteremia caused by *Klebsiella Pneumoniae* KPC. Of the 104 individuals treated with CAZ/AVI, the 30-day mortality rate was 36.5%. In the control group treated with alternative drug regimens, the same mortality rate was 55.8%, with  $p = 0.005$ . Individuals treated with single-drug regimens compared to those treated with CAZ/AVI in monotherapy achieved significantly higher 30-day mortality rates (21/27 [77.8%] vs. 9/22 [40.9%],  $P = 0.008$ ). A similar outcome was documented in patients treated with combination regimens (29/82 [35.4%] in the CAZ-AVI group vs. 37/77 [48.1%] in the control group), ( $P = 0.10$ ).

[21]

In a multicenter study from 2022, 49 patients were examined, all suffering from *Klebsiella Pneumoniae* KPC bloodstream infection. The results of the 30-day mortality treatment are as follows: Group of 29 patients treated with colistin 51.7%, group of 9 patients treated with colistin and CAZ/AVI 0%, group of 11 patients treated with monotherapy with CAZ/AVI 9%.

[22]

In another retrospective study from 2021, a population of 90 individuals infected with *Klebsiella Pneumoniae* KPC was studied. Forty-two individuals were treated with CAZ/AVI, and in 26 of them, an additional antibiotic from the group of aminoglycosides, glycopeptides, fluoroquinolones, polymyxin, or fosfomycin was added to the treatment. In this group, a 30-day mortality rate of 19% was achieved. In the second group of 48 individuals treated with other active antibiotics excluding CAZ/AVI, a 30-day mortality rate of 48.3% was achieved.

## **Discussion:**

Analyzing our results, it is essential to emphasize that the overall context of antibiotic resistance in infections caused by *Klebsiella Pneumoniae* KPC requires a complex approach. Despite the growing role of ceftazidime/avibactam as a promising option, it should also be noted that the presence of other factors, such as severe patient conditions or delays in the application of effective drugs, may influence the ultimate treatment outcomes. [22]

It is worth considering the challenge of developing resistance of bacteria to traditional antibiotics. Historically, in the treatment of carbapenem-resistant bacteria infections, aminoglycosides, polymyxins (colistin [COL], and polymyxin B), tigecycline, and fosfomycin were commonly used. Increasing resistance rates limit their effectiveness [22][9], and infections caused by *K. pneumoniae* resistant to colistin are associated with higher mortality than infections by colistin-sensitive *K. pneumoniae*[9]. At the same time, it has been observed that combining ceftazidime/avibactam, especially with carbapenems, fosfomycin, and tigecycline, effectively reduces mortality in cases of infections caused by *Klebsiella Pneumoniae* KPC[19].

Some studies suggest that such a therapeutic combination may be a key element in improving treatment outcomes, being a promising alternative in the face of the growing antibiotic resistance problem[19]. Currently, other treatment methods are being investigated, such as viral phage therapy, which has shown to inhibit bacterial growth and have the ability to destroy bacterial biofilm. Considering the much better safety profile of phages than antibiotics, we believe this topic is worth attention [23]. A very interesting direction of treating bacterial infections of *K. pneumoniae* was described in another study where rCST9/rCSTC, recombinant cystatin 9 and cystatin C-human inhibitors of cysteine proteinase, were used for treatment. It was shown that such treatment allows for the use of lower antibiotic doses. However, this direction requires further research as, for ethical reasons, the study was conducted on mice[24]. Another intriguing aspect is the use of predatory bacteria,



such as *Micavibrio aeruginosavorus*, *Bdellovibrio bacteriovorus*, and other *Bdellovibrio* organisms. Predation as an interaction occurs in nature in all ecosystems [25].

It is also essential to emphasize the urgent need for further research into new active substances, such as imipenem-relebactam[14], meropenem-vaborbactam, and plazomycin [18][28], and the addition of known substances like aztreonam[29], or erapenem[30], which may be valuable alternatives in treating KPC infections. The problem of antibiotic resistance is so serious that the Infectious Diseases Society of America has launched a special program seeking new antimicrobial drugs [26]. In the face of limited effectiveness of available antibiotics, it is noteworthy that the use of ceftazidime/avibactam in combination with aztreonam shows a synergistic effect against *Klebsiella pneumoniae*, indicating the possibility of effectively countering carbapenem resistance [14][9].

Similar treatment outcomes to ours, demonstrating the superiority of treating carbapenem-resistant Enterobacteriaceae, including *Klebsiella Pneumoniae*, with CAZ/AVI over other antibiotic regimens, have already been reported in the available literature[14].

It is worth noting that controversies regarding combination therapy vs. monotherapy are evident in our results. Despite suggestions of lower mortality with ceftazidime/avibactam monotherapy, further research is needed, especially in the context of patients with more severe conditions [21][20].

Overall, our work highlights the importance of continuous monitoring of the effectiveness of KPC infection treatment and the search for new strategies to counter the growing challenges associated with antibiotic resistance. The WHO classifies carbapenem-resistant *K. pneumoniae* as a critical threat to health [27]. Further clinical and experimental studies are necessary to provide more comprehensive knowledge and enable the development of optimal therapeutic protocols.

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