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In vitro activity of imipenem/relebactam and ceftazidime/avibactam against carbapenem-resistant *Klebsiella pneumoniae* from blood cultures in a University hospital in Serbia

SANJA ZORNIC^{1*}, IVANA PETROVIC¹ and
BOJANA LUKOVIC²

¹ Department of Microbiology, University Clinical Center Kragujevac, Kragujevac, Serbia

² Academy of Applied Studies Belgrade, College of Health Sciences, Belgrade, Serbia

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RESEARCH ARTICLE



ABSTRACT

The study aimed to investigate prevalence of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) blood culture isolates and their susceptibility to two new antibiotics, imipenem/relebactam and ceftazidime/avibactam. Out of 765 isolates recovered from blood cultures in a tertiary care hospital in Serbia between 2020 and 2023, 143 non-repetitive *K. pneumoniae* strains were included in this study. Minimum inhibitory concentration (MIC) values of the examined antimicrobial drugs was determined by VITEK 2 system, MIC test strip (imipenem/relebactam and ceftazidime/avibactam), and broth microdilution method (tigecycline and colistin). Carbapenemase-encoding genes (*bla*_{KPC}, *bla*_{OXA-48-like}, *bla*_{NDM}, *bla*_{VIM}, *bla*_{IMP}) were detected using a multiplex-PCR assay, the BioFire-Blood Culture Identification 2-panel. This closed molecular assay is designed for the BioFire® FilmArray® system, enabling automated sample preparation, amplification, detection, and analysis (bioMérieux, France). Results revealed that *K. pneumoniae* was the most common isolate from blood cultures in 2022. The prevalence of *K. pneumoniae* was about 11.6% in 2020 and 2021, while in 2022 it raised to over 30%. Also, the frequency of CRKP increased from 11.76% in 2020, through 15.29% in 2021 to 72.94% in 2022. The majority of CRKP carried *bla*_{OXA-48-like} (60.0%), followed by *bla*_{KPC} (16.47%), and *bla*_{NDM} (8.24%) genes, while 14.12% harboured both *bla*_{OXA-48-like} and *bla*_{NDM} genes. Only 25.88% of CRKP isolates were resistant to ceftazidime/avibactam, while 51.76% were resistant to imipenem/relebactam and colistin. The rapid spread of CRKP is particularly concerning because therapeutic options are limited to a few antibiotics. While imipenem/relebactam and colistin showed similar antimicrobial activity against CRKP clinical isolates, ceftazidime/avibactam proved to be the most effective antibiotic.

KEYWORDS

carbapenem-resistant, *Klebsiella pneumoniae*, imipenem/relebactam, ceftazidime/avibactam, colistin

INTRODUCTION

In the past two decades *Klebsiella pneumoniae* has emerged as a significant opportunistic pathogen and a major cause of morbidity and mortality in the healthcare settings. Furthermore, it is one of the ESKAPE microorganisms, a group of clinically important pathogens that have the potential for substantial antimicrobial resistance [1]. Although carbapenems represent the first-line therapy for severe *K. pneumoniae* infections, carbapenem-resistant *K. pneumoniae* (CRKP) has rapidly disseminated worldwide. Carbapenem resistance in *K. pneumoniae* is mostly associated with the acquisition of carbapenemase genes which encode carbapenem hydrolyzing enzymes and the three most important are KPC-type, metallo-β-lactamases (VIM, IMP, NDM), and OXA-48 type enzymes [2]. Patients infected

*Corresponding author.

E-mail: sanjazornic@gmail.com

with CRKP have higher mortality rates than those infected with carbapenem-sensitive strains, especially those with bloodstream infections (BSI) and intensive care unit (ICU) admission [3]. CRKP is one of the critical-priority pathogens on the World Health Organization (WHO) priority list of antibiotic-resistant bacteria for effective drug development [4]. Various combinations of β -lactam- β -lactamase inhibitors have been designed and approved for the therapy of infections caused by carbapenem-resistant bacterial pathogens [5].

Therefore, the aims of this study were: *i*) to assess the prevalence and antimicrobial resistance patterns of *K. pneumoniae* blood isolates, *ii*) to evaluate the prevalence of carbapenemase-encoding genes (*bla*_{KPC}, *bla*_{OXA-48-like}, *bla*_{NDM}, *bla*_{VIM}, and *bla*_{IMP}) among CRKP blood isolates, and *iii*) to compare *in vitro* activity of the old last resort drug - colistin and new antimicrobials - imipenem/relebactam and ceftazidime/avibactam against CRKP.

MATERIAL AND METHODS

The research was designed as a cross-sectional study conducted from January 1st 2020 to January 1st 2023, in a tertiary care hospital, University Clinical Center (UCC) Kragujevac, which provides healthcare service for a population of about two million people in central Serbia. The Ethics Committee of the UCC Kragujevac approved this study (reference number 01/22–23; January 24, 2022). No informed consent was required, because all patients were deidentified and clinical samples re-coded. During the study period, all non-redundant clinical isolates (one per infected patient), recovered from blood cultures and reported to the Central Asian and European Surveillance of Antimicrobial Resistance (CAESAR) network were further analyzed.

K. pneumoniae was recovered from blood cultures as a part of the routine work conducted at the Microbiology laboratory at UCC Kragujevac, using an automated blood culture system, Bact/ALERT (bioMérieux, France). Each positive sample was cultured on conventional bacteriological media [(MacConkey agar and sheep blood agar (Oxoid, Germany)) and processed with a multiplex-PCR assay, the BioFire-Blood Culture Identification 2-panel (BCID-2). This closed molecular assay is designed for the BioFire® Film-Array® system, enabling automated sample preparation, amplification, detection, and analysis (bioMérieux, France). BCID-2 panel can detect 33 microbes associated with bloodstream infections and the ten most common resistance genes (including acquired carbapenemase genes *bla*_{KPC}, *bla*_{OXA-48-like}, *bla*_{NDM}, *bla*_{IMP}, *bla*_{VIM})). (bioMérieux, France). The test was performed according to the manufacturer's instructions.

The VITEK 2 system (bioMérieux, France) [AST-GN71 and AST-GN72 cards] was used to determine the minimum inhibitory concentration (MIC) to amoxicillin-clavulanic acid, piperacillin-tazobactam, ceftriaxone, ceftazidime, imipenem, meropenem, ertapenem, trimethoprim-sulfamethoxazole, ciprofloxacin, gentamicin and amikacin.

The susceptibility to imipenem-relebactam and ceftazidime-avibactam was determined by a MIC gradient test strip (Liofilchem, Italy). MIC for colistin was evaluated by ComASP Colistin (Liofilchem, Italy) and MIC for tigecycline was assessed by the broth microdilution method with Mueller-Hinton broth (Bio-Rad, UK), respectively. A meropenem-resistant isolate (MIC > 8 $\mu\text{g mL}^{-1}$) was referred as a carbapenem-resistant one [6]. The susceptibility categories were evaluated following the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines [7]. For all strains tested to tigecycline, we used breakpoints for Enterobacterales (*Escherichia coli*, $\text{S} \geq 0.5$) [7]. *K. pneumoniae* ATCC 700603 was used as quality control strain.

Based on the obtained results, we calculated the prevalence and resistance rates of *K. pneumoniae* during the study period. Since the antibiotic resistance of invasive *K. pneumoniae* isolates from UCC Kragujevac is monitored annually within the CAESAR network, we compared the prevalence and resistance rates of reported isolates in 2020, 2021 and 2022.

RESULTS

During the study period, 765 non-redundant clinical isolates from blood cultures were reported to the Central Asian and European Surveillance of Antimicrobial Resistance (CAESAR) network for Serbia and 143 of them were identified as *K. pneumoniae*. While the number of blood isolates was similar every year, the prevalence of *K. pneumoniae* was increasing: 25/215 (11.63%) [2020], 32/275 (11.64%) [2021] and 86/275 (31.27%) [2022], respectively (Fig. 1).

The antibiotic resistance patterns of 143 *K. pneumoniae* blood isolates are shown in Table 1. Isolates exhibited high resistance to the most antimicrobials, especially third-generation cephalosporins, trimethoprim-sulfamethoxazole, gentamicin, and amoxicillin-clavulanic acid, with resistance rates ranging from 88.11% to 90.91%. Resistance to carbapenems reached from 37.06% for imipenem up to the 59.44% for meropenem and ertapenem. It is interesting that

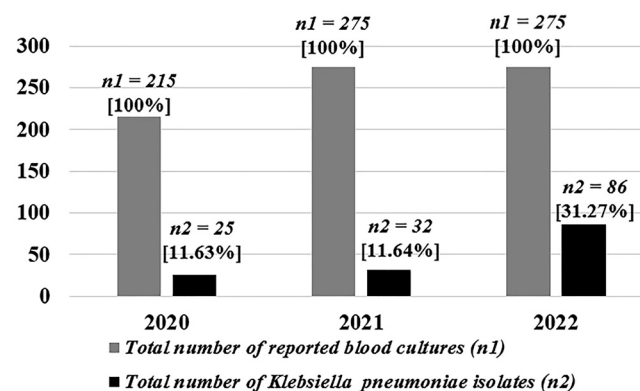


Fig. 1. Prevalence of *Klebsiella pneumoniae* blood isolates during the past three years

Table 1. Antimicrobial resistance of *Klebsiella pneumoniae* blood isolates

Antimicrobial agent	MIC $\mu\text{g mL}^{-1}$	Overall resistance ($n = 143$) No. (%)
Amoxicillin/clavulanic acid	<8–32	130 (90.91)
Piperacillin/tazobactam	<8–128	100 (69.93)
Ceftriaxone	<2–64	126 (88.11)
Ceftazidime	<4–64	126 (88.11)
Cefepime	<4–64	115 (80.42)
Gentamicin	<2–16	126 (88.11)
Amikacin	<8–64	104 (72.73)
Trimethoprim/ sulfamethoxazole	<4–19	126 (88.11)
Ciprofloxacin	<0.5–4	116 (81.12)
Tigecycline	<0.5	60 (41.96)
Meropenem	<8–16	85 (59.44)
Ertapenem	<0.5–8	85 (59.44)
Imipenem	<4–16	53 (37.06)
Imipenem/relebactam	<2–32	44 (30.77)
Ceftazidime/avibactam	<8–32	22 (15.38)
Colistin	<2–16	44 (30.77)

MIC (minimum inhibitory concentration); n = number of *Klebsiella pneumoniae* isolates

colistin and imipenem/relebactam had the same resistance rates (30.77%), while ceftazidime/avibactam showed the strongest *in vitro* activity with 15.38% of resistant isolates.

As expected, majority of CRKP blood isolates were obtained from ICUs (38.82%), followed by the emergency center (35.29%). Most patients were elderly men (69.41%) with median age of 68 years. The most prevalent comorbidities were chronic obstructive pulmonary disease (36.47%), hypertension (27.06%), heart insufficiency (21.18%) and diabetes mellitus (21.18%), respectively. More than 30% of patients underwent an invasive procedure, had central line, were mechanically ventilated or had a surgical intervention. More details are shown in Table 2.

The prevalence of CRKP carrying different carbapenemase-encoding genes and resistance rates to imipenem/relebactam, ceftazidime/avibactam and colistin are shown in Table 3.

The majority of CRKP isolates carried *bla*_{OXA-48-like} (60%), followed by *bla*_{KPC} (16.47%), and *bla*_{NDM} (8.24%) carbapenemase-encoding genes. Twelve isolates harboured both *bla*_{OXA-48-like} and *bla*_{NDM} genes. The number of CRKP strains carrying above mentioned genes expanded almost five times from 2020 to 2022. One isolate had both *bla*_{NDM} and *bla*_{VIM} genes, simultaneously. In this study *bla*_{IMP} gene was not detected.

The prevalence of CRKP recovered from blood cultures increased from 11.76% in 2020, through 15.29% in 2021, until it reached 72.94% in 2022. Ceftazidime/avibactam had the greatest *in vitro* activity on all CRKP, with only 25.88% resistant isolates, while imipenem/relebactam and colistin had the same resistance rate of 51.76%. Ceftazidime/avibactam was the most effective against *bla*_{OXA-48-like} positive CRKP with 88.24% susceptible isolates and the least effective against *bla*_{NDM} positive CRKP with 28.57% susceptible strains.

Table 2. Demographic and clinical characteristics of study patients with carbapenem-resistant *Klebsiella pneumoniae* in blood culture

Characteristics	Number of patients ($n = 85$)
Admission ward	No. (%)
Emergency center	30 (35.29)
General intensive care unit	23 (27.06)
COVID-19 intensive care unit	10 (11.76)
Surgery	6 (7.06)
Urology	5 (5.88)
Internal ward	5 (5.88)
Oncology ward	3 (3.53)
Neurology ward	2 (2.35)
Infectious diseases ward	1 (1.18)
Median age (within the range 22–90)	68
Gender	
Male	59 (69.41)
Female	26 (30.59)
Comorbidity	
Chronic obstructive pulmonary disease	31 (36.47)
Hypertension	23 (27.06)
Heart insufficiency	18 (21.18)
Diabetes mellitus	18 (21.18)
Renal failure	13 (15.29)
COVID-19 pneumonia	11 (12.94)
Cerebrovascular disease	10 (11.76)
Malignancy	7 (8.24)
Chronic liver disease	3 (3.53)
Neuromuscular disorders	3 (3.53)
Hematological disorders	3 (3.53)
Severe burns	1 (1.18)
Medical interventions	
Central venous catheter	33 (38.82)
Surgical procedure	29 (34.12)
Mechanical ventilation	29 (34.12)
Urinary catheter	20 (23.53)

Imipenem/relebactam proved to be the most successful against *bla*_{KPC} positive CRKP with 35.71% resistant isolates, while the worse result was against the *bla*_{NDM} positive CRKP with 71.43% resistant strains (Table 3).

DISCUSSION

K. pneumoniae has emerged as one of the most challenging antibiotic-resistant pathogens, since it can cause a variety of infections, including BSI, and exhibits a remarkable propensity to acquire antimicrobial resistance. Our results show that the number of *K. pneumoniae* recovered from blood cultures at the UCC Kragujevac during 2022 was three times higher than in previous years (31.27% v.s. ~11.6%). In particular, CRKP are challenging pathogens due to the limited treatment options, high mortality rates, and potential for rapid dissemination in health care settings [3, 8, 9]. This study confirmed a rapid increase in CRKP prevalence at the UCC Kragujevac, with a rise from 11.76% in 2020 to 72.94% in 2022.



Table 3. The prevalence of carbapenem-resistant *Klebsiella pneumoniae* carrying different carbapenemase-encoding genes and resistance rates to imipenem/relebactam, ceftazidime/avibactam and colistin

		No. (% of n)					Total number
		<i>bla</i> _{OXA-48-like}	<i>bla</i> _{KPC}	<i>bla</i> _{NDM}	<i>bla</i> _{OXA-48-like} / <i>bla</i> _{NDM} *	<i>bla</i> _{NDM} / <i>bla</i> _{VIM} *	
	<i>n</i>	51 (60.0)	14 (16.47)	7 (8.24)	12 (14.12)	1 (1.18)	85 (100.0)
<i>year</i>	2020	8 (15.69)	0	1 (14.29)	0	1 (100.0)	10 (11.76)
	2021	8 (15.69)	2 (14.29)	1 (14.29)	2 (16.67)	0	13 (15.29)
	2022	35 (68.63)	12 (85.71)	5 (71.43)	10 (83.33)	0	62 (72.94)
	IMI/REL	27 (52.94)	5 (35.71)	5 (71.43)	6 (50.00)	1 (100.0)	44 (51.76)
CAZ/AVI		6 (11.76)	2 (14.29)	5 (71.43)	8 (66.67)	1 (100.0)	22 (25.88)
Colistin		15 (17.65)	11 (78.57)	7 (100.0)	10 (83.33)	1 (100.0)	44 (51.76)

n = The number of CRKP (carbapenem-resistant *Klebsiella pneumoniae*) isolates with different carbapenemase-encoding genes; IMI/REL: imipenem/relebactam; CAZ/AVI: ceftazidime/avibactam;

* both genes detected.

According to the WHO annual reports for antimicrobial resistance of invasive isolates from 2020 to 2021, Serbia reported a 44.5% CRKP in 2020 and 62% CRKP in 2021, which places it among the European and Central Asian countries with the highest percentage of CRKP, together with Belarus, Georgia, Greece, Moldova, Romania, Russia, and Ukraine [10, 11]. According to this data, it seems that our institution had a significantly lower prevalence of CRKP (11.76% and 15.29%) compared to the rest of Serbia. However, in 2022, the prevalence of CRKP (72.94%) surpassed the levels observed in previous years, suggesting a sudden emergence and rapid spread of resistant strains within UCC Kragujevac. Thus, we can assume that we have now exceeded the average number of CRKP invasive isolates in Serbia.

The emergence of carbapenem-resistant strains is especially concerning due to limited treatment options for life-threatening infections in critically ill patients [12, 13]. As is the case in most countries in Europe and worldwide, in UCC Kragujevac the ICUs are the most critical departments for the spread of CRKP strains [14–18]. The COVID-19 ICUs were particularly suitable for the spread of resistant strains, so according to the recent research, the prevalence of CRKP in COVID-19 ICU ranged from 0.35 to 53% [19], while in our hospital, it was 11.76%. Additionally, studies on CRKP infections showed that the majority of affected patients were male, over 60 years of age with severe comorbidities and invasive procedures such as central venous catheterization or mechanical ventilation, which aligns with our data [19].

A study conducted in Serbia from 2013 to 2014, involving 51 CRKP isolates from 14 hospitals across the country, found that 27.3% of *K. pneumoniae* strains carried the *bla*_{NDM} gene, 8.3% carried *bla*_{OXA-48}, and 0.8% carried *bla*_{KPC}. Moreover, 5.4% of the strains carried both *bla*_{OXA-48} and *bla*_{NDM} genes. It is important to note that these isolates were obtained from various samples [20]. Another study from 2016 to 2020, which included 114 CRKP isolates from the community rather than hospitals in Serbia, revealed that *bla*_{OXA-48} was the predominant gene responsible for carbapenemase production, consistent with our own research findings [21].

Based on our study, which examined CRKP strains from blood cultures in a broader region encompassing central and eastern Serbia for the first time, it is evident that this shift in the prevalence of different carbapenemase-coding genes is still ongoing.

Similarly, a study conducted in Slovenia from 2014 to 2017 examined 32 CRKP isolates and found that 53.1% of them carried the *bla*_{OXA-48} gene, 15.6% carried *bla*_{NDM}, and 21.9% carried both *bla*_{OXA-48} and *bla*_{NDM} genes. Additionally, one isolate harboured *bla*_{KPC} and *bla*_{VIM} genes simultaneously [22]. A study conducted in a tertiary-type ICU hospital in Turkey from 2016 to 2018 showed that 68.8% of CRKP produced OXA-48 type of carbapenemases and 6.3% KPC-type and metallo-β-lactamases, which is similar to our study with the exception of the number of KPC-positive isolates, which was almost three times higher (16.47%) (Table 3) [23]. Research on carbapenem-resistant *Enterobacteriaceae* in Poland, conducted from 2019 to 2021, revealed that the most common carbapenemases produced by *K. pneumoniae* were OXA-48 (71%), KPC (26%), and NDM (2.5%), which is similar to our results [24]. This distribution is not surprising since OXA-48-type carbapenemases have predominantly been found in Mediterranean countries in recent years [25].

For the treatment of carbapenem-resistant Gram-negative bacterial infections, fosfomycin, polymyxins, and combinations of carbapenems with various antimicrobials were used with limited success [26]. In recent years, colistin was used as the only effective antibiotic for the treatment of CRKP, although resistance to colistin is also constantly increasing [27]. A study conducted in Serbia from 2013 to 2017, which included isolates from the five largest cities in the country, revealed that CRKP clinical isolates exhibited a colistin resistance rate of 10.6% [28].

According to the report from the reference laboratory monitoring antimicrobial resistance of invasive isolates in Serbia, there was a proportional increase in colistin resistance among invasive *K. pneumoniae* isolates in the subsequent years. In 2020, the colistin resistance rate was 31.1%, and in 2021 it reached 41.5%. However, there is no available data on the colistin resistance of isolates that were



concurrently resistant to carbapenems [29]. Our data, including the year 2022, revealed that the overall resistance of *K. pneumoniae* invasive isolates to colistin was 30.77%. However, among CRKP isolates, that percentage exceeded 50%. Compared to previous data, this significant increase indicates a remarkably rapid spread of colistin-resistant CRKP isolates.

New β -lactam- β -lactamase inhibitor combinations, such as imipenem/relebactam and ceftazidime/avibactam have shown variable success against carbapenem-resistant strains. In our study, imipenem/relebactam showed similar activity to colistin (resistance rate 51.76% for both) but performed better than colistin for strains carrying *bla*_{KPC} genes (resistance rate 35.71% vs. 78.57%). Furthermore, we found that only 14.29% of *bla*_{KPC} - positive strains were resistant to ceftazidime/avibactam.

In a study by Gaibani et al., it was observed that patients with imipenem/relebactam-resistant *bla*_{KPC} - positive *K. pneumoniae* blood culture isolates achieved complete recovery after the application of ceftazidime/avibactam in combination with gentamicin [30].

According to the INFORM (International Network for Optimal Resistance Monitoring) study, conducted from 2015 to 2017, 73% of meropenem non-susceptible isolates were susceptible to ceftazidime/avibactam, which is consistent with the results we obtained (25.88% of resistant strains) [31].

Similar to other studies [32–35], strains from UCC Kragujevac that carried the *bla*_{NDM} gene were more resistant to ceftazidime/avibactam than to other carbapenemase-producing isolates (resistance rate 71.43%). Some of these studies showed that the degree of resistance decreased when ceftazidime/avibactam was combined with aztreonam [32, 34] or another drug [35] which presents new therapeutic possibilities.

Although this study is limited by the fact that is a single-center study, in summary, it reveals a significant rise in the prevalence of CRKP in Serbia. Carbapenem-resistance is mostly associated with horizontal gene transfer of *bla*_{OXA-48-like}, *bla*_{KPC} or *bla*_{NDM} genes. Therefore, it is crucial to prioritize the care of the most vulnerable patient groups in ICU units, particularly those who have undergone surgical interventions, have central venous catheters, or require mechanical ventilation. Furthermore, our research indicates that ceftazidime-avibactam is a more effective treatment option than colistin for most carbapenem-resistant strains. Compared to colistin, imipenem-relebactam is also more effective against *bla*_{KPC}-positive strains. However, strains that produce metallo- β -lactamases remain the most challenging therapeutic problem. These findings can assist clinicians in selecting appropriate therapies while emphasizing the need for further research and the development of new antimicrobial drugs.

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