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Activity of carbapenems and tigecycline against ESBL-producing *Escherichia coli* and *Klebsiella* spp.

Atividade de carbapenêmicos e tigeciclina diante de Escherichia coli *e* Klebsiella *spp. produtoras de ESBL*

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ABSTRACT

The indiscriminate use of carbapenems in the fight against multidrug resistant Gram-negative bacteria leads to the emergence of resistance to these antimicrobial agents. We examine the *in vitro* activity of carbapenems and tigecycline against ESBL-producing *E. coli* and *Klebsiella* spp. isolated in a single hospital at two different periods eight years apart. Overall resistance to carbapenems ranged from 18.7% in 2007 to 19.1% in 2015/2016. We found no isolates resistant to tigecycline, but two intermediary profiles in the 2015/2016 period. Tigecycline is an important option for treating multidrug resistant Gram-negative infections and helps in the fight against global dissemination of resistance to carbapenems.

Key words: carbapenems; *Escherichia coli; Klebsiella*.

INTRODUCTION

In recent years, the uncritically use of carbapenems for treating multidrug resistant (MDR) gram-negative infections has boosted the global dissemination of carbapenem-resistant *Enterobacteriaceae*[1]. Extended-spectrum beta-lactamases (ESBL)-producing *Escherichia coli* and *Klebsiella* spp. isolates with acquired carbapenemases are the most prevalent gram-negative species among the MDR bacteria in the Americas[2-4] and also other continents[5, 6]. Furthermore, the emergence of cefotaximase-Munich (CTX-M) ESBL-producing bacteria evidenced these days poses significant challenge for antibiotic treatment, since this ESBL family often exhibits a MDR profile[7-9].

The combination of ESBL production and carbapenem resistance in MDR Gram-negative isolates limits the antimicrobial therapy to few antimicrobial agents, such as colistin and tigecycline[9, 10]. Due to its low toxicity and to reduce induction of carbapenem resistance, tigecycline has been suggested as an alternative to carbapenems for the treatment of infections caused by ESBL-producing strains[6]. Resistance to tigecycline is not widely disseminated, but was already found in multicenter studies from some countries such as the United States[11], United Arab Emirates[10], and Brazil[4], mainly in *K. pneumoniae* isolates.

In this study, we examine the *in vitro* activity of carbapenems and tigecycline against all ESBL-producing *E. coli* and *Klebsiella* spp. isolated in a single hospital at two different periods eight years apart. The hospital has a total number of 232 beds (10 intensive care unit beds) and is a regional reference center located in the central region of Rio Grande do Sul, Brazil. The first period runs from April to November 2007 (before the use of tigecycline in the mentioned hospital). The second period, from April 2015 to January 2016. All ESBL-producing *E. coli* and *Klebsiella* spp. isolated during both periods were selected to be included in this study; ESBL production was assessed in routine susceptibility testing by combined disc method using discs of cefotaxime (30 µg), ceftazidime (30 µg) and cefpodoxime (30 µg) placed at a distance of 20 mm distant from amoxicillin-clavulanic acid (30/10 µg) discs (Sensidisc, DME, Brazil). ESBL test and susceptibility of the isolates to carbapenems and tigecycline was determined by the Kirby-Bauer disc diffusion technique on Mueller-Hinton agar plates using discs of ertapenem (10 µg), imipenem (10 µg) and

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meropenem (10 µg) (Sensidisc, DME), and tigecycline strips (Oxoid M.I.C. Evaluator, England) according to the European Committee of Antimicrobial Susceptibility Testing (EUCAST) breakpoints. Quality control was performed using *K. pneumoniae* ATCC 700603 and *E. coli* ATCC 25922.

The species distribution, clinical source and antimicrobial resistance of isolates selected in both periods evaluated in this study are shown in the **Table**. The high prevalence of *K. pneumoniae* and *E. coli* isolated from urinary tract infections (UTI) found in our study were also reported in other studies[3, 10]. These two species are quite common in hospitalized patients UTI, and especially *K. pneumoniae* sometimes appears as a MDR strain even possessing the *Klebsiella pneumoniae* carbapenemase (KPC) gene[8].

Overall resistance to carbapenems in our study was 18.7% in 2007 and 19.1% in 2015/2016. Recent multicenter studies have shown decreasing *in vitro* susceptibility of ESBL-producing *K. pneumoniae* isolates to carbapenems[3,8], mainly meropenem[3]. We also found a higher prevalence of *K. pneumoniae* resistant to carbapenems, but mainly to ertapenem. Moreover, we found an interesting prevalence of *E. coli* isolates resistant to imipenem (24%). Interestingly, for *E. coli* isolates, other studies reported better susceptibility to imipenem[4, 10] and higher resistance to meropenem[3].

Regarding the clinical source of each isolate, the body fluid and site which presented more isolates resistant to carbapenems were urine (n = 7) and respiratory tract (n = 3) in 2007; and urine (n = 8) in 2015/2016. All isolates resistant to carbapenems in the 2015/2016 period were from urine samples. Skin wound and fluids had reduced number of isolates and did not present any isolate resistant to carbapenems.

Tigecycline presented a very good *in vitro* activity against all isolates included in this study. The only two isolates (one *E. coli* and one *K. pneumoniae*) with intermediate profile to this antimicrobial agent [minimum inhibitory concentration (MIC) = 2 µg/ml] were both found in the 2015/2016 period. In other studies, resistance to tigecycline is higher in *K. pneumoniae* when compared to *E. coli* isolates[4, 5]. Both isolates in our study were from male patients with chronic kidney disease and history of previous UTI. The *E. coli* isolate was from a 49-year-old patient, paraplegic by spinal cord injury, indwelling urinary catheter user, hypertensive, with recent history of septicemia and use of ciprofloxacin, nitrofurantoin and meropenem. The *K. pneumoniae* isolate was recovered from a 72-year-old hypertensive patient with peripheral vascular disease, type 2 diabetes *mellitus*, with repeated admissions including 20 days in intensive care unit in October 2015 and use of levofloxacin (prolonged curse), ampicillin + sulbactam, azithromycin and nystatin.

In this study we confirm the absence or low occurrence of *E. coli* and *Klebsiella* spp. nosocomial isolates resistant to tigecycline reported by other investigators[1, 10, 11]. As limitations, we highlight the absence of molecular tests to confirm phenotypic results or evaluate clonality, the prevalence of urinary isolates and the low reproducibility of tigecycline strips. However, in the hospital environment, the ESBL-resistant genes are easily transferable to other microorganisms through plasmids and, subsequently, the resistance to carbapenems is induced by its extensive use. The resistance to carbapenems found in our study, along with a recent report of KPC-producing *Klebsiella* spp. in another city hospital[8], demonstrates the importance of antimicrobial resistance surveillance and further researches into the presence of KPC-type carbapenemases in all *Enterobacteriaceae* family.

CONFLICT OF INTEREST

None to declare.

TABLE – Species distribution, source and antimicrobial resistance of *E. coli* and *Klebsiella* spp. in 2007 and 2015/2016

Year of isolation	Species	n (%)	Clinical source				Antimicrobial resistance			
			Urine	Respiratory tract	Skin wound	Fluids	Ertapenem n (%)	Imipenem n (%)	Meropenem n (%)	Tigecycline n (%)
2007	*E. coli*	10 (15.6)	9	0	1	0	1 (10)	0 (0)	0 (0)	0 (0)
	K. pneumoniae	51 (79.7)	25	22	2	2	5 (9.8)	2 (3.9)	3 (5.9)	0 (0)
	K. oxytoca	3 (4.7)	0	3	0	0	1 (33.3)	1 (33.3)	1 (33.3)	0 (0)
	Total	64 (100)	34	25	3	2	7 (10.9)	3 (4.7)	4 (6.2)	0 (0)
2015/2016	*E. coli*	25 (53.2)	23	0	2	0	0 (0)	6 (24)	0 (0)	0 (0)*
	K. pneumoniae	21 (44.7)	15	3	0	3	2 (9.5)	2 (9.5)	2 (9.5)	0 (0)*
	K. oxytoca	1 (2.1)	1	0	0	0	0 (0)	0 (0)	0 (0)	0 (0)
	Total	47 (100)	39	3	2	3	2 (4.2)	8 (17)	2 (4.2)	0 (0)

**One* E. coli *and one* K. pneumoniae *isolate presented MIC = 2 µg/ml (intermediate); fluids are blood (*n *= 4) and ascitic fluid (*n *= 1).*

MIC: minimum inhibitory concentration.

RESUMO

O uso indiscriminado de carbapenêmicos na luta contra bactérias Gram-negativas multirresistentes favorece o aparecimento de resistência a esses agentes antimicrobianos. Examinamos a atividade in vitro *de carbapenêmicos e tigeciclina em* Escherichia coli *e* Klebsiella *spp. isolados de um único hospital, em dois períodos diferentes, separados por oito anos. A resistência aos carbapenêmicos variou de 18,7% em 2007 a 19,1% em 2015/2016. Não encontramos isolados resistentes a tigeciclina, mas dois isolados intermediários no período 2015/2016. A tigeciclina é uma importante opção de tratamento para infecções causadas por bactérias Gram-negativas multirresistentes e ajuda na luta contra a disseminação da resistência aos carbapenêmicos.*

Unitermos: *carbapenêmicos*; Escherichia coli; Klebsiella.

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