Review article

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SUSCEPTIBILITY PATTERN OF CARBAPENEM-RESISTANT CLINICAL ISOLATES OF *ACINETOBACTER SPP.*

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Acinetobacter spp. is an opportunistic Gram-negative organism which causes infections in seriously ill, hospitalized individuals, mostly surgical patients, those on artificial ventilation, as well as those on long-term antibiotic treatments. The characteristic of clinical isolates of *Acinetobacter spp*. is resistance to a large number of antibiotics. Carbapenems are the approach of choice in the treatment of severe infections, although resistance to these has also been reported in the literature. Our study aims to establish the proportion of carbapenem-resistant clinical isolates of *Acinetobacter spp*. and to examine their susceptibility to other classes of antibiotics.

The study involved 175 isolates of *Acinetobacter spp*. from the material of patients hospitalized at the Clinical Centre Niš in the period from January to September 2016. Patient material consisted of endotracheal aspirates and samples from the patients with soft tissue infections. Testing of susceptibility to antimicrobial drugs was done using disk diffusion methodology on Mueller Hinton agar with gentamicin, amikacin, tobramycin, ciprofloxacin, levofloxacin, cotrimoxazole, imipenem, and meropenem disks (Bio-Rad, France). Susceptibility testing and interpretation of inhibition zones was done abiding by the EUCAST standard guidelines. Isolates resistant to imipenem and meropenem were tested for susceptibility to colistin and tigecycline, establishing with the Etest assay (Liofilchem, Italy) their minimum inhibitory concentrations (MICs). The MIC values for colistin were interpreted based on the EUCAST recommendations, while the MIC values for tigecycline were interpreted according to the recommendations by the Food and Drug Administration (FDA). The isolates resistant to at least three classes of antibiotics were considered multiresistant (MDR).

Of 175 examined clinical isolates of *Acinetobacter spp*., 50 (28.57%) isolates were obtained from endotracheal aspirates, and 125 from the patients with soft tissue infections. Twenty-nine (16.57%) isolates were susceptible to the tested carbapenems. Carbapenem-resistant isolates were mostly susceptible to tobramycin (26.76%), while only 8.9% were susceptible to cotrimoxazole, 1.37% to ciprofoxacin, and 0.69% (1 isolate) to levofloxacin. All tested isolates (137) were sensitive to colistin (MIC ranging from 0.5 μg/ml to 2.0 μg/ml). Of 106 isolates tested to tigecycline, 83 (78.30%) were susceptible (MIC≤2 μg/ml), while 23 isolates showed reduced susceptibility (MIC ranging from 3.0 μg/ml to 6.0 μg/ml). For colistin, MIC_{50} and MIC_{90} were 1.0 μg/ml and 1.5 μg/ml, respectively, and for tigecycline 1.5 μg/ml and 3.0 μg/ml, respectively. All carbapenem-resistant *Acinetobacter spp*. isolates were mutiresistant.

In our study, there were no isolates resistant to colistin, the last-resort antibiotic. It is required only for infections caused by MDR isolates, with continuous susceptibility surveillance. *Acta Medica Medianae 2016;55(4):86-91.*

Key words: *Acinetobacter spp*, carbapenem, resistance

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Introduction

Acinetobacter spp. is an opportunistic Gram-negative organism which has been one of the most important causative agents of hospital infections for over a decade. *Acinetobacter spp*. Characte-ristics enabling its existence in non-living environment are the ability to exist in dry conditions, but also its resistance to disinfectants. In addition, congenital resistance mechanisms as well as the ability to rapidly acquire resistance to antimicrobial drugs, make possible for the ogranism to survive in hospital surroundings. *Acinetobacter spp*. Causes infections in seriously ill hospitalized patients, most commonly surgical cases and those on artificial ventilation, as well as in those on long-term antibiotic therapy. In hospital patients, the organism causes pneumonia, urinary tract infections, infections of the central nervous system, and bo-

ne, soft tissue, and blood infections. Infections are usually the result of the microorganism entering the body through wounds, catethers, and mechanical (artificial) ventilation systems, mostly in patients hospitalized for longer periods of time. In these cases, use of adequate antimicrobial therapy can have an impact on the clinical outcome of the disease (1).

Clinical isolates of *Acinetobacter spp*. are commonly resistant to a large number of antibiotic agents. Their resistance is partly the consequence of poor permeability of the outer membrane of the microorganism, and partly their ability to acquire resistance genes from adjacent microorganisms via horizontal transfer. While most of *Acinetobacter spp.* isolates during the 1970s were sensitive to most commonly used antibiotics, the resistance of the microorganism is increasing steadily. Up to 2007, multiple resistance of *Acinetobacter baumannii* had been reported in as much as 70% of isolates. Carbapenems are the drugs of choice in the therapy of serious infections caused by multiresistant strains, but resistance to these has also been described in the literature (2, 3). In the study by Sohail et al., resistance of *Acinetobacter spp.* to imipenem was found in 90.9% of isolates. Resistance to carbapenems is usually associated with resistance to other classes of antibiotics, so that colistin and tigecycline represent a valid therapeutic option for carbapenem-resistant isolates (4). Since the sensitivity of *Acinetobacter spp*. isolates in local environments can be variable and may change with time, the therapy should be based on the results of sensitivity testing. The aim of our study was to establish the proportion of carbapenem-resistant clinical isolates of *Acinetobacter spp*. and to test their sensitivity to other classes of antibiotics.

Material and Methods

The study involved 175 isolates of *Acinetobacter spp.* from the material taken from patients hospitalized in the Clinical Center Niš in the period from January to September 2016. Patient material consisted of endotracheal aspirates and samples from the patients with soft tissue infections (wound swabs and puncture samples). Isolation of the bacteria was performed applying standard microbiological methodology. Testing of sensitivity to antimicrobial drugs was done using disk diffusion methodology on Mueller Hinton agar and disks of gentamicin, amikacin, tobramycin, ciprofloxacin, levofloxacin, cotrimoxazole, imipenem, and meropenem (Bio-Rad, France). Testing of sensitivity and interpretation of inhibition zones was done abiding by the EUCAST standard guidelines (5). Isolates resistant to imipenem and meropenem were tested for sensitivity to colistin and tigecycline, establishing via the Etest assay (Liofilchem, Italy) their minimum inhibitory concentrations (MICs). Based on the EUCAST recommendations, MIC values for colistin were interpreted (resistance >2 μg/ml, susceptibility ≤2 μg/ml), while MIC values for tigecycline were interpreted according to the recommendations by the Food and Drug Administration (FDA) (resistance ≥8 μg/ml, susceptibility ≤2 μg/ml). Multiresistant (MDR) isolates were considered those resistant to at least three classes of antibiotics. The Pseudomonas aeruginosa ATCC27853 strain was used for quality control.

Results

Of 175 examined clinical isolates of *Acinetobacter spp.*, 50 (28.57%) isolates were obtained from endotracheal aspirates, and 125 from the patients with soft tissue infections (wound swabs, puncture samples). Twenty-nine (16.57%) isolates were susceptible to the tested carbapenems (imipenem and meropenem). Carbapenem-susceptible isolates were susceptible to gentamycin in 17.24 %, amikacin in 27.58%, tobramycin in 79.31%, ciprofloxacin in 17.24%, levofloxacin in 20.69%, and cotrimoxazole in 24.14% of cases. Among the carbapenem-susceptible isolates, only 5 isolates were multiresistant.

Table 1. Distribution of carbapenem-resistant *Acinetobacter spp.* isolates

Clinics	Patients samples				Total
	Aspirate		Wound swab/puncture sample		
	№	%	№	%	
Clinic of General Surgery	12	27.9	36	34.95	48
Clinic of Neurosurgery	6	13.95	12	11.65	18
Clinic of Orthopedics	0	/	10	9.7	10
Clinic of Urology	0	/	6	5.8	6
Clinic of Cardiovascular and Transplantation Surgery	5	11.63	9	8.73	14
Clinic of Vascular Surgery	0	/	3	2.91	3
Clinic of Plastic and Reconstructive Surgery	0	/	6	5.8	6
Clinic of Infectious Diseases	12	27.9	4	3.88	16
Others	8	18.6	17	16.5	25
Total	43	100	103	100	146

Table 2. Susceptibility of carbapenem-resistant *Acinetobacter spp*. isolates to other antimicrobial agents by disk diffusion method

Antimicrobial agent	Susceptible	
	№	%
Gentamycin	0	0
Amikacin	0	0
Tobramycin	38	26.76
Ciprofloxacin	2	1.37
Levofloxacin	1	0.69
Cotrimoxazole	13	8.90

Of 146 (83.43%) carbapenem-resistant isolates of *Acinetobacter spp*., 105 (71.92%) were from the material of patients hospitalized in surgical clinics. Approximately one third of isolates (29.45%) were obtained from endotracheal aspirates. The distribution of these isolates accross the clinics of the Clinical Centre Niš and their origin (by the type of patient material) are shown in Table 1.

Disk diffusion was the method we used to examine the susceptibility to gentamycin, amikacin, tobramycin, ciprofloxacin, levofloxacin, and cotrimoxazole. Carbapenem-resistant isolates were mostly susceptible to tobramycin (26.76%), while only 8.9% were susceptible to cotrimoxazole, 1.37% to ciprofloxacin, and 0.69% (1 isolate) to levofloxacin (Table 2).

By way of determination of minimum inhibitory concentration, the susceptibility to colistin and tigecycline was assessed. All tested isolates (137) were susceptible to colistin (MIC ranging from 0.5 μg/ml to 2.0 μg/ml). Of 106 isolates tested to tigecycline, 83 (78.30%) were susceptible (MIC ≤2 μg/ml), while 23 isolates showed reduced susceptibility (MIC ranging from 3.0 μg/ml to 6.0 μg/ml) (Table 3).

For colistin, MIC_{50} and MIC_{90} were 1.0 μg/ml and 1.5 μg/ml, respectively, and for tige-cyclin 1.5 μg/ml and 3.0 μg/ml, respectively. All carbapenem-resistant isolates of *Acinetobacter spp*. were multiresistant.

Table 3. Susceptibility of carbapenem-resistant *Acinetobacter spp.* isolates to colistin and tigecyclin

AML*	MIC range (μg/ml)									№ of tested isolates
	0,38	0,5	0,75	1,0	1,5	2,0	3,0	4,0	6,0	
COL*	0	16	3	56	46	16	0	0	0	137
TGC*	1	1	15	10	29	27	19	3	1	106

AML*- antimicrobial agent, COL*- colistin, TGC*- tigecyclin

Discussion

Acinetobacter spp. is an opportunistic organism which has been increasingly causing hospital infections in seriously ill, immunocompromised patients on long-term hospital care. It is the cause of pneumonia in patients on mechanical ventilation, and also causes infections of the soft tissue, central nervous system, urinary tract, as well as sepsis. Although characterized by low virulence, this microorganism has got the ability to survive in low humidity environments and can develop resistance to a significant number of antimicrobial agents, and has the ability to form a biofilm. Although infections occur mostly in those with serious underlying medical conditions, inadequate therapy can be linked to clinical outcome. Congenital resistance to antimicrobial agents, as well as the ability to acquire resistance, greatly affect the available therapeutic options. Hospital isolates of *Acinetobacter spp*. are often mutiresistant, and carbapenems and colistin are usually the treatment of choice (2, 6).

In our study, most of carbapenem-resistant isolates originates from the material obtained from surgical patients, which agrees to the literature data. The risk of infection by carbapenem-resistant *Acinetobacter spp*., in addition to the underlying disease, are surgical interventions and use of invasive procedures (7).

Only 16.57% of isolates were susceptible to carbapenems, and less than one fifth (17.24%) of these isolates were multiresistant in our study. The proportion of clinical isolates of *Acinetobacter spp*. resistant to carbapenems in the studies worldwide varies depending on the geographical region and year of study: 90.9% in Pakistan; 94.6 % in Romania; 91% in Greece; 55% in Thailand; 59% in Indonesia (4, 8, 9, 10, 11).

The data from the Study for Monitoring Antimicrobial Resistance Trends (SMART), which reviewed the isolates from 48 countries in 2013-2014, showed that the highest percentage of isolates of *Acinetobacter baumannii* resistant to imipenem was obtained from the Middle East countries (91.4%) and the lowest from North American countries (36.2%) (12). All 146 carbapenem-resistant isolates of *Acinetobacter spp*. in our study were MDR (multidrug-resistant). These isolates demonstrated low susceptibility to ciprofloxacin, levofloxacin, and cotrimoxazole (1.37%; 0.69%; and 8.9%, respectively), and of all the tested aminoglycosides were susceptible only to tobramycin (26.8%). Similar results were reported by Piewngam et al., with 77.6% of MDR among carbapenem-resistant isolates (13).

The isolates involved in the SMART study which were MDR, were also in a high percentage resistant to some of the tested antibiotics. In our study, there were no isolates susceptible to amikacin, while MDR isolates in the SMART study were most commonly susceptible to this antibiotic (from 11% to 38%) (12). A high percentage of resistance to gentamicin (83.3%) and amikacin

(99%), and only 27% to ciprofloxacin, of carbapenem-resistant isolates, was detected by Sarada et al. (14). A higher percentage of isolates resistant to tobramycin (97%) compared to gentamicin and netilmicin (75% and 74%, respectively) was reported by Joshi et al. in India, while only 19% of isolates were resistant to amikacin (15).

Colistin is an old antibiotic from the group of polymyxins, the use of which was abolished during the 1970s due to its nephrotoxicity. The reason for therapeutic use of this old antibiotic is multiple drug resistance of *Acinetobacter spp*., especially its resistance to carbapenems. All the isolates in this study were susceptible to colistin, and MIC_{50} and MIC_{90} were 1.0 μg/ml and 1.5 μg/ml, respectively. Similar results have been reported by other authors as well. The value of MIC_{50} for isolates reported in the study by Mezzatesta et al. was 0.5 μg/ml, while Sarada et al. reported MIC_{50} of 2.0 μg/ml for carbapenem-resistant isolates, with one isolate resistant to colistin in each of the studies (14, 16).

Around 10% of tested isolates of Acinetobacter baumannii were resistant to colistin, as shown by Piewngam et al. There were no differences in susceptibility to colistin of MDR and non-MDR isolates, but MDR isolates had a broader range of MICs (13).

Although rare isolates of Acinetobacter baumannii were resistant to colistin, resistance to this last-resort antibiotic was often associated with resistance to other antibiotics used to treat the infections caused by this microorganism, so that there is no effective antimicrobial drug to treat them. A recent study by Oikonomou et al. in Greece demonstrated that 86 isolates were resistant to carbapenems and colistin, and only 13% of these were susceptible only to tigecyclin (9).

Tigecyclin is a new antibiotic that can be used in the therapy of soft tissue infections caused by multiresistant strains of *Acinetobacter spp*. An in vitro study of tigecyclin activity by Mezzatesta et al. demonstrated that there was no difference in the activity of this antibiotic against carbapenem-susceptible and carbapenem-resistant isolates. Susceptibility to tigecyclin was reported in 93% of isolates (16). Of the total number of isolates resistant to carbapenems in our study, there were 21.7% of isolates with reduced susceptibility to tigecyclin, which was markedly higher compared to the results obtained by Sarada et al., but similar to the results obtained by Dizbay et al., where 25.8% of isolates were resistant (14, 17). Follow-up of the effects of therapy with colistin and tigecyclin in patients with pneumonia caused by *Acinetobacter baumannii* showed that there was not any significant difference in clinical outcome, but the authors thought that a combined treatment approach could have produced better results compared to monotherapy (18).

Conclusion

With the advancement of modern medicine, the number of severely ill and immunocompromised hospital patients is on a constant rise too, making *Acinetobacter spp*., a low-virulence microorganism, a significant cause of infections. The widespread presence of carbapenem-resistant isolates in our study necessitates continued surveillance of resistance figures. Although there were no isolates resistant to the last-resort antibiotic colistin, it should be reserved only for the infections caused by MDR isolates, with constant surveillance of susceptibility.

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OSETLJIVOST KLINIČKIH IZOLATA *ACETINOBACTER SPP.* REZISTENTNIH NA KARBAPANEM

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Acinetobacter spp. je oportunistički Gram negativni organizam koji dovodi do infekcija teško obolelih hospitalizovanih bolesnika, najčešće hirurških i onih na veštačkoj ventilaciji, kao i kod bolesnika na dugotrajnoj terapiji antibioticima. Osobina kliničkih izolata *Acinetobacter spp*. je rezistentcija na veliki broj antibiotika. Karbapenemi predstavljaju lek izbora u terpiji teških infekcija, pri čemu se u literaturi beleži rezistencija i na ove antibiotike. Cilj našeg istraživanja bio je da se utvrdi zastupljenost karbpenem rezistentnih kliničkih izolata *Acinetobacter spp*. i ispita njihova osetljivost na ostale klase antibiotika.

Istraživanjem je obuhvaćeno 175 izolata *Acinetobacter spp*. izolovanih iz materijala bolesnika hospitalizovanih u Kliničkom centru Niš u periodu od januara do septembra 2016. godine. Bolesnički materijal su činili endotrahealni aspirati i uzorci bolesnika sa infekcijom mekih tkiva. Ispitivanje osetljivosti na antimikrobne lekove izvršeno je primenom disk difuzione metode na Mueller Hinton agaru diskovima gentamicina, amikacina, tobramicina, ciprofloksacina, levofloksacina, kotrimoksazola, imipenema i meropenema (Bio-Rad, France). Testiranje osetljivosti i interpretacija zona inhibicije sprovedeno je po uputstvu EUCAST standarda. Izolati rezistentni na imipenem i meropenem testirani su na osetljvost na kolistin i tigeciklin određivanjem minimalnih inhibitornih koncentracija (MIC) primenom E testa (Liofilchem, Italy). Na osnovu preporuka EUCAST izvršena je interpretacija vrednosti MIC za colistin, dok su vrednosti MIC za tigeciklin interpretirane na osnovu preporuka Agencije za hranu i lekove (The Food and Drug Administration–FDA). Multirezistentnim izolatima (MDR) smatrani su izolati rezistentni na najmanje tri klase antibiotika.

Od ukupno 175 ispitivanih kliničkih izolata *Acinetobacter spp*. iz endotrahealnih aspirata dobijeno je 28,57% izolata, a 125 iz uzoraka bolesnika sa infekcijom mekih tkiva. Na testirane karbapeneme bilo je osetljivo 29 (16,57%) izolata. Karbapenem rezistentni izolati su u najvećem procentu bili osetljivi na tobramicin (26,76%), dok je samo 8,9% bilo osetljivo na kotrimoksazol, 1,37% na ciprofloksacin i 1 (0,69%) na levofloksacin. Svi testirani izolati (137) bili su osetljivi na kolistin, MIC u rasponu od 0,5 μg/ml do 2,0 μg/ml. Od 106 izolata testiranih na tigeciklin 83 (78,30%) je bilo osetljivo (MIC≤2 μg/ml), dok je 23 izolata pokazalo smanjenu osetljivost, MIC u rasponu od 3,0 μg/ml to 6,0 μg/ml. Za kolistin MIC_{50} i MIC_{90} su iznosili 1,0 μg/ml i 1,5 μg/ml, a za tigeciklin 1,5 μg/ml i 3,0 μg/ml. Svi karbapenem rezistentni izolati *Acinetobacter spp*. bili su multirezistentni.

U našem istraživanju nije bilo izolata rezistentnih na rezervni antibiotik, kolistin, neophodno je primenjivati ga samo kod infekcija izazvanih MDR izolatima, uz kontinuirano praćenje osetljivosti. *Acta Medica Medianae 2016;55(4):86-91.*

Ključne reči: *Acinetobacter spp, carbapenem, rezistencija*