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ANTIMICROBIAL SUSCEPTIBILITY OF *ENTEROBACTERIACAE* ISOLATED FROM INTESTINAL MICROBIOTA OF RESIDENTS OF THE REPUBLIC OF GUINEA AND RUSSIA (SAINT PETERSBURG)

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Abstract. It is known that resistant *Enterobacteriaceae* strains can be a part of human microbiota. While colonizing the body of a healthy person, resistant strains do not cause diseases, while the healthy person becomes carrier and source of such strains or the resistance genes to the external environment. The aim of the study was to compare the antimicrobial susceptibility of opportunistic *Enterobacteriaceae* isolated from feces of residents of the Republic of Guinea (121 strains) and Russia, Saint Petersburg (897 strains). The antimicrobial susceptibility was determined by the disc-diffusion method according to the national russian Clinical Guideline “Antimicrobial susceptibility testing of microorganisms” using discs and Muller-Hinton agar manufactured by Oxoid. Resistance mechanisms were tested in bacterial strains non-susceptible to beta- lactams using confirmatory phenotypic and molecular tests. Resistant strains were detected significantly more often in the intestinal microbiota of residents of the Republic of Guinea, than of Saint Petersburg (83.5 and 28.7 per 100 strains studied, respectively), including strains with multidrug resistance (47.9 and 11.1, respectively). The residents of the Republic of Guinea have a high frequency of isolation of *Enterobacteriaceae* resistant to “old” antibiotics, which were often used in the 1970s, but rarely used in Russia and other European countries: tetracyclines (63.2), trimethoprim/ sulfamethoxazole (59.5) and aminopenicillins (48.4). The frequency of detection of strains resistant to modern clinically significant antibiotics (extended spectrum cephalosporins, fluoroquinolones, aminoglycosides) was the same in residents of the Republic of Guinea and Saint Petersburg. Resistance to beta-lactams in *Enterobacteriaceae* strains isolated both from the residents of the Republic of Guinea and from Saint Petersburg is due to the same mechanism — the production of beta-lactamases — broad-spectrum and extended spectrum- of various genetic families. This data corresponds to world global trends in the antimicrobial resistance in *Enterobacteriaceae*: resistance to aminopenicillins in *E. coli* is due to the production of broad-spectrum beta-lactamases TEM-1 (80% of strains from residents of the Republic of Guinea and 86.5% from Saint Petersburg), and resistance to extended spectrum cephalosporins — the production of extended spectrum beta-lactamases of the CTX-M1 genetic group (72.7 and 67.6% respectively). Our research has shown that the intestinal microbiota of the inhabitants of different continents (Europe and Africa) contains the strains (*Klebsiella pneumoniae* and *Escherichia coli*) resistant to clinically significant antibiotics (beta-lactams) due to single mechanism globally spread in *Enterobacteriaceae*.

Key words: *resistance, Enterobacteriaceae, Republic of Guinea, intestine microbiota, antimicrobial susceptibility, beta-lactamase, E. coli, K. pneumoniae.*

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ЧУВСТВИТЕЛЬНОСТЬ К АНТИМИКРОБНЫМ ПРЕПАРАТАМ ШТАММОВ ЭНТЕРОБАКТЕРИЙ, ВЫДЕЛЕННЫХ ПРИ ИЗУЧЕНИИ МИКРОБИОТЫ КИШЕЧНИКА ЖИТЕЛЕЙ ГВИНЕЙСКОЙ РЕСПУБЛИКИ И РОССИИ (САНКТ-ПЕТЕРБУРГ)

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Резюме. Известно, что резистентные к антибиотикам штаммы энтеробактерий могут входить в состав микробиоты кишечника. Колонизируя организм здорового человека, устойчивые штаммы не вызывают заболеваний желудочно-кишечного тракта, при этом здоровый человек становится носителем и источником выделения таких штаммов или детерминант резистентности во внешнюю среду. Цель исследования состояла в сравнительной оценке чувствительности к антибиотикам штаммов условно-патогенных энтеробактерий, выделенных из проб испражнений жителей Гвинейской Республики (121 штамм) и Санкт-Петербурга (897 штаммов). Чувствительность к антибиотикам определяли диско-диффузионным методом согласно Клиническим рекомендациям «Определение чувствительности микроорганизмов к антимикробным препаратам» с использованием дисков производства Oxoid. У штаммов бактерий, нечувствительных к бета-лактамным препаратам, изучили механизмы резистентности, используя подтверждающие фенотипические тесты и молекулярные методы. У жителей Гвинейской Республики устойчивые к антибиотикам штаммы в составе микробиоты кишечника выявлены достоверно чаще, чем у жителей Санкт-Петербурга (83,5 и 28,7 на 100 исследованных штаммов соответственно), включая штаммы с множественной резистентностью (47,9 и 11,1 соответственно). У жителей Гвинейской Республики высока частота выделения штаммов энтеробактерий, устойчивых к «старым» АМП, которые часто применяли в 70-е гг. прошлого столетия, но редко используются в настоящее время в РФ и других европейских странах: тетрациклинам (63,2), триметоприм/сульфаметоксазолу (59,5) и аминопенициллинам (48,4). Частота выявления штаммов, устойчивых к современным клинически значимым антибиотикам (цефалоспорины, фторхинолоны, аминогликозиды) практически не отличалась у жителей Гвинейской Республики и Санкт-Петербурга. Резистентность к бета-лактамным препаратам штаммов, выделенных как у жителей Гвинейской Республики, так и Санкт-Петербурга, обусловлена практически одним механизмом — продукцией бета-лактамаз широкого и расширенного спектра различных генетических семейств. Выявленные закономерности соответствуют глобальным тенденциям формирования резистентности к антибиотикам у штаммов энтеробактерий в мире: устойчивость к аминопенициллинам у *E. coli* обусловлена продукцией бета-лактамазы широкого спектра TEM-1 (80,0% штаммов от жителей Гвинейской Республики и 86,5% — Санкт-Петербурга), а устойчивость к цефалоспоринам расширенного спектра — продукцией бета-лактамаз расширенного спектра генетической группы CTX-M1 (72,7 и 67,6% соответственно). Наши исследования показали, что в составе нормальной микробиоты кишечника жителей разных континентов (Европа и Африка) присутствуют бактерии (*K. pneumoniae* и *E. coli*), штаммы которых характеризуются резистентностью к клинически значимым антибиотикам (бета-лактамам), обусловленной единым механизмом, глобально распространенным в популяциях энтеробактерий.

Ключевые слова: *резистентность, Enterobacteriaceae, Гвинейская Республика, нормальная микробиота кишечника, чувствительность к антибиотикам, бета-лактамазы, E. coli, K. pneumoniae.*

Introduction

At present, the development of antimicrobial resistance (AMR) of infectious agents has an adverse effect on human health due to a decrease in the clinical effectiveness of etiotropic therapy. Multidrug resistant strains of microorganisms are the cause of severe forms of health-care infections, as well as other infectious diseases (tuberculosis, shigellosis, salmonellosis, typhoid fever). In modern conditions, according to the WHO assessment, the AMR is a global problem that must be overcome without delay. In this regard, in 2015 the World Health Assembly adopted a global plan of action to combat AMR [1]. One of the ways to “contain” antibiotic resistance is to monitor the circulation of resistant strains of microorganisms, as well as genes that determine the AMR. Two species of *Enterobacteriaceae* (*Klebsiella pneumoniae* and *Escherichia coli*) are included in the list of indicator microorganisms which are monitored for resistance to clinically relevant antibiotics, in the EU countries. Particular attention is paid to strains resistant to extended spectrum cephalosporins (ESC) and carbapenems (producing extended spectrum beta-lactamases (ESBL) and carbapenemases) [6].

The results of studies conducted in the Russian Federation in the last decade have shown that resistant strains of *Enterobacteriaceae*, causative agents of both health-care and community-acquired infections, were isolated from various clinical samples in Russian hospitals, especially in intensive care units (ICU). In 2013–2016 in population of nosocomial strains 50–70% of *E. coli* were resistant to ESC and fluoroquinolones, more than 20–30%

were resistant to aminoglycosides. In the population of *K. pneumoniae* the resistance was more pronounced: 80–90% strains were resistant to ESC and fluoroquinolones, more than 60% — to aminoglycosides, carbapenem resistance has appeared (about 10%). High levels of resistance were also observed in strains isolated under community-acquired conditions: about 30% of *E. coli* strains and more than 50% of *K. pneumoniae* strains were resistant to fluoroquinolones (every second strain); about 20% of *E. coli* and 40% *K. pneumoniae* showed resistance to aminoglycosides; the proportion of *K. pneumoniae* strains resistant to carbapenems was about 2% [2, 4, 5, 8]. It is known that resistant *Enterobacteriaceae* strains can be a part of human microbiota. While colonizing the body of a healthy person, resistant strains do not cause diseases, while the healthy person becomes carrier and source of such strains or the resistance genes to the external environment. Strains of various bacteria, carrying the genes responsible for the production of ESBL and carbapenemases, are found in urban wastewater, sewage, soil, feces of agricultural and domestic animals [10].

The aim of the study was to compare the antimicrobial susceptibility of opportunistic *Enterobacteriacae* strains isolated from feces of residents of the Republic of Guinea and Russia (Saint Petersburg).

Materials and Methods

We studied the antimicrobial susceptibility of 1018 *Enterobacteriacae* strains isolated in 2015–2016 from feces of residents of the Republic of Guinea (121 strains) and Saint Petersburg (897 strains) [9]. The collection included 604 strains of *E. coli* and 414 strains of other *Enterobacteriacae (Klebsiella* spp., *Enterobacter* spp., *Proteus* spp., *Citrobacter* spp., *Hafnia alvei).* The antimicrobial susceptibility was determined by the disc-diffusion method according to the national russian Clinical Guideline "Antimicrobial susceptibility testing of microorganisms" [3] using discs and Muller–Hinton agar manufactured by Oxoid. The following antibiotics were included in the study: aminopenicillins (ampicillin and amoxicillin/clavulanic acid); ESC (ceftazidime and cefotaxime); carbapenems (meropenem); quinolones (nalidixic acid and ciprofloxacin); aminoglycosides (gentamicin, tobramycin, amikacin); tetracyclines (tetracycline); nitrofuranes (nitrofurantoin); trimethoprim/sulfamethoxazole and chloramphenicol. As many species of *Enterobacteriacae* have natural resistance to aminopenicillins, susceptibility to these antibiotics was determined only in *E. coli* and *Proteus mirabilis.*

Resistance mechanisms were tested in bacterial strains non-susceptible to beta-lactams using confirmatory tests: phenotypic (a double discs synergy test, the ESBL+AmpC Screen Kit by Rosco Diagnostica, Denmark) and molecular tests (PCR with electrophoretic detection with specific primers to genes encoding beta-lactamases of different molecular classes: TEM, SHV, OXA, CTX-M, AmpC), using the primers and conditions described previously [7], reaction mixture contained 2xTaq Master mix green HS (Alkor Bio, Russia) and the corresponding primers in a final concentration of 0.4 μM.

Results and Discussion

The collection of *Enterobacteriacae* strains isolated from the inhabitants of the Republic of Guinea and Saint Petersburg was represented by strains susceptible to antibiotics (16.5 and 71.3%, respectively), resistant to 1–2 classes of antibiotics (35.5 and 17.6%, respectively), as well as strains with multiple resistance to 3 or more classes of antibiotics (47.9 and 11.1%, respectively) (Table 1).

The frequency of isolation of resistant strains varied among residents of the Republic of Guinea and Saint Petersburg, depending on the antibiotics (Table 2). All the strains retained susceptibility to carbapenems. In the collection of strains isolated from the inhabitants of the Republic of Guinea, a high frequency of resistance to three classes of antibiotics was noted: tetracyclines — 63.2 per 100 strains studied, trimethoprim/sulfamethoxazole — 59.5 and aminopenicillins — 48.4. Resistance to quinolones was 17.4, to nitrofuranes — 12.0, to chloramphenicol — 9.9, to ESC — 9.1 and to aminoglycosides — 6.6. In the collection of strains isolated from residents of Saint Petersburg, the frequency of resistant

Table 1. Resistance phenotypes of *Enterobacteriacae* isolated from residents of the Republic of Guinea and Saint Petersburg (per 100 strains studied)

Resistance phenotypes	Republic of Guinea (n = 121)			Saint Petersburg (n = 897)		
	n	per 100 strains studied	95% CI	n	per 100 strains studied	95% CI
Susceptible	20	16.5	11.0–24.2	640	71.3	68.3–74.2
Resistant (total):	101	83.5	75.7–89.0	257	28.7	25.8–31.7
– to 1–2 antibiotic classes	43	35.6	27.6–44.4	158	17.6	15.3–20.2
– to 3 and more antibiotic classes	58	47.9	39.2–56.8	99	11.1	9.1–13.3
ESBL-producing	11	9.1	5.2–15.5	68	7.6	6.0–9.5

Table 2. Antimicrobial resistance of *Enterobacteriaceae* isolated from residents of the Republic of Guinea and Saint Petersburg (per 100 strains studied)

АМП		Republic of Guinea (n = 121)			Saint Petersburg (n = 897)		
		n	per 100 strains studied	95% CI	n	per 100 strains studied	95% CI
β-lactams	Aminopenicillines[1]	45	46.9[2]	37.2–56.8	96	18.8[3]	15.6–22.4
	ESC	11	9.1	5.2–15.5	68	7.6	6.0–9.5
	Carbapenems	0	0	0–3.1	0	0	0–0.4
Quinolones		21	17.4	11.6–25.1	79	8.8	7.1–10.8
Tetracyclines[1]		74	63.2[4]	54.2–71.4	131	14.6	12.4–17.1
Aminoglycosides		8	6.6	3.4–12.5	37	4.1	3.0–5.6
Nitrofurans[1]		14	12.0[4]	7.3–19.1	43	4.8	3.6–6.4
Trimethoprim/sulfamethoxazole		72	59.5	50.6–67.8	65	7.2	5.7–9.1

[1] susceptibility of *Enterobacteriaceae* naturally susceptible to this antimicrobials was studied;
[2] susceptibility of *E. coli* and *Proteus mirabilis* (96 strains) was studied;
[3] susceptibility of *E. coli* and *Proteus mirabilis* (511 strains) was studied;
[4] susceptibility of *Enterobacteriaceae* (117 strains) was studied without *Proteus* spp. naturally resistant to nitrofurans;
ESC — extended spectrum cephalosporins.

strains was significantly lower and was 18.8 and 14.6, respectively, for aminopenicillins and tetracyclines. The strains resistant to other antibiotics were isolated in 4.1–8.8 per 100 strains studied. During study strains resistant to beta-lactams (ampicillin and ESC) were used to detect genes encoding the production of beta- lactamases of frequently occurring molecular classes: TEM, SHV, OXA, CTX- M and AmpC.

As many species of *Enterobacteriaceae* (*Klebsiella* spp., *Enterobacter* spp., *Citrobacter* spp., *Hafnia alvei*) are characterized by natural resistance to aminopenicillins, so their susceptibility to this antibiotics was not evaluated. 141 strains of *E. coli* resistant to aminopenicillins were detected: 45 strains from the inhabitants of the Republic of Guinea and 96 strains from residents of Saint Petersburg. Genes encoding the production of broad-spectrum beta-lactamase (BSBL) — TEM-1, are found in the overwhelming majority of strains (80.0 and 83.3%, respectively); OXA — in 3 strains (6.7%) isolated from the inhabitants of the Republic of Guinea, and 5 strains (5.2%) isolated in Saint Petersburg; SHV — in one strain isolated in Saint Petersburg. The genes of BSBL of the two molecular classes, TEM and OXA, were simultaneously identified in three strains (3.1%), isolated from the inhabitants of Saint Petersburg. Genes of frequently occurring BSBLs (TEM, SHV, OXA) were not identified in 13 strains characterized, possibly, by other mechanisms of resistance.

A molecular study of 79 strains of *Enterobacteriaceae* resistant to ESC showed that *K. pneumoniae* strains, isolated both from the inhabitants of the Republic of Guinea (2 strains) and from Saint Petersburg (13 strains), possessed the genes of ESBLs

Table 3. Beta-lactamases in *Enterobacteriaceae* (*E. coli* и *K. pneumoniae*), isolated from residents of the Republic of Guinea and Saint Petersburg

Beta-lactamases	Republic of Guinea			Saint Petersburg		
	n	%	95% CI	n	%	95% CI
Strains resistant to aminopenicillins						
Total strains	45	100	–	96	100	–
TEM	36	80.0	66.2–89.1	83	86.5	78.2–91.9
SHV	0	0	0–7.9	1	1.0	0.2–5.7
OXA	3	6.7	2.3–17.9	5	5.2	2.2–11.6
Other BSBLs	6	13.3	6.3–26.2	7	7.3	3.6–14.3
Strains resistant to ESC						
Total strains	11	100	–	68	100	–
TEM	0	0	0–25.9	2	2.9	0.8–10.1
SHV	0	0	0–25.9	2	2.9	0.8–10.1
AmpC CMY	0	0	0–25.9	1	1.5	0.3–7.9
CTX-M, of which:	9	81.8	52.3–94.9	63	92.7	83.9–96.8
– CTX-M1	8	72.7	43.4–90.3	46	67.6	55.8–77.6
– CTX-M9	1	9.1	1.6–37.7	17	25.1	16.2–36.4
Other ESBLs	2	18.2	5.1–47.7	0	0	0–5.3

BSBL — broad spectrum beta-lactamase; ESC — extended spectrum cephalosporines; ESBL — extended spectrum beta-lactamase.

of the CTX-M genetic family, of CTX-M1 genetic group (Table 3). In an overwhelming majority of *E. coli* strains (9 from the inhabitants of the Republic of Guinea and 55 from the inhabitants of Saint Petersburg) we identified genes encoding ESBLs of the CTX-M genetic family (81.8% and 92.7%, respectively) that belonged to two genetic groups: CTX-M1 (72.7 and 67.6%, respectively) and CTX-M9 (9.1 and 25.1%, respectively). Also, *E. coli* strains isolated in Saint Petersburg, discovered genes encoding ESBL production in TEM and SHV genetic families (2,9%), and genes encoding cephalosporinase molecular class C production (AmpC, of the CMY genetic group) in one strain (1.5%). The genes of widespread ESBLs (CTX-M, TEM, SHV, AmpC) were not detected in 2 strains of *E. coli* in the Guinean Republic, possibly characterized by other resistance mechanisms.

Studies have shown that resistant strains of *Enterobacteriacae* were isolated in the intestinal microbiota of both the residents of the Republic of Guinea and Saint Petersburg. It should be noted that the resistant strains were detected significantly more often in the residents of the Republic of Guinea, than of Saint Petersburg (83.5 and 28.7 per 100 strains studied, respectively), including strains with multidrug resistance (47.9 and 11.1, respectively). The residents of the Republic of Guinea have a high frequency of isolation of *Enterobacteriacae* resistant to “old” antibiotics, which were often used in the 1970s, but rarely used in Russia and other European countries to treat infections of different locations: tetracyclines (63.2), trimethoprim/ sulfamethoxazole (59.5) and aminopenicillins (48.4). The frequency of detection of strains resistant to modern clinically significant antibiotics (ESC, fluoroquinolones, aminoglycosides) was the same in residents of the Republic of Guinea and Saint Petersburg. It has been established that the resistance to beta-lactams in *Enterobacteriacae* strains isolated both from the residents of the Republic of Guinea and from Saint Petersburg is due to one mechanism — the production of beta-lactamases — broad-spectrum and extended spectrum — of various genetic families. This data corresponds to world global trends in the antimicrobial resistance in *Enterobacteriacae*: resistance to aminopenicillins in *E. coli* is due to the production of broad-spectrum beta-lactamases TEM-1 (80% of strains from residents of the Republic of Guinea and 86.5% from Saint Petersburg), and resistance to ESC — the production of ESBLs of the CTX-M1 genetic group (72.7 and 67.6%, respectively).

Our research has shown that the normal microbiota of the inhabitants of different continents (Europe and Africa) contains the strains *(Klebsiella pneumoniae* and *Escherichia coli)* resistant to clinically significant antibiotics (beta-lactams) due to single mechanism globally spread in *Enterobacteriacae*.

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