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Antimicrobial resistance in clinical *Escherichia coli* isolates obtained from animals

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SUMMARY
The article presents data on the phenotypic and genotypic characteristics of antimicriobial resistance in *Escherichia coli* clinical isolates recovered from bovine microbiota (secretions from mammary glands, cervical swabs). 127 *Escherichia coli* isolates were studied, i.e. 44 from mammary glands secretions and 83 from cervical swabs. Disk diffusion method was used to study antimicrobial resistance of the cultures; minimum inhibitory concentrations of antimicrobials were determined in a serial dilution method; resistance genes were detected by polymerase chain reaction. The carried out research demonstrates a wide distribution of the isolates belonging to the phenotype resistant to ansamycins (rifampicin), semi-synthetic penicillins (ampicillin and amoxicillin), tetracyclines (doxycycline). The isolates showed a lower level of resistance to macrolides (azithromycin), amphenicols (levomycetin) and aminoglycosides (tobramycin). It was found that *Escherichia coli* clinical isolates are sensitive to third-generation cephalosporins and fluoroquinolone antimicrobials. However, since 28.46% of cultures demonstrate intermediate resistance to third-generation cephalosporins and 49.02% of *Escherichia coli* DNA samples isolated from mammal gland secretions had blaDHA gene associated with resistance to this group of antimicrobials, these antimicrobials could be hardly recommended as antibiotics of choice. Absence of VIM carbapenemase-encoding gene in the DNA of the recovered isolates and a low level of phenotypic resistance (10.22% of isolates from cervical swabs) can be one of the reasons for recommending first-line carbapenems as antibiotics of choice to treat animal diseases associated with *Escherichia coli*, along with fluoroquinolones as reserve antimicrobials. It was found that the recovered *Escherichia coli* isolates are more sensitive to combination antibiotics than to mono-antibiotics.

Keywords: phenotypic and genetic resistance, *Escherichia coli*, isolates, genetic markers, microbiota, Gram-negative bacteria, extended-spectrum β-lactamases, antibiotics

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Антибиотикорезистентность клинических изолятов *Escherichia coli*, выделенных от животных

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РЕЗЮМЕ

Представлены данные о фенотипической и генотипической характеристике антибиотикорезистентности клинических изолятов *Escherichia coli*, выделенных из микробных биотопов (секрет молочной железы, цервикальные смывы) крупного рогатого скота. Исследовано 127 изолятов кишечной палочки, в том числе 44 – из секрета молочной железы, 83 – из цервикальных смывов. Антибиотикорезистентность культур изучали диско-диффузионным методом, минимальные ингибирующие концентрации антибактериальных препаратов определяли методом серийных разведений, гены резистентности детектировали с помощью полимеразной цепной реакции. В результате исследований показано широкое распространение изолятов микроорганизмов с фенотипом резистентности к ансамицинам (рифампицину), полусинтетическим пенициллинам (ампициллину и амоксициллину), тетрациклинам (доксициклину). Меньший уровень устойчивости изоляты проявляли к макролидам (азитромицину), амфениколам (левомицетину) и аминогликозидам (тобрамицину). Установлено, что клинические изоляты *Escherichia coli* чувствительны к цефалоспоринам III поколения и противомикробным средствам из группы фторхинолонов. Однако регистрация у 28,46% культур промежуточной резистентности к цефалоспоринам III поколения и выявление гена blaDHA, ассоциированного с развитием устойчивости к данной группе препаратов в 49,02% образцов ДНК эшерихий, изолированных из секрета молочной железы, не позволяют рекомендовать их в качестве препаратов выбора. Отсутствие гена VIM, кодирующего продукцию карбапенемаз в ДНК у выделенных изолятов, и низкий уровень фенотипической устойчивости (10,22% изолятов из цервикальных смывов) может служить одной из предпосылок для рекомендации использования карбапенемов 1-го ряда в качестве препаратов выбора для терапии заболеваний животных, ассоциированных с *Escherichia coli*, наряду со фторхинолонами, однако только в качестве препаратов резерва. Установлено, что выделенные изоляты *Escherichia coli* демонстрировали бóльшую чувствительность к комбинированным противомикробным лекарственным средствам в сравнении с монопрепаратами.

Ключевые слова: фенотипическая и генетическая резистентность, *Escherichia coli*, изоляты, генетические маркеры, микробные биотопы, грамотрицательные бактерии, *β*-лактамазы расширенного спектра, антибиотики

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INTRODUCTION

Escherichia coli is the most widespread Gram-negative bacterial pathogen, that poses both clinical and epidemiological problems resulting in a number of infectious and inflammatory diseases in animals [1–3].

Violation of antimicrobial chemotherapy schemes and protocols observed now in livestock production causes occurrence of *E. coli* resistant strains in animals. Those strains can be transmitted to humans, inter alia, through objects and food products contaminated with bacteria resistant to antibiotics, which is a serious epidemiological threat [3–7].

Antimicrobial resistance of *E. coli* isolates is explained both by the natural resistance of the microorganism to the main clinically significant antimicrobial substances and by the genetically determined molecular mechanisms of resistance and virulence, mostly developed due to the horizontal transfer of a gene encoding them [8–11]. Extrachromosomal factors form the basis for rapidly emerging resistance, which can be developed within 1–2 years [12].

Monitoring data on antimicrobial resistance (AMR) of *E. coli* clinical isolates from animals in the Russian Federation are incomplete and differ depending on the region and on the study period [13–15].

At the same time, in order to ensure effective antimicrobial therapy for farm animals, it is necessary to look into *E. coli* resistance to antimicrobials.

In connection with the above, the aim of this work was to study phenotypic and genotypic characteristics of antimicrobial resistance in *E. coli* clinical isolates recovered from cattle in the Ural region.

MATERIALS AND METHODS

The tested samples. From 2016 to 2021, *E. coli* isolates (n = 127) recovered from bovine clinical materials were received from different livestock farms of the Ural region.

Nutrient media or reagents. The following differential diagnostic nutrient media were used in the work: Endo medium, Levin medium, sorbitol medium, meat-peptone agar (MPA), blood agar, Manka agar, Olkenitsky's medium, Simmons medium (FBIS SRCAMB, Russia). Biochemical properties of bacterial cultures were determined with a set of reagents "Biochemical assay plates for enterobacteria differentiation (PBDE)" (RPC Diagnostic Systems, Russia) according to the manufacturer's instructions.

Microbiological tests were carried out in accordance with the "Methodical guidance on bacteriological diagnosis of colibacillosis in animals", approved by the Ministry of Agriculture of the Russian Federation on July 27, 2000 No. 13-7-2/2117 [16].

The following biochemical properties of isolated *E. coli* cultures were studied: production of urease, *β*-D-galactosidase, *β*-glucosidase, phosphatase, lysine decarboxylase,

ornithine decarboxylase, arginine dihydrolase, nitrite reductase, hydrogen sulfide, indole, acetoin (acetylmethylcarbinol); fermentation of glucose, sucrose, mannitol, trehalose, lactose, mannoses, xyloses, riboses, cellobioses, malonate, citrate, sodium citrate with glucose, inositol, sorbitol, arabinose, maltose.

The results of biochemical reactions were assessed visually. The isolated cultures were identified in accordance with Bergey's Manual of Determinative Bacteriology[1].

The resistance phenotype observed in 15 recovered isolates to the following antimicrobials (included into 10 groups: ansamycin, tetracyclines, third-generation cephalosporins, penicillins, macrolides, second generation fluoroquinolones, amphenicols, aminoglycosides, glycopeptides, carbapenems) was determined in a disk diffusion test in accordance with MUK 4.2.1890-04 "Determination of sensitivity of microorganisms to antimicrobials" [17]. For the purposes of this work we used standard commercial disks (LLC "NITSF", Russia) with the known active ingredient content: meropenem – 10 μg, ciprofloxacin – 5 μg, rifampicin – 5 μg, ofloxacin – 5 μg, ampicillin – 10 μg, amoxicillin – 20 μg, levomycetin – 30 μg, doxycycline – 30 μg, ceftriaxone – 30 μg, enrofloxacin – 5 μg, tetracycline – 30 μg, azithromycin – 15 μg, vancomycin – 30 μg, gentamicin – 120 μg, tobramycin – 10 μg. The results were interpreted in accordance with the recommendations of the European Committee on Antimicrobial Susceptibility Testing [18].

Minimum inhibitory concentrations (MIC) of antimicrobials, including combined pharmaceuticals intended for treatment of inflammatory diseases of the mammary gland and organs of reproductive tract (for isolates recovered from mammary gland secretions and cervical swabs of animals), was determined in a serial dilution method with addition of a bacterial suspension containing 10^7 bacteria in 1 mL. Broth and a suspension of bacteria without an antibiotic were used to control the purity of the growth of cultures, and broth with an antibiotic without culture was used to control the sterility of the medium. The inoculations were incubated in a thermostat for 24 hours [17].

Molecular genetic tests using polymerase chain reaction (PCR) were carried out in accordance with the instructions for commercial test systems. We used a DNA isolation kit Diatom DNA Prep 200 for our work (Isogen Laboratory LLC, Russia). Genetic determinants of AMR resistance were detected in PCR using reagent kits from "Lytech" Co. Ltd. (Russia). We detected blaDHA gene encoding plasmid-mediated *β*-lactamase AmpC and causing resistance of *Enterobacteriaceae* bacteria to protected penicillins and broad-spectrum cephalosporins [16, 17, 19, 20]; CTX-M gene encoding extended-spectrum *β*-lactamases, which is moved by mobile genetic elements (transposons, integrons, IS elements) and is associated with development of multi-resistance; VIM gene located on a non-conjugative plasmid, which includes class 1 integron and causes production of carbapenemases. Real-time PCR was performed using analyzer from Applied Biosystems QuantStudio™ 5 (Thermo Fisher Scientific Inc., USA).

[1] Bergey's Manual of Determinative Bacteriology: two volumes. Vol. 1. Ed. J. G. Holt, N. Krieg, P. Snit, J. Staley, S. Williams. 9th ed. Moscow: Mir; 1997. 432 p.

For statistical data analysis we used a standard Microsoft Excel 2010 package and methods of descriptive statistics: percentages, frequencies, frequency distribution, etc.

RESULTS AND DISCUSSION

Detecting AMR E. coli isolates with a disk-diffusion method. The figure below shows results of AMR study for 127 *E. coli* isolates recovered from bovine biological materials.

The AMR profile of *E. coli* isolates recovered from mammary glands secretions was characterized by high resistance levels (54.54%) to the penicillin group, i.e. 49.99% of cultures were resistant to ampicillin, and 4.55% to amoxicillin. Resistance to rifampicin and the tetracycline group was observed in 47.72% and 45.46% of *E. coli* isolates, respectively. 15.91% of *E. coli* cultures were resistant to amphenicol group (levomycetin). Resistance to aminoglycosides (tobramycin) was detected in 11.36% of isolates. The minimum number of AMR *E. coli* isolates was found in relation to the following groups of antimicrobials: second-generation fluoroquinolones (ciprofloxacin – 2.27%, enrofloxacin – 4.55%, ofloxacin – 6.82%), macrolides (azithromycin – 4.55%), third generation cephalosporins (ceftriaxone – 6.82%).

It was found that 31.81% of *E. coli* isolates recovered from secretion of the bovine mammary glands showed intermediate resistance to tobramycin, which belongs to the group of aminoglycosides. 29.55% of isolated *E. coli* cultures demonstrated intermediate resistance to levomycetin, 22.73% of *E. coli* isolates demonstrated resistance to ciprofloxacin and ceftriaxone. Intermediate resistance to representatives of tetracycline (doxycycline) group and second-generation fluoroquinolone group (enrofloxacin) was reported in 15.91% of isolates.

As for *E. coli* isolates from bovine cervical swabs, phenotypes resistant to penicillin antimicrobials were predominant: 42.17 and 36.15% of cultures were resistant to ampicillin and amoxicillin. 53.01% of isolates demonstrated resistance to rifampicin, which is the main representative of the ansamycin group. 25.30% of *E. coli* isolates were resistant to doxycycline, and 7.23% were resistant to tetracycline. The minimum number of *E. coli* isolates was resistant to third-generation cephalosporins (3.61%) and aminoglycosides, namely gentamicin (2.41%). 32.53% of isolates demonstrated intermediate resistance to ceftriaxone, which is a representative of the third-generation cephalosporins. Intermediate resistance to the carbapenem group was revealed in 30.65% of isolates. 27.02% of *E. coli* cultures had intermediate resistance to levomycetin. Intermediate resistance to representatives of second-generation fluoroquinolones, namely ciprofloxacin, ofloxacin and enrofloxacin, was demonstrated by 16.87, 22.8, and 16.87% of isolates, respectively.

AMR tests of 127 isolates of *E. coli* estimated that many of them had polyresistance: 64.5% of the studied cultures were resistant to four AMR classes, 54.33% – to five classes. 16.6% of bacterial isolates were multi-resistant, i.e. demonstrated resistance to six AMR classes.

Determination of minimum inhibitory concentrations (MIC) of commercial antimicrobials. *E. coli* isolates obtained from the secretion of the mammary gland (13.64%) demonstrated the highest rate of resistance to medicines, which include cloxacillin (penicillin group) as

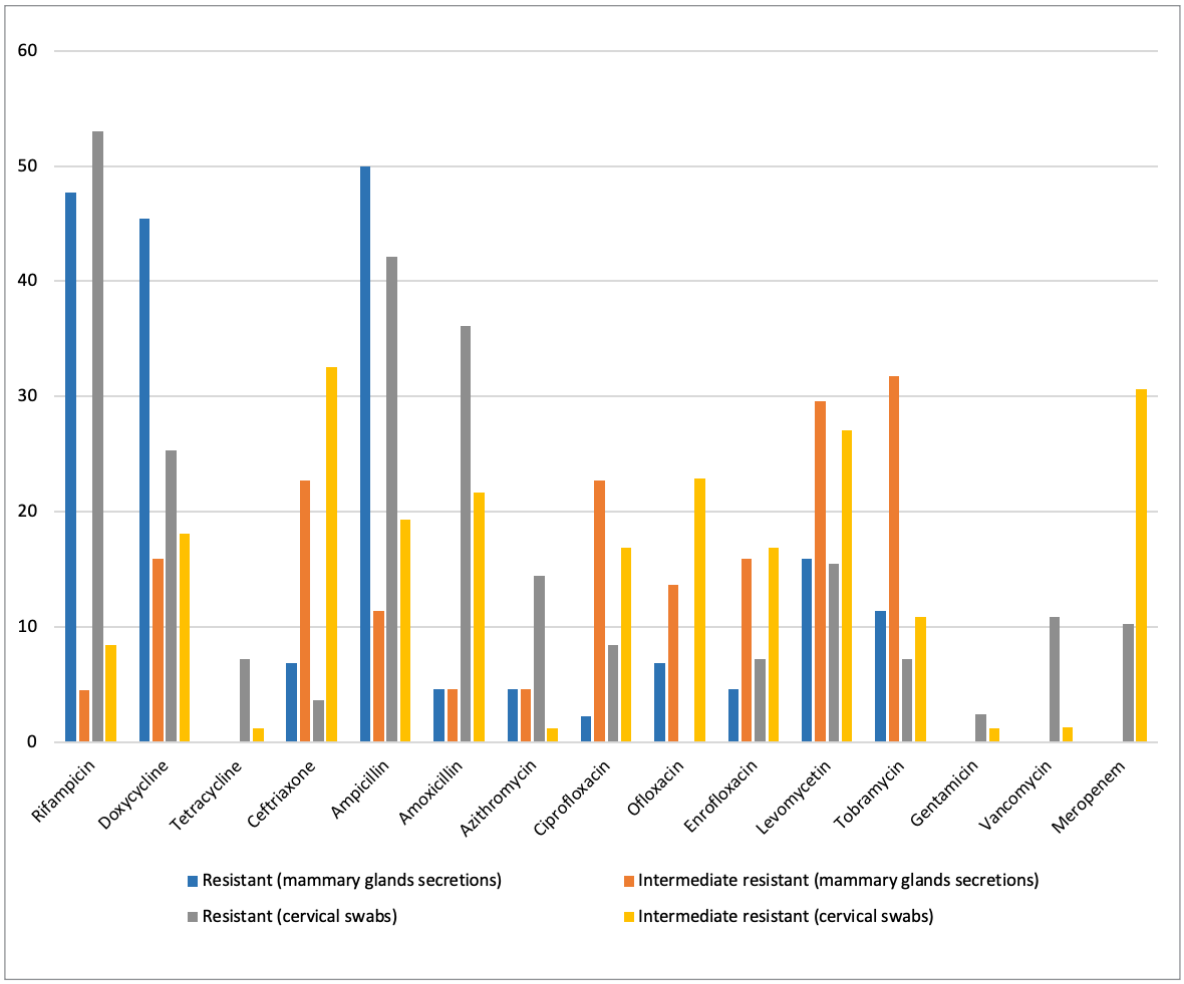

Fig. AMR profile of E. coli clinical isolates recovered from cattle (%)

the active substance. Cloxacillin-based combination of antibiotics were most active against *E. coli*. So, the combined use of such antimicrobials as cloxacillin + benzathine and cloxacillin + neomycin, sulfate + dexamethasone + trypsin caused resistance in only 6.82% of isolates, and combination of cloxacillin + ampicillin + benzathine acid caused resistance in 2.27% of isolates. 6.81% of *E. coli* cultures demonstrated resistance to antimicrobials belonging to the first-generation cephalosporins based on cefalonium and cefapirin. The least rate of resistance was observed to combination of antibiotics from tetracyclines (2.27%) and aminoglycosides (1.30%) groups. 4.34 and 4.55% of isolates showed intermediate resistance to second and third generation cephalosporin antimicrobials, respectively.

E. coli cultures isolated from cervical swabs of cows demonstrated the highest level of resistance to antimicrobials based on a synthetic antifungal agent from the imidazole derivatives – 12.05%. 6.02% and 8.40% of isolates were resistant to commercial antimicrobials containing substances from macrolide and ansamycin groups, respectively. 4.82% of isolates had intermediate resistance to a polypeptide antibiotic based on colistin sulfate and tylosin tartrate. 4.80% of isolates demonstrated intermediate resistance to the antimicrobial based on chlortetracycline hydrochloride.

Detecting genetic determinants of E. coli resistance. Molecular and genetic studies revealed that 9.56% of *E. coli* isolates have CTX-M gene in specific regions of DNA, which causes resistance of *Enterobacteriaceae* bacteria to first-generation fluoroquinolones and cephalosporins (cefazolin), in this case 6.95% of cultures were isolated from mammary glands secretions and 2.61% were isolated from cervical swabs. blaDHA gene, which accounts for resistance to protected penicillins (ampicillin, amoxicillin, ticarcillin, piperacillin, tazobactam) and the third- and the forth- generation cephalosporins (cefotaxime, cefoperazone, ceftriaxone, ceftibuten, ceftazidime, cefixime, cefpodoxime, cefodizime, cefetamet), had been identified in 49.02% of *E. coli* DNA samples isolated from mammary gland secretions. VIM gene encoding production of carbapenemases and accounting for resistance to the 1st line carbapenems (meropenem, imipenem, doripenem) was not detected in any of the *E. coli* DNA samples.

CONCLUSION

Analysis of the phenotypic and genotypic characteristics of 127 *E. coli* clinical isolates showed that microorganism cultures (64.5%) resistant to ansamycins, semi-synthetic penicillins, tetracyclines (doxycycline) prevail.

Fluoroquinolones were most active against *E. coli* and therefore can be recommended to treat reproductive

diseases in cows caused by this pathogen. Clinical isolates of *E. coli* were sensitive to third generation cephalosporins. However, since 28.46% of isolates in this group had shown intermediate resistance and due to detection of blaDHA gene in 49.02% of *E. coli* DNA samples, these antimicrobials cannot be recommended to treat infections caused by *E. coli* [21].

The conducted research reveals high resistance to carbapenems (10.22%), which is a bad prognosis confirming general epidemiological trend towards spread of microorganisms resistant to these antimicrobials. It should be emphasized that carbapenems are used in medicine only as reserve antimicrobials [22]. The absence of VIM gene does not exclude other carbapenemase-producing genes.

In general, the tendency to develop resistance to carbapenems and third-generation cephalosporins is a marker of polyresistance of bacteria belonging to the *Enterobacteriaceae* family [23].

The recovered isolates turned out to be sensitive to antimicrobials included into combined pharmaceuticals. However, their widespread use poses a risk of developing cross-resistance to antimicrobials from different groups and polyresistance.

The results of studying phenotypic and genotypic characteristics of antimicrobial resistance in *E. coli* clinical isolates recovered from cattle in the Ural region are important for a systematic approach to rational drug use and to AMR control and containment in livestock production.

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