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URINE MICROBIAL LANDSCAPE IN CHILDREN WITH URINARY TRACT INFECTIONS IN RYAZAN REGION

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Abstract. The aim was to study a spectrum of urine pathogens and their sensitivity to antimicrobial drugs (AMD) in urinary tract infections (UTIs) in children of the Ryazan Region. **Study Design:** a retrospective study. **Patients and Methods**. We conducted a retrospective local laboratory monitoring of urinary microflora and analyzed its sensitivity to AMD in 111 patients aged 2 months to 17 years old who were undergoing traditional UTI therapy in the 2020 year. The study group comprised 75 (67.6%) girls and 36 (32.4%) boys. Pathogen isolation and type identification were performed using urine specimens collected in sterile disposable plastic containers prior to

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antimicrobial therapy. The material was delivered for analysis within 2 hours from collection. For testing pathogen sensitivity to antimicrobials, we used the phenotyping diffusion test and an analytical test for carbapenems inactivation. Study Results. Prevailing causative agents of UIs were Escherichia coli (50.4%) and K. pneumonia (14.4%). Resistance determinants were found in 9.0% and 2.7% of E. coli and K. pneumonia urological strains, respectively. The main mechanism of resistivity was the production of wide-spectrum plasmid β-lactamases. The highest activity in E. coli was demonstrated by generation III-IV cephalosporins, aminoglycosides, fosfomycin (100%), nitrofurantoin (91.3%), and aminopenicillins (76.1–86.9%). For K. pneumonia, generation III-IV cephalosporins and aminoglycosides were most potent (100%). All resistant pathogens were sensitive to cefoperazone sulbactam, meropenem, imipenem, aminoglycosides (100%); tigecycline, nitrofurantoin, and fosfomycin were most potent against E. coli. **Conclusion.** Children with UTIs in Ryazan Region had mostly gram-negative bacteria in their urine (85.6%), Enterobacterales (81.1%) being a prevailing type. Antimicrobials resistance determinants were quite rare (17.8%) in these urine isolates; all of them were ESBL class A producers. These characteristic features of antibiotic resistance of urine pathogenic Enterobacteria strains allow using β-lactam antibiotics in empiric initial treatment and emphasize the need for a patient-specific selection of antimicrobials.
Keywords: antibacterial therapy, antibiotic resistance, children, urinary tract infections, Escherichia coli, Klebsiella pneumonia.

Introduction. Urinary tract infections (UTI) are a group of microbial-inflammatory diseases in which, in most cases, antibiotic therapy is required. UTIs occur in 10-15% of cases among hospitalized young children with fever. Girls suffer from UTI more often, which is associated with anatomical and physiological features of the body [1, 2]. According to the American Academy of Pediatrics (AAP), antimicrobial therapy (AMT) is recommended for the treatment of UTI in children, the drugs of choice are protected aminopenicillins (amoxicillin+clavulanic acid), co-trimoxazole (trimethoprim+sulfamethoxazole) or cephalosporins of II–III generations, as well as ureidopenicillins [3, 4].

The spectrum of urine microflora released during UTI is diverse and it depends on age, gender, the path of infection and the form of the disease. Enterobacter, Staphylococcus and Enterococcus are the most common pathogens of urinary system infection. Total specific gravity of Enterobacter (among them, Escherichia coli predominates), Enterococcus (mainly Enterococcus faecalis and Enterococcus faecium) and Staphylococcus (mainly Staphylococcus aureus and Staphylococcus saprophyticus) in the structure of etiological agents of nonspecific UTI reaches 90-95%, they are associated with the development of both cystitis and pyelonephritis [5, 6]. Such a pattern is associated with the specific features of these pathogens [7-10]. According to the results of the DARMIS study, the total proportion of representatives of the Enterobacteria family in UTI was 79.8%, of which E. coli was detecting in 61.4% of patients [7].

The relevance of the rational choice of an antimicrobial drug (AMD) in the treatment of UTI in children is due to the increase in antibiotic resistance of the microflora, even in community-acquired diseases [11-13].

Antibiotic resistance (AR) in the modern world — is a global problem, which affects the interests of everything the world community and jeopardizes the treatment of many infectious diseases. Back in 2001, World Health Organization (WHO) proposed a global strategy for curbing antimicrobial resistance. Resistance to AMD is emphasized in the WHO report (2014), it has a global scale and poses a threat to the life and health of children and adolescents [14, 15]. According to the estimates of internationalexperts, AR is the cause of more than 700 thousand deaths annually (including 22 thousand cases in Europe). It is assumed that by 2050 this figure may increase to 10 million people [15]. Published in 2016, a global meta-analysis on the AR of uropathogens in children, It includes 58 studies and about 78 thousand strains of E. coli. It showed that AR is significantly higher in countries where AMD sells without a prescription in contrast to countries where antibiotics are selling strictly by prescription. E. coli strains isolated from urinary pathways in children who had previously received AMD had a higher level of AR, which persisted for 6

months [8]. The results of the study attract attention DARMIS (2017), indicating an increase in resistance to most AMD and among community-acquired strains of the order Enterobacter, in particular E. coli, in Russia [7].

Monitoring of urine microflora resistance has an international meaning. Research of ECO-SENS Project held in Europe and Canada, confirmed the assumption of the existence of significant geographical differences in the level and nature of AR of microorganisms (MO). For example, the selection frequency E. coli strains resistant to co-trimoxazole fluctuated from 12.2% in the UK to 25.7% in Spain, and to ciprofloxacin - 0.6% and 14.7%, respectively [12].

Strategy for the Prevention of AR adopted for the period up to 2030 in the Russian Federation in 2017. Its goals are to prevent and limit AR on the territory of the Russia [15]. Among the tasks are ensuring systemic monitoring of prevalence AR and the study of the mechanisms of its occurrence.

To conduct local monitoring of the resistance of UTI pathogens due to the existence of regional differences in the level of AR is important. Data of the structure of urine pathogens and their sensitivity of AMD in various forms of UTI obtained in the course of multicenter prospective epidemiological studies (UTIAP-I, UTIAP-II, ARMID, ARIMB). The Research Institute of Antimicrobial Chemotherapy and Smolensk State Medical University and the Scientific and Methodological Center of the Ministry of Health of Russia organized studies for monitoring antibiotic resistance [15]. Among urine pathogens with resistance determinants currently dominated by representatives of the order Enterobacterales, which are producers of extended spectrum plasmid β-lactamases (ESBL class A), causing flora resistance to β-lactam antibiotics. An alarming increase in the frequency of detection carbapenemase, β-lactamase, AmpC, combined mechanisms (ESBL+AmpC/MBL/OXA, combinations of the indicated mechanisms of resistance to AMDs with loss of porins, an isolated variant of loss of porins, which is the phenotype of resistance to all β-lactams, including carbapenems, in the absence of carbapenemases production) [15]. Thus, regional research and monitoring resistance are of great importance for effective treatment of UTIs and prevention of complications, which determines relevance of our work.

The aim of the study: to study the structure of uropathogens and the phenotypes of their sensitivity to AMD in UTI in children in Ryazan and Ryazan region.

PATIENTS AND METHODS. A retrospective local laboratory monitoring of the urine microflora carried out with an assessment of the level sensitivity to AMD in 111 patients aged 2 months to 17 years who received conservative treatment for UTI in the pediatric department of the Ryazan City Clinical Hospital № 11 in 2020. Among the examined were 75 (67.6%) girls and 36 (32.4%) boys.

Isolation and species identification of pathogens were carried out on the basis of a bacteriological laboratory of Ryazan City Clinical Hospital № 11 from urine samples collected after the preliminary toilet of the external genital organs into sterile disposable plastic containers prior to starting antimicrobial therapy. The material was delivered to the study within 2 hours from the moment of collection.

The study was carried out on a microbiological analyzer Labsystems iEMS Reader using BACT programs, commercial test systems ENTEROtest 16 (Erba Lachema, Czech Republic), analytical chromogenic method (Paper indicator systems for MO identification, firm "Microgen", Russia) and immunological latex method for the detection of antigens of Streptococcus of groups A, B, C and D (Oxoid Ltd., UK). To determine the sensitivity category of MO to AMP used the phenotypic disk diffusion method (DDM)[1] and an analytical method for the inactivation of carbapenems[2]. Used the current version of the EUCAST manual during laboratory monitoring of the results obtained by definition of sensitivity categories.

Clinically significant growth was taken into account when identifying in urine samples of representatives of the order Enterobacterales and non-fermenting gram-negative bacteria (Pseudomonas aeruginosa, Acinetobacter baumannii) in any quantity, since when screening for products ESBL, AmpC and CPE (carbapenemasoproducing strains of enterobacteria) were founding to produce clinically and/or epidemiologically significant mechanisms of resistance, including in

extremely low titers (less than 10^3 CFU/ml). One of the reasons for the detection of problematic resistant pathogens (PRV) in extremely low or low titers may be their asymptomatic carriage [16].
When seeding other MOs, such as representatives of the genus Staphylococcus, Streptococcus or fungi, a microbial load of ≥ 104 CFU/ml was recognizing as a clinically significant titer. Statistical data processing was carried out using the computer program "Microbiologist's Journal" (developer — «Vostochnaya Korona» LLP).•

Results. In the microbial landscape of the urological flora from 204 samples urine of 111 children, a significant proportion of gram-negative MO - 85.6% (n = 95) - with absolute dominance of MO of the order Enterobacterales as in general spectrum of flora - 81.1% (n = 90), and within the gram-negative group - 94.7% (n = 90) (Table 1).
The dominant pathogen was E. coli as a whole in the etiological structure of UTI pathogens (50.4%), and in the group of enterobacteria (order Enterobacterales) (62.2%). The dominant bacteriuria in children with UTI was E. coli without resistance determinants, it was sown in 41.4% of the total MO spectrum. The frequency of occurrence of resistance determinants within the E. coli species was 9.0%: E. coli ESBL - 8.1%, E. coli ESBL + AGMP (AGMP - aminoglycoside-modifying enzymes that cause ineffectiveness of the aminoglycoside group) - 0.9%.
The second place in terms of prevalence was occupied by K. pneumoniae, accounting for 14.4% in the total spectrum of MO and 17.7% among order Enterobacterales. Resistance determinants were detected in 2.7% of strains of this PRV type: K. pneumonia ESBL - 1.8%, K. pneumoniae ESBL + plasmid AmpC - 0.9%.

Table 1

Flora in urine of children with urinary tract infections in 2020 year

Taxonomic nomenclature of microorganisms (MO)	No. of children (n = 111)	Share in the identification spectrum of MOs , %	MOs share in the rank, group, type , %
Gram-negative MOs	95	85,6	–
Enterobacterales	90	81,1	94,7
Escherichia coli: •E. coli; •E. coli ESBL, class A; •E. coli ESBL, class A + AGFe	56 46 9 1	50,4 41,4 8,1 0,9	62,2 51,1 10,0 1,1
Klebsiella pneumoniae: •K. pneumoniae; •K. pneumonia ESBL, classA ; •K. pneumoniae ESBL, class A + plasmid AmpC	16 13 2 1	14,4 11,7 1,8 0,9	17,7 14,4 2,2 1,1
Enterobacter cloacae complex: •E. cloacae complex; •E. cloacae complex ESBL, class A ; •E. cloacae complex ESBL, class A+AGMe	10 8 1 1	9,0 7,2 0,9 0,9	11,1 8,9 1,1 1,1
Proteus mirabilis: •Morganella morganii;	8 6	7,2 5,4	8,9 6,7

• [1] European Committee for Antimicrobial Susceptibility Testing. Limit value tables for interpretation **MPC** values and diameters of growth inhibition zones. Version 10.0, 2020. URL: http://www.eucast.org (Accessed -10.10.2021).
[2] EUCAST guidelines for the identification of mechanisms of resistance and resistance of particular clinical and/or epidemiological meaning. Version 2.0 July 2017 URL: http://old.antibiotic.ru/iacmac/ru/docs/eucast/eucast-guideline-on-detection-of-resistance-mechanisms-2.0-rus.pdf (Accessed - 10.10.2021).

•M. morganii ESBL, class A ; •P. mirabilis	1 1	0,9 0,9	1,1 1,1
Non-fermentable gram-negative bacteria: •P. aeruginosa; •Acinetobacter calcoaceticus complex	5 4 1	4,5 3,6 0,9	100,0 80,0 20,0
Gram-positive MOs	16	14,4	–
Candida albicans	7	6,3	100,0
Streptococcus spp. (S. agalactiae, group B)	4	3,6	100,0
Enterococcus spp.: •E. faecium; •E. faecalis	3 2 1	2,7 1,8 0,9	100,0 66,7 33,3
Staphylococcus spp. (S. aureus)	2	1,8	100,0

Note. Legend for Table 1 and Table 2: AGMe: aminoglycoside-modifying enzymes making aminoglycosides inefficient.

The Enterobacter cloacae complex and the group were less frequently distinguishedProteus mirabilis (P. mirabilis and Morganella morganii species are merged due to their taxonomic proximity).

In isolated cases in E. coli (n=1) and E. cloacae complex ESBL (n=1) met combined mechanism resistance to β-lactam AMPs and production of AGMf. In the identified gram-negative flora, it was not detected production of isolated cephalosporinases AmpC and carbapenemase - MBL class B, carbapenemase K. pneumoniae, a group of OXA-48-like class D.

Proportion of non-fermenting Gram-negative bacteria in the total spectrum was 4.5%, they are represented mainly P. aeruginosa - 3.6%. Seeding of gram-positive MO received in 14.4% of cases, which is 5.6 times less than gram-negative MO. The spectrum of Gram-positive MOs included Candida albicans, Streptococcus agalactiae group B, Enterococcus spp. and Staphylococcus aureus. Resistance determinants inherent in Gram-positive flora (MRSA, M-phenotype, inducible MLSB phenotype, VRE) were not identified.

Resistance determinants found in MO belonging to the order Enterobacterales (n=16): 17.8% of the total order Enterobacterales (Table 2) and 14.4% in the total spectrum causative agents of UTIs in children. ESBL class A production was determined in all cases, and in three of them combined resistance mechanisms were identified: ESBL+AGMf (E. cloacae complex, E. coli) and ESBL+plasmid AmpC (K. pneumoniae).

Table 2

Intragroup incidence of antimicrobials resistance determinant production in Enterobacterales isolated from children urine, n (%)

Mechanisms of resistance	Total MOs (n=90)	E. coli (n = 56)	K. pneumoniae (n=16)	Enterobacter cloacae complex (n=10)	Group Proteus mirabilis (n=8)
No mechanisms	74 (82,2)	46 (82,1)	13 (81,2)	8 (80)	7 (87,5)*
Mechanisms	16 (17,8)	10 (17,9)	3 (18,8)	2 (20)	1 (12,5)**
ESBL class A: • ESBL classA; • ESBL class A+AGMe; • ESBL class A+plasmid AmpC	16 (17,8) 13 (14,5) 2 (2,2) 1 (1,1)	10 (17,9) 9 (16,1) 1 (1,8) 0	3 (18,8) 2 (12,5) 0 1 (6,3)	2 (20) 1 (10) 1 (10) 0	1 (12,5)** 1 (12,5)** 0 0

** Morganella morganii and Proteus mirabilis.*

*** Morganella morganii.*

Share of combined mechanisms in the totalidentification spectrum of the order Enterobacterales was insignificant - 3.3% (n=3). The main carrier of acquired determinants of resistance was E. coli,

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making up 9.0% of the total microbial landscape of the urological flora, and 11.1% of the order Enterobacterales (n=10).

In all cases of detection of resistance mechanisms, the analytical method of inactivation was used carbapenems. As a result of the testing carbopenemase producers were not found among representatives of the order Enterobacterales. However, this method is not allows to differentiate the type of production of carbapenemase - MBL class B, a group of OXA-48-like class D, but at the same time effectively reveals the fact of hydrolysis of meropenem by a microorganism.

Evaluation of AMD activity against the main UTI pathogens in children showed that against E. coli with normal susceptibility phenotype 100% active in vitro III-IV generation cephalosporins, aminoglycosides and fosfomycin. For this type of MO, the stability frequency to nitrofurantoin was 8.7%, to penicillins-ESBL inhibitors - 13.1-23.9%, to ampicillin - 52.2%.

With respect to E. coli, which has resistance determinants of ESBL and ESBL+AGMf, unprotected penicillins, cephalosporins of I-IV generations, monobactams (aztreonam) are expectedly ineffective, but a high (100%) in vitro activity of cefoperazone-sulbactam, carbapenems, fosfomycin, nitrofurantoin was noted, tigecycline, aminoglycosides (in the absence of AGMF production). The activity level of protected penicillins is 40–50%, which is almost 2 times less in comparison with that against E. coli without a resistance mechanism.

The III–IV generation cephalosporins and aminoglycosides showed high activity (100%) against K. pneumonia with the usual sensitivity phenotype. The activity index of protected of penicillin’s was significantly lower than cephalosporins for K. pneumoniae and protected penicillin’s for E. coli (40–60% and 76.1–86.9%, respectively).

When K. pneumoniae was detecting - a producer of ESBL and ESBL+AmpC — zero activity of unprotected and protected penicillins, III-IV generation cephalosporins, monobactam was determined. Against K. pneumoniae, the producer of ESBL and ESBL+AmpC, cefoperazone-sulbactam, carbapenems, aminoglycosides were highly active (100%) in vitro, and chloramphenicol was 33.3%. Among PRVs, there were no Enterobacterales producing carbapenemase (CPE), - MBL, KRS and a group of OXA-48-like.

Conclusion

The results of the local microbiological monitoring conducted in 2020 year indicated that in children with urinary tract infections tracts (UTIs) in the Ryazan region, predominantly gram-negative bacteria (85.6%) were sown from urine, among which representatives of the order Enterobacterales (81.1%) dominated, in particular E. coli (50.4%) and K. pneumoniae (14.4%). The frequency of occurrence of microorganisms of another species/genus affiliation was significantly lower (1.8–9%). Similar taxonomic structure of UTI pathogens in children is generally the characteristic of most regions the Russian Federation [17].

Among urine pathogenic strains bacteria belonging to the order Enterobacterales, determinants of resistance to antimicrobial drugs (AMD) detected relatively rarely - in 17.8% of urine isolates, moreover, all of them belonged to class A ESBL producers. Combined stability mechanisms (in particular, ESBL+AGM enzymes and ESBL+plasmid AmpC) registered in isolated cases. In the studied sample, bacterial strains were absent urine isolates of microorganisms-producers of carbapenemas. These data indicate that the dominant causative agents of UTIs in children of Ryazan region still have limit arsenal mechanisms of resistance to AMD.

Identified features of antibiotic resistance of urine pathogenic strains of Enterobacteria as priority UTI pathogens in children, on the one hand, allow the use ofβ-lactam antibiotics for empiric starting therapy, on the other hand, determine the need for introduction of a personalized approach to the selection of AMS to improve the effectiveness of conservative treatment in similar patients.

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