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Urine Microbial Spectrum In Children With Urinary Tract Infection

Belykh Natalia Anatolievna
Doctor of Medical Sciences, Associate Professor Ryazan
State Medical Academician I.P. Pavlov University
Tereshchenko Sofia Viktorovna
head of bacteriological laboratory, bacteriologist,
GBU RO "City Clinical Hospital No. 11". 390037, Russia, Ryazan, st.
Anikeeva Natalia Alexandrovna
Candidate of Medical Sciences, Associate Professor of the Department of Faculty and Polyclinic pediatrics with the course of pediatrics FDPO FGBOU VO
Ryazan State Medical University named after A.I. acad. I.P. Pavlova
Mukhamadieva Lola Atamuradovna
Doctor of Medical Sciences, Associate Professor,
Head of the 3rd Department of Pediatrics and Medical Genetics
Samarkand State Medical University
Kuldashev Sardor Furkatevich
Assistant of the Department of Pediatrics No. 3 and Medical Genetics
Samarkand State Medical University

Annotation: The aim of the study was to study the spectrum of urinary pathogens and their sensitivity to antimicrobial drugs (AMP) in urinary tract infections (UTIs) in children of the Ryazan region. We carried out a retrospective local laboratory monitoring of the urine microflora and analyzed its sensitivity to antibiotics in 111 patients aged 2 months to 17 years who received conventional therapy. The study group consisted of 75 (67.6%) girls and 36 (32.4%) boys. To test the sensitivity of pathogens to antimicrobials, a phenotypic diffusion test and an analytical test for carbapenem inactivation were used. It was established that the predominant causative agents of urinary incontinence were Escherichia coli (50.4%) and K. pneumonia (14.4%). Resistance determinants were found in 9.0% and 2.7% of E. coli and urological strains of K. pneumonia, respectively. The main mechanism of resistance was the production of broad-spectrum plasmid β-lactamases. III-IV generation cephalosporins, aminoglycosides, fosfomycin (100%), nitrofurantoin (91.3%) and aminopenicillins (76.1-86.9%) showed the highest activity against E. coli. With regard to K. pneumonia, the most effective (100%) were III-IV generation cephalosporins and aminoglycosides. All resistant pathogens were sensitive to cefoperazone, sulbactam, meropenem, imipenem, aminoglycosides (100%); nitrofurantoin and fosfomycin were most active against E. coli. In children with UTI in the Ryazan region, gram-negative bacteria (85.6%) prevailed in the urine, enterobacteria predominated (81.1%). Antimicrobial resistance determinants were quite rare (17.8%) in these urine isolates; they were all class A ESBL producers.

Key words: antibiotic therapy, antibiotic resistance, children, urinary tract infections, Escherichia coli, Klebsiella.

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

The spectrum of the microflora of urine excreted during UTI is diverse and depends on age, gender, route of infection and the form of the disease. Enterobacter, staphylococcus and enterococcus are the most common causative agents of urinary tract infections. The total share of enterobacters (among them E. coli predominates), enterococci (mainly Enterococcus faecalis and Enterococcus faecium) and staphylococci in the structure of etiological agents of nonspecific UTI reaches 90-95%, it is associated with the development of both cystitis and pyelonephritis [5, 6] . This pattern is associated with the specific features of these pathogens [7-10]. According to the results of studies, the total proportion of representatives of the Enterobacteria family in UTI was 79.8%, of which E. coli was detected in 61.4% of patients [7].

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

Antibiotic resistance (AR) in the modern world is a global problem that affects the interests of the entire world community and threatens the treatment of many infectious diseases. Back in 2001, the World Health Organization (WHO) proposed a global strategy to curb antimicrobial resistance. Resistance to AMD is emphasized in the WHO report (2014), has a global scale and poses a threat to the life and health of children and adolescents [14, 15]. According to international experts, AR causes more than 700,000 deaths annually (including 22,000 cases in Europe)

It is assumed that by 2050 this figure may increase to 10 million people [15]. A global meta-analysis on AR of uropathogens in children published in 2016 includes 58 studies. He showed that the AR is significantly higher in countries where antibiotics are sold without a prescription, in contrast to countries where antibiotics are sold strictly by prescription. E. coli strains isolated from the urinary tract of children who received antibiotics had a higher level of AR, which persisted for 6 months [8].

Attention is drawn to the results of a study (2017), indicating an increase in resistance to most antibiotics among community-acquired strains of the Enterobacter order, in particular E. coli, in Russia [7].

Monitoring the resistance of the microflora of urine is of international importance. Studies of the ECO-SENS project, conducted in Europe and Canada, confirmed the assumption of the existence of significant geographical differences in the level and nature of microbial AR (MO). For example, the frequency of selection of E. coli strains resistant to co-trimoxazole ranged from 12.2% in the UK to 25.7% in Spain, and to ciprofloxacin - 0.6% and 14.7%, respectively [12].

In 2017, the Russian Federation adopted the AR Prevention Strategy for the period up to 2030. Its goals are the prevention and limitation of AR in Russia [15]. Among the tasks is to provide systematic monitoring of the prevalence of AR and study the mechanisms of its occurrence.

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It is important to conduct local monitoring of the resistance of UTI pathogens due to the presence of regional differences in the level of AR. Data on the structure of urinary pathogens and their sensitivity to AMD in various forms of UTI were obtained in the course of multicenter prospective epidemiological studies.
Among urinary pathogens with resistance determinants, representatives of the order Enterobacterales currently predominate.
Thus, regional studies and monitoring of resistance are of great importance for the effective treatment of UTIs and the prevention of complications, which determines the relevance of our work.

The purpose of the study: to study the structure of uropathogens and the phenotypes of their sensitivity to antibiotics in UTIs in children from Ryazan and the Ryazan region.

Materials and research methods. A retrospective local laboratory monitoring of the urine microflora with an assessment of the level of sensitivity to antibiotics was carried out in 111 patients aged 2 months to 17 years who received conservative treatment for UTIs in the pediatric department of the Ryazan City Clinical Hospital No. 11 in 2020. Among the examined patients there were 75 (67.6%) girls and 36 (32.4%) boys.
Isolation and species identification of pathogens was carried out at the bacteriological laboratory of the Ryazan City Clinical Hospital No. 11 from urine samples collected after the preliminary toilet of the external genital organs in sterile disposable plastic containers before the start of antimicrobial therapy. The material was delivered to the study within 2 hours from the moment of sampling.
The study was carried out on a Labsystems iEMS Reader microbiological analyzer using BACT programs, commercial test systems ENTEROtest 16 (Erba Lachema, Czech Republic), an analytical chromogenic method (Paper indicator systems for the identification of MOs, Microgen, Russia) and an immunological latex method for detecting antigens. streptococci of groups A, B, C and D (Oxoid Ltd., UK). To determine the sensitivity category of MO to AMP, the phenotypic disk diffusion method (MDM)N and the analytical method of carbapenem inactivation I were used. Used the current version of the EUCAST guidelines in the laboratory monitoring of the results obtained by determining the sensitivity categories.
Clinically significant growth was taken into account when urine samples of representatives of the order Enterobacterales and non-fermenting gram-negative bacteria (Pseudomonas aeruginosa, Acinetobacter baumannii) were detected in any quantity, since when screening for ESBL, AmpC and CPE products (carbapenemasoproducing strains of enterobacteria) they produce clinically and / or epidemiologically significant mechanisms of resistance, including in extremely low titers (less than 104 CFU / ml). One of the reasons for the detection of problem-resistant pathogens (PRV) in extremely low or low titers may be their asymptomatic carriage [16]. When inoculating other MOs, such as representatives of the genus Staphylococcus, Streptococcus, or fungi, a microbial load of ≥ 104 CFU/mL was recognized as a clinically significant titer. Statistical data processing was carried out using the computer program “Microbiologist’s Journal” (developed by Vostochnaya Korona LLP).

Research results. In the microbial spectrum of the urological flora from 204 urine samples of 111 children, a significant proportion of gram-negative MOs - 85.6% (n = 95) - with an absolute predominance of Enterobacterales order MOs, and in the total flora spectrum - 81.1. % (n=90), and in the group of gram-negative - 94.7% (n=90) (Table 1).

In the etiological structure of causative agents of UTIs, in general, Escherichia coli dominated (50.4%), and in the group of enterobacteria (Enterobacterales order) (62.2%). Dominant

bacteriuria in children with UTI was Escherichia coli without resistance determinants, it was sown in 41.4% of the total MO spectrum. The frequency of occurrence of resistance determinants in E. coli species was 9.0%: E. coli RSVLP (extended spectrum β-lactamase plasmid plasmid (ESBL-extended spectrum plasmid β-lactamases) - 8.1%, E. coli ESBL + AGMP (AGMP - enzymes that modify aminoglycosides, causing the inefficiency of the aminoglycoside group) - 0.9%.

The second place in terms of prevalence is occupied by K. pneumoniae, which account for 14.4% in the total spectrum of PO and 17.7% among the Enterobacterales order. Resistance determinants were detected in 2.7% of PRV strains of this type: K. pneumoniae ESBL - 1.8%, K. pneumoniae ESBL + AmpC plasmid - 0.9%.

Table 1

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

Taxonomic nomenclature microorganisms (MO)	No. of children (n = 111)	Share on identification range MO, %	MO participate in 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:	8	7,2	8,9

•Morganella morganii;	6	5,4	6,7
•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 rendering aminoglycosides ineffective.

Less commonly, the Enterobacter cloacae complex and the Proteus mirabilis group were distinguished (P. mirabilis and Morganella morganii species are combined due to their taxonomic proximity).
In isolated cases, E. coli (n=1) and E. cloacae of the ESBL complex (n=1) had a combined mechanism of resistance to β-lactam AMPs and AGMP production. In the identified gram-negative flora, no production of isolated cephalosporinases AmpC and carbapenemase - MBL class B, carbapenemase K. pneumoniae, group OXA-48-like class D was detected.
The proportion of non-fermenting gram-negative bacteria in the total spectrum was 4.5%, they are represented mainly by P. aeruginosa - 3.6%. Seeding of gram-positive microorganisms was obtained in 14.4% of cases, which is 5.6 times less than that of gram-negative microorganisms. The spectrum of Gram-positive microorganisms included Candida albicans, Group B Streptococcus agalactiae, Enterococcus spp. and Staphylococcus aureus. Resistance determinants inherent in Gram-positive flora (MRSA, M-phenotype, MLSB-induced phenotype, VRE) were not identified.
Resistance determinants were found in microorganisms belonging to the order Enterobacterales (n=16): 17.8% of the total Enterobacterales order (Table 2) and 14.4% of the entire spectrum of UTI pathogens in children. In all cases, class A ESBL production was determined, and in three of them, combined resistance mechanisms were identified: ESBL+AGMf (E. cloacae complex, E. coli) and ESBL+AmpC plasmid (K. pneumoniae)

Table 2
Intragroup frequency of production of antimicrobial resistance determinants in enterobacteria isolated from the urine of children, n (%)

Механизмы сопротивление	Общий МО (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 +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 и Proteus mirabilis.**
**** Morganella morganii.**

The share of combined mechanisms in the total range of identification of the Enterobacterales order was insignificant - 3.3% (n=3). The main carrier of the acquired resistance determinants was E. coli, accounting for 9.0% of the entire microbial landscape of the urological flora and 11.1% of the Enterobacterales order (n=10).

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

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

With regard 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 high (100%) in vitro activity of cefoperazone-sulbactam, carbapenems, fosfomycin, nitrofurantoin, tigecycline, aminoglycosides (in the absence of AGMP production). The level of activity of protected penicillins is 40–50%, which is almost 2 times less than that for E. coli without a resistance mechanism.

Cephalosporins and aminoglycosides III–IV generation showed high activity (100%) against K. pneumonia with a common susceptibility phenotype. The activity index of protected penicillins was significantly lower than that of cephalosporins for K. pneumoniae and protected penicillins for E. coli (40–60% and 76.1–86.9%, respectively).

When K. pneumoniae, a producer of ESBL and ESBL+AmpC, was detected, zero activity of unprotected and protected penicillins, III-IV generation cephalosporins, and monobactam was determined. In relation to K. pneumoniae, the producer of ESBL and ESBL+AmpC, cefoperazone-sulbactam, carbapenems, aminoglycosides, chloramphenicol are highly active (100%) in vitro - 33.3%. Among the PRVs, carbapenemase-producing Enterobacterales (CPE) - MBL, KRS and the OXA-48-like group were absent.

Conclusions.

The results of local microbiological monitoring conducted in 2020 showed that in children with urinary tract infections (UTIs) in the Ryazan region, predominantly Gram-negative bacteria (85.6%) were cultured from the urine, including representatives of the order Enterobacterales (81.1%), in particular, E. coli (50.4%) and K. pneumoniae (14.4%), the frequency of occurrence of microorganisms of another species/genus was significantly lower (1.8–9%). A similar taxonomic structure of UTI pathogens in children is generally typical for most regions of the Russian Federation [17].

Among urinary pathogenic strains of bacteria belonging to the order Enterobacterales, determinants of resistance to antimicrobial drugs (AMPs) were detected relatively rarely - in 17.8% of urine isolates, all of which belonged to class A ESBL producers. Combined mechanisms of stability (in particular, ESBL+ enzymes AGM and ESBL + AmpC plasmid) were registered in isolated cases. In the test sample, there were no strains of bacteria, urine isolates of microorganisms producing carbapenem. These data indicate that the dominant UTI pathogens in children in the Ryazan region still have a limited arsenal of resistance mechanisms to AMD.

The revealed features of antibiotic resistance of uropathogenic strains of enterobacteria as priority causative agents of UTIs in children, on the one hand, allow the use of β-lactam antibiotics for empirical initial therapy, on the other hand, determine the need for a personalized approach to the choice of AMS to improve the effectiveness of conservative treatment in such patients.

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