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MONITORING OF *ENTEROBACTERIA STRAINS* WITH PRODUCING OF B-LACTAMASES IN MALES WITH INFECTIOUS-INFLAMMATORY DISEASES OF UROGENITAL TRACT

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Ключевые слова: *условно-патогенная микрофлора, урогенитальный тракт, энтеробактерии, β-лактамазы, антибиотики; резистентность*

Abstract. Monitoring of *Enterobacteria strains* with producing β-lactamases in males with infectious-inflammatory diseases of urogenital tract. Sklyar T.V., Lavrentieva K.V., Kurahina N.V., Lykholat T.Yu., Papiashvili M.G., Lykholat O.A., Stepanskyi D.O. *This article presents the findings of investigation of the microflora of 257 males with infectious-inflammatory diseases of the urogenital tract using the test system "Androflor". The role of representatives of conditionally pathogenic microflora as the main etiological agent in occurrence of infectious-inflammatory diseases of the urogenital tract in males was shown. Its composition in 39.3±3.0% of cases was represented by bacteria of family Enterobacteriaceae, in 10.9±1.9% – by Enterococcus spp., in 3.1±1.1% – by Haemophilus spp. and in 0.4±0.1% of cases – by P. aeruginosa. Out of 101 strains of enterobacteria, 27 representatives had the ability to synthesize β-lactamases 26.7±4.4% of cultures), in particular: 16 isolates of E. coli, 5 isolates of P. mirabilis and 6 isolates of K. pneumoniae. The selected strains of enterobacteria producing β-lactamases appeared to be resistant at least to 6 tested antibiotics, which allowed referring them to categories of multi-resistant. All cultures producing β-lactamases showed resistance to penicillines – ampicillin and amoxiclav. In this case, resistance to at least one of the antibiotics of cephalosporin group of the third generation was noted. In addition, 83.3±2.1% of the examined isolates were characterized by resistance to macrolides – erythromycin and azithromycin, as well as to co-trimoxazole and fosfomicin. The obtained data are of practical importance to develop efficient schemes of antibiotic therapy for infectious-inflammatory diseases of the urogenital tract, caused by strains of enterobacteria producing β-lactamases.*

Реферат. Моніторинг штамів ентеробактерій, здатних до синтезу β-лактамаз, серед чоловіків з інфекційно-запальними захворюваннями урогенітального тракту. Скляр Т.В., Лаврентьєва К.В., Курагіна Н.В., Лихолат Т.Ю., Папіашвілі М.Г., Лихолат О.А., Степанський Д.О. *У статті представлено результати дослідження мікрофлори 257 чоловіків з інфекційно-запальними захворюваннями урогенітального тракту з використанням тест-системи «Андрофлор». Показано роль представників умовно-патогенної транзиторної мікрофлори як головних етіологічних агентів у виникненні інфекційно-запальних захворювань урогенітального тракту в чоловіків. Її склад представлено в 39,3±3,0% випадків бактеріями родини Enterobacteriaceae, у 10,9±1,9% – Enterococcus spp., у 3.1±1,1% – Haemophilus spp. і в 0,4±0,1% випадків – P. aeruginosa. Зі 101 штаму ентеробактерій здатність до синтезу β-лактамаз мали 27 представників (26,7±4,4% культур), а саме: 16 ізолятів E. coli, 5 – P. mirabilis і 6 – K. pneumoniae. Виділені штами ентеробактерій, що синтезують β-лактамази, виявилися стійкими до щонайменш 6 тестованих антибіотиків, що дозволило віднести їх до категорії мультирезистентних. Усі культури зі здатністю до синтезу β-лактамаз проявили резистентність до препаратів пеніцилінового ряду – ампіциліну та амоксиклаву. При цьому відмічено стійкість хоча б до одного з антибіотиків групи цефалоспоринів III покоління. Окрім того, 83,3±2,1% дослідних ізолятів характеризувалися резистентністю до макролідів – еритроміцину та азитроміцину, а також до ко-тримоксазолу і фосфоміцину. Отримані дані мають практичне значення для розробки раціональних схем антибіотикотерапії інфекційно-запальних захворювань урогенітального тракту, викликаних штамами ентеробактерій, здатних до синтезу β-лактамаз.*

One of the most common causes of physiological disorders of reproductive system of males is infectious-inflammatory diseases of the urogenital tract (UGT) [10, 12]. A special role in occurrence of infectious pathologies of the UGT belongs to transient microflora, and mainly *Escherichia coli*, as well as *Proteus mirabilis* and *Klebsiella pneumoniae* [3].

Until recently, the most effective preparations of empirical therapy for infections of the UGT, caused by these etiological agents were β-lactams and fluoroquinolones. In recent years, there has been a significant increase in resistance of enterobacteria to preparations of the fluoroquinolone group and to β-lactam antibiotics, which is a serious problem of modern medicine, because it severely limits its therapeutic capabilities against infectious-inflammatory diseases of the UGT [11].

One of the main mechanisms of resistance of enterobacteria to β-lactams is their production of extended-spectrum of β-lactamases (ESBL). Thanks to the plasmid localization of genes, ability to synthesize ESBL spreads very quickly and continues to spread both among microorganisms inside the family *Enterobacteriaceae*, and beyond it [6, 10]. That is why it is important to identify ESBL-producing enterobacteria, capable of destroying a β-lactam ring of antibiotics that are most frequently used in clinical practice (cephalosporins of the third generation and to less extent of the fourth generation) to treat infectious-inflammatory diseases of the UGT.

Based of the relevance of the theme, the aim of the investigation was to research the spectrum of the microflora of the male urogenital tract in the pathology, to analyze the frequency of occurrence of ESBL-producing enterobacteria among representatives of family *Enterobacteriaceae* and to determine their antibiotic susceptibility.

MATERIALS AND METHODS OF RESEARCH

The spectrum of the microflora of the urogenital tract in the pathology was determined in 257 male patients, aged from 25 to 62 (median – 43 years). The urethra scrape was taken as clinical material.

The reasearch of the obtained biological samples was carried out with the method of polymerase chain reaction (PCR) using the ampliphier DT-96/DT-322 (LLC SPO "DIK-technology", RF) in real time (PCR-RV) using the system "Androflor" (LLC SPO "DIK-technology", RF), which makes it possible to identify the DNA of microorganisms (normoflora, resident and transient opportunistic pathogenic microflora, obligate pathogens), regardless of their cultural and morphological characteristics, to determine the number of genome equivalents (GE/ml) of cells of microorganisms in 1 ml of a clinical samples, expressed through lg X copies of DNA/sample, to describe the microbial structure of the biotope in general, to identify the main etiologic agent and to access its importance in the development of a pathological process.

During isolation of the representative of transient opportunistic pathogenic microflora, which is the main etiological agent of infectious-inflammatory diseases of the UGT of males from biomaterial, at the next stage of research it was obtained in pure culture on the nutritional medium, identified with the use of the standard bacteriological methods, and sensitivity to antibacterial preparations was determined with the help of the disc-diffusion method in accordance with CLSI/NCCLS criteria. The degree of sensitivity of the tested cultures was evaluated according to the system of SIR, by which a test-object is referred to one of the categories: sensitive (S – sensitive), intermediately resistant (IR) or resistant (R – resistant) [8]. The spectrum of antibiotic preparations included: ampicillin, amoxiclav, ciprofloxacin, levofloxacin, amikacin, gentamycin, erythromycin,

azithromycin, cefotaxime, ceftriaxone, ceftazidime, cefepime, imipenem, fosfomicin, furaginum, co-trimoxazole, nitroxoline.

If the main etiological agent was a representative of family *Enterobacteriaceae,* its ability to produce ESBL was determined by the method of double discs. To apply the method, the discs with amoxicillin / clavulanat (20/10 µg), cefotaxime (30 µg), ceftriaxone (30 µg) and ceftazidime (30 µg) were used [9].

The research was conducted in accordance with the principles of bioethics set out in the WMA Declaration of Helsinki "Ethical principles for medical research involving human subjects" and "Universal Declaration on Bioethics and Human Rights" (UNESCO).

Statistical analysis was performed using MS Excel 2010 (license number K9366093I 2016). Mean and relative values are presented as arithmetic mean (M) and frequency (P, %) with standard error (± m). The correction was used to calculate the error for 100% [1].

RESULTS AND DISCUSSION

According to the results of research using the test-system "Androflor", it was found that obligate pathogens *C. trachomatis, M. genitalium, N. gonorrhoeae, T. vaginalis* were found in 14.4±2.2% of biomaterial samples (37 out of 257 people) (Fig. 1).

From the obligate pathogens, bacteria *C. trachomatis* were detected most often in the clinical samples – DNA of the pathogen was identified in 10.1±1.9% of samples, and *M. genitalium, N. gonorrhoeae, T. vaginalis* were found much less. The percentage of their detection does not exceed the value of 1.6±0.8%.

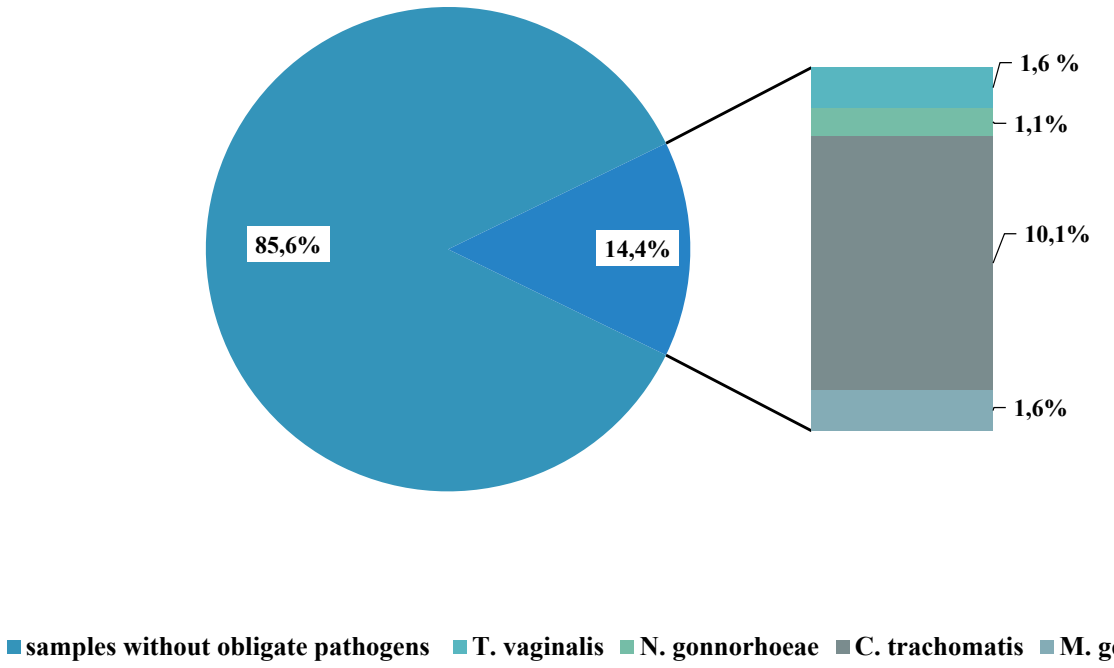

Fig. 1. The frequency of DNA detection of obligate pathogens in the clinical samples

We found that 31.9±2.9% (n=82) of cases of disruption of microbiocenosis of UGT in males were caused by an imbalance in the composition of its resident microflora, as a result of exceeding the titre of either one of the representatives, or of some of them as a part of associations (Fig. 2).

Thus, on the background of a decrease in titres of normoflora, the dysbiosis of UGT in 24.1±2.7% of the cases was caused by development of the opportunistic anaerobes *Bacteroides spp.*, in 14.0±2.2% – *Eubacterium spp.,* in 10.1±1.9% – *Anaerococcus spp. G. vaginalis* was detected Less often (in 5.8±1.5% of the patients), *Peptostreptococcus spp.* and *Candida spp.* were detected with the same frequency (in 3.9±1.2% of the patients), and *Ureaplasma spp.* (in 3.1±1.1% of the patients). In particular cases, percentage of which did not exceed 1.9±0.9%, dysbiotic disorders were associated with prevailing of *M. hominis, A. cluster* and *Megasphaera spp.*

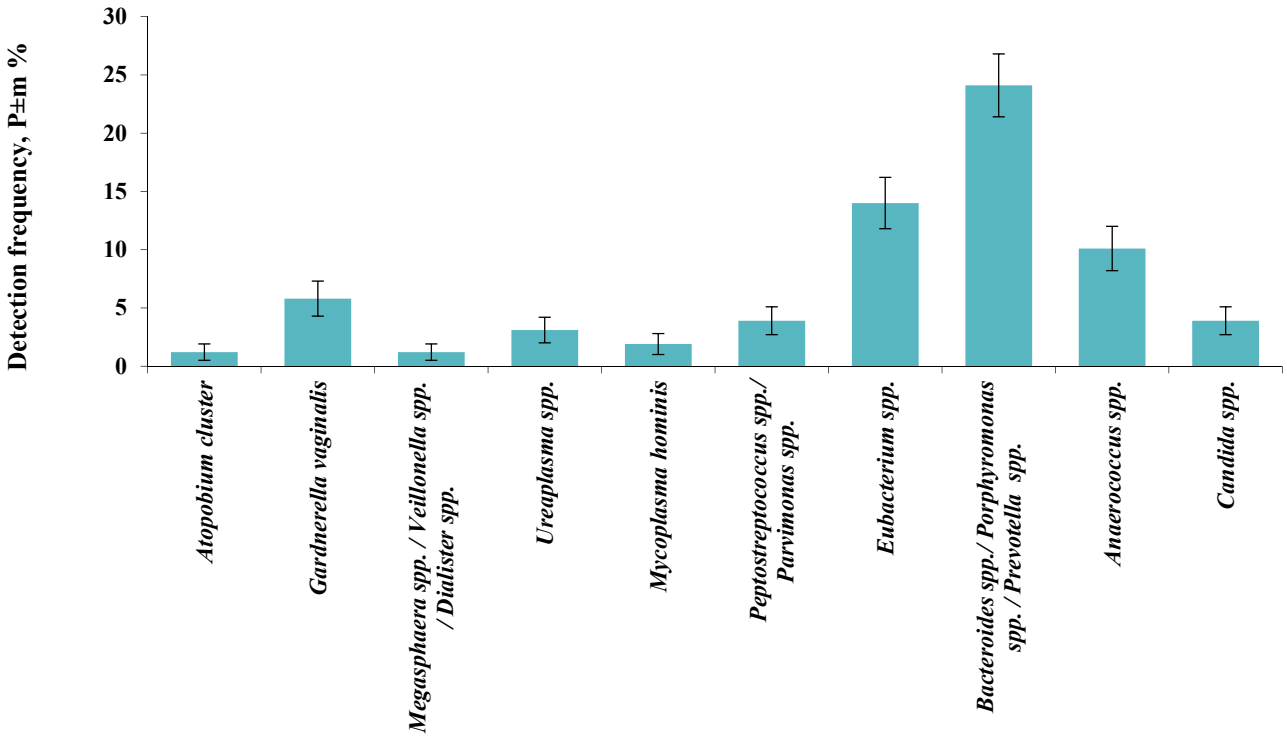

Fig. 2. The frequency of detection of resident opportunistic pathogenic microflora in samples of clinical material on the background of decrease in normal microflora

With regard to the transient microflora, it may be noted that most frequently the infectious-inflammatory process of the organs of UGT in the examined men was caused by representatives of family *Enterobacteriaceae*, the DNA of which was detected in 39.3±3.0% of clinical samples (Fig. 3). In 10.9±1.9% of the samples in biomaterial, there was DNA of *Enterococcus spp.,* in 3.1±1.1% – *Haemophilus spp*. and only in 0.4±0.1% – *P. aeruginosa*.

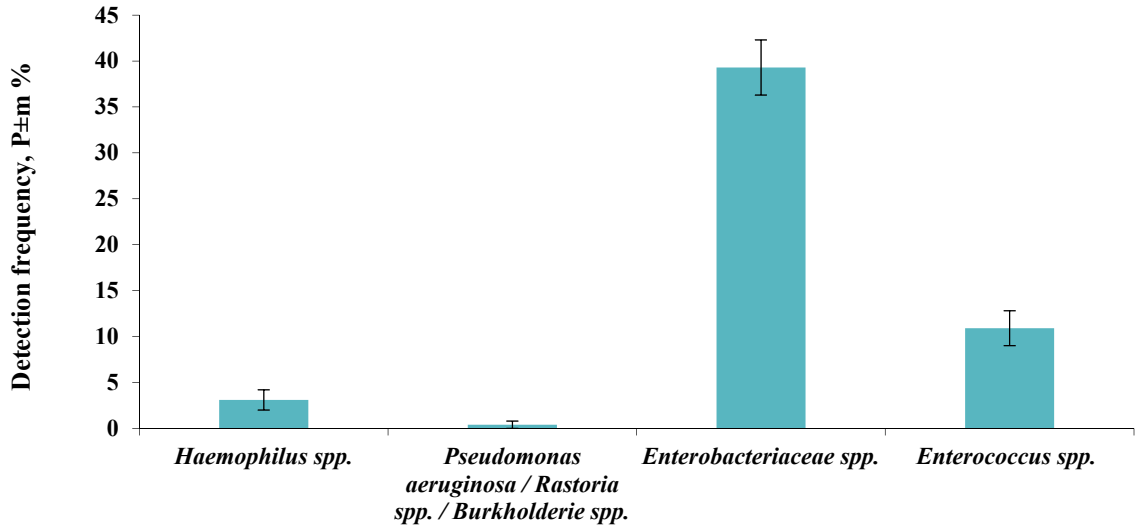

Fig. 3. The frequency of detection of representatives of transient opportunistic pathogenic microflora in clinical material samples

The number of genomic equivalents of the cells of transient microflora in 1 ml of a clinical sample, expressed through lg X copies of DNA / sample, on average made up: for bacteria of family *Enterobacteriaceae* – 4.8±0.2, *Enterococcus spp.* – 4.3±0.2, *Haemophilus spp.* – 2.5±0.1, *P. aeruginosa / Ralstonia spp. / Burkholderia spp.* – 2.5±0.2.

Since, genome equivalents of bacteria of family *Enterobacteriaceae* were most frequently found in large titres in the clinical material from the transient microflora, which emphasizes their important role in occurrence of infectious and-inflammatory diseases of the UGT in males, the next stage of the work was their isolation in the pure culture on the relevant nutrient media and performance of species identification.

Altogether, 101 strains of bacteria – representatives of family *Enterobacteriaceae* were separated from the analyzed clinical samples; they were represented in 63.4±4.8% of the cases by *Escherichia coli*, in 5.9±0.4% – by *Proteus vulgaris,* in 14.9±1.5% – by *Proteus mirabilis.* 10.9±1.1% of strains from the total number of enterobacteria were identified as *Klebsiella pneumoniae,* another 4.9±0.2% – as *K. oxytoca* (Fig. 4).

When examining sensitivity of representatives of family Enterobacteriaceae to antibiotics with the use of the disc-diffusion method, it was found that the most effective preparations to E. *coli* strains were imipenem and nitroxoline, which suppressed the growth of 93.8±3.0% and 90.6±3.6% of cultures, respectively. A fairly high percentage of susceptible strains of *E. coli* was to fosfomicin, cefepime and levofloxacin: 81.2±4.9% and 71.9±5.6%, respectively. *E. coli* strains were most resistant to ampicillin and erythromycin. More than 90.6±3.4% of the isolated cultures appeared to be resistant to these preparations (Table 1).

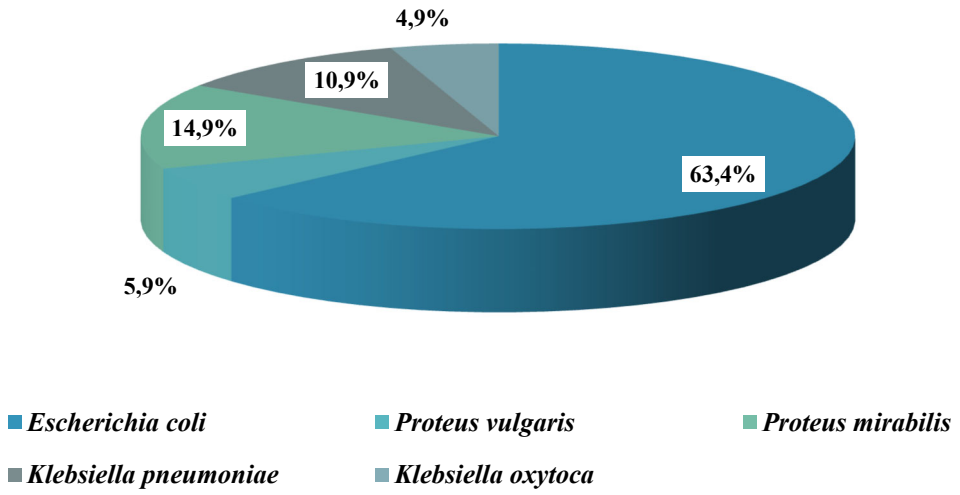

Fig. 4. Species composition and proportion of bacteria strains of family *Enterobacteriaceae*

P. mirabilis strains showed a high degree of resistance to all tested antibacterial preparations. Thus, all the tested isolates possess resistance to ampicillin. 93.3±6.4% were resistant to erythromycin, 86.7±2.8% – to amoxiclav, 80.0±1.3% – to azithromycin. Imipenem, which suppressed the growth of 86.7±5.8% of cultures, was most effective to *P. mirabilis*. The percentage of strains, sensitive to the rest of antibacterial preparations, did not exceed the value of 66.7±2.5%.

100.0±9.2% of the examined isolates of *P. vulgaris* were susceptible to imipenem and cefepime, and 83.3±5.2% – to two other antibiotics of cephalosporin group – ceftriaxone and ceftazidime. Ampicillin and erythromycin proved to be totally ineffective to all strains of *P. vulgaris*.

With regard to the strains of *K. pneumoniae*, a very low percentage of sensitive isolates were observed among them. Only 90.9±8.7% of cultures possessed sensitivity to imipenem and 72.7±3.4% – to levofloxacin, nitroxoline and amikacin. The percentage of sensitive strains to other antibacterial preparations did not exceed 54.6±1.3%. Resistance to antibiotics of the penicillin group, such as ampicillin and amoxiclav, was found in 90.9±8.7% of strains of *K. pneumoniae*. 100.0±5.6% of cultures were resistant to erythromycin.

Table 1

Sensitivity to antibiotics of bacteria strains of family *Enterobacteriaceae*, isolated from samples of clinical material from males with infectious-inflammatory diseases of UGT (abs. number/%)

Antibacterial preparation	*E. coli*, n=64			*P. mirabilis*, n=15			*P. vulgaris*, n=6			*K. pneumoniae*, n=11			*K. oxytoca*, n=5		
	R	S	IR	R	S	IR	R	S	IR	R	S	IR	R	S	IR
Ampicillin	58/ 90.6	2/ 3.1	4/ 6.3	15/ 100.0	0/ 0.0	0/ 0.0	6/ 100.0	0/ 0.0	0/ 0.0	10/ 90.9	0/ 0.0	1/ 9.1	4/ 80.0	0/ 0.0	1/ 20.0
Amoxiclav	42/ 65.6	8/ 12.5	14/ 21.9	13/ 86.6	1/ 6.7	1/ 6.7	5/ 83.3	0/ 0.0	1/ 16.7	10/ 90.9	0/ 0.0	1/ 9.1	4/ 80.0	0/ 0.0	1/ 20.0
Ciprofloxacin	36/ 56.2	20/ 31.3	8/ 12.5	5/ 33.3	4/ 26.7	6/ 40.0	3/ 50.0	1/ 16.7	2/ 33.3	4/ 36.4	4/ 36.4	3/ 27.2	2/ 40.0	2/ 40.0	1/ 20.0
Levofloxacin	10/ 15.6	46/ 71.9	8/ 12.5	2/ 13.3	10/ 66.7	3/ 20.0	1/ 16.7	4/ 66.6	1/ 16.7	1/ 9.1	8/ 72.7	2/ 18.2	1/ 20.0	3/ 60.0	1/ 20.0
Erythromycin	60/ 93.7	0/ 0.0	4/ 6.3	14/ 93.3	0/ 0.0	1/ 6.7	6/ 100.0	0/ 0.0	0/ 0.0	11/ 100.0	0/ 0.0	0/ 0.0	5/ 100.0	0/ 0.0	0/ 0.0
Azithromycin	48/ 75.0	4/ 6.3	12/ 18.7	12/ 80.0	0/ 0.0	3/ 20.0	5/ 83.3	0/ 0.0	1/ 16.7	9/ 81.8	0/ 0.0	2/ 18.2	3/ 60.0	0/ 0.0	2/ 40.0
Cefotaxime	20/ 31.3	16/ 25.0	28/ 43.7	5/ 33.3	7/ 46.7	3/ 20.0	0/ 0.0	4/ 66.7	2/ 33.3	6/ 54.6	3/ 27.2	2/ 18.2	0/ 0.0	3/ 60.0	2/ 40.0
Ceftriaxone	16/ 25.0	28/ 43.7	20/ 31.3	4/ 26.7	9/ 60.0	2/ 13.3	0/ 0.0	5/ 83.3	1/ 16.7	4/ 36.4	4/ 36.4	3/ 27.2	0/ 0.0	4/ 80.0	1/ 20.0
Ceftazidime	10/ 15.6	42/ 65.7	12/ 18.7	3/ 20.0	8/ 53.3	4/ 26.7	0/ 0.0	5/ 83.3	1/ 16.7	3/ 27.2	6/ 54.6	2/ 18.2	0/ 0.0	5/ 100.0	0/ 0.0
Cefepime	4/ 6.3	52/ 81.2	8/ 12.5	2/ 13.3	10/6 6.7	3/ 20.0	0/ 0.0	6/ 100.0	0/ 0.0	3/ 27.2	7/ 63.7	1/ 9.1	0/ 0.0	5/ 100.0	0/ 0.0
Imipenem	2/ 3.1	60/ 93.8	2/ 3.1	0/ 0.0	13/ 86.7	2/ 13.3	0/ 0.0	6/ 100.0	0/ 0.0	0/ 0.0	10/ 90.9	1/ 9.1	0/ 0.0	5/ 100.0	0/ 0.0
Fosfomicin	1/ 1.6	52/ 81.2	11/ 17.2	6/ 40.0	5/ 33.3	4/ 26.7	2/ 33.3	1/ 16.7	3/ 50.0	3/ 27.2	2/ 18.2	6/ 54.6	2/ 40.0	1/ 20.0	2/ 40.0
Furaginum	24/ 37.5	26/ 40.6	14/ 21.9	6/ 40.0	3/ 20.0	6/ 40.0	3/ 50.0	1/ 16.7	2/ 33.3	5/ 45.4	2/ 18.2	4/ 36.4	2/ 40.0	0/ 0.0	3/ 60.0
Co-trimoxazole	16/ 25.0	30/ 46.9	18/ 28.1	5/ 33.3	4/ 26.7	6/ 40.0	3/ 50.0	2/ 33.3	1/ 16.7	4/ 36.4	4/ 36.4	3/ 27.2	2/ 40.0	2/ 40.0	1/ 20.0
Nitroxoline	4/ 6.3	58/ 90.6	2/ 3.1	4/ 26.7	9/ 60.0	2/ 13.3	0/ 0.0	4/ 66.7	2/ 33.3	2/ 18.2	8/ 72.7	1/ 9.1	1/ 20.0	3/ 60.0	1/ 20.0
Gentamycin	16/ 25.0	38/ 59.4	10/ 15.6	7/ 46.7	6/ 40.0	2/ 13.3	1/ 16.7	3/ 50.0	2/ 33.3	3/ 27.2	6/ 54.6	2/ 18.2	1/ 20.0	3/ 60.0	1/ 20.0
Amikacin	12/ 18.7	44/ 68.8	8/ 12.5	6/ 40.0	8/ 53.3	1/ 6.7	0/ 0.0	4/ 66.7	2/ 33.3	1/ 9.1	8/ 72.7	2/ 18.2	0/ 0.0	4/ 80.0	1/ 20.0

Notes: R – resistant; IR – intermediately resistant; S – sensitive; n – number of strains.

All isolated strains of *K. oxytoca* retained resistance to erythromycin. 80.0±1.9% of cultures were resistant to ampicillin and amoxiclav. Cefepime, ceftazidime and imipenem suppressed the growth of 100.0±1.6% of *K. oxytoca* strains.

27 cultures of the isolated bacteria of family *Enterobacteriaceae* had the ESBL-synthesizing ability, which made 26.7±4.4% of the total number of opportunic pathogenic enterobacteria. 25.0±5.4% of

E. coli strains, 33.3±2.2% of *P. mirabilis* and 54.5±5.0% of *K. pneumoniae* had this ability.

The current research found that the isolated strains of ESBL-producing enterobacteria were resistant to at least 6 tested antibiotics. All ESBL-producing cultures showed resistance to preparations of the penicillin group – ampicillin and amoxiclav with simultaneous resistance to at least one of the antibiotics of cephalosporin group (Table 2).

Table 2

Sensitivity to antibiotics of ESBL-synthesizing bacterial strains of family *Enterobacteriaceae*, isolated from clinical material of males with infectious-inflammatory diseases of the UGT (abs. number /%)

Antibiotics	*E. coli*, n=16			*P. mirabilis*, n=5			*K. pneumoniae*, n=6		
	R	S	IR	R	S	IR	R	S	IR
Ampicillin	15/93.7	0/0.0	1/6.3	5/100.0	0/0.0	0/0.0	6/100.0	0/0.0	0/0.0
Amoxiclav	14/87.4	1/6.3	1/6.3	5/100.0	0/0.0	0/0.0	6/100.0	0/0.0	0/0.0
Ciprofloxacin	4/25.0	6/37.5	6/37.5	1/20.0	1/20.0	3/60.0	2/33.3	1/16.7	3/50.0
Levofloxacin	9/56.3	4/25.0	3/18.7	2/40.0	2/40.0	1/20.0	1/16.7	3/50.0	2/33.3
Erythromycin	15/93.7	0/0.0	1/6.3	5/100.0	0/0.0	0/0.0	6/100.0	0/0.0	0/0.0
Azithromycin	14/87.4	0/0.0	2/12.6	5/100.0	0/0.0	0/0.0	5/83.3	0/0.0	1/16.7
Cefotaxime	14/87.4	0/0.0	2/12.6	3/60.0	2/40.0	0/0.0	3/50.0	2/33.3	1/16.7
Ceftriaxone	11/68.7	1/6.3	4/25.0	1/20.0	2/40.0	2/40.0	1/16.7	2/33.3	3/50.0
Ceftazidime	6/37.4	5/31.3	5/31.3	2/40.0	1/20.0	2/40.0	3/50.0	2/33.3	1/16.7
Cefepime	4/25.0	4/25.0	8/50.0	2/40.0	2/40.0	1/20.0	3/50.0	2/33.3	1/16.7
Imipenem	0/0.0	15/93.7	1/6.3	0/0.0	0/0.0	5/100.0	0/0.0	5/83.3	1/16.7
Fosfomicin	1/6.3	10/62.5	5/31.2	3/60.0	1/20.0	1/20.0	3/50.0	2/33.3	1/16.7
Furaginum	6/37.5	3/18.6	7/43.9	0/0.0	3/60.0	2/40.0	1/16.7	1/16.7	4/66.7
Co-trimoxazole	12/75.0	0/0.0	4/25.0	2/40.0	1/20.0	2/40.0	3/50.0	2/33.3	1/16.7
Nitroxoline	1/6.3	13/81.1	2/12.6	3/60.0	2/40.0	0/0.0	2/33.3	3/50.0	1/16.7
Gentamicin	7/43.9	4/25.0	5/31.3	2/40.0	1/20.0	2/40.0	2/33.3	2/33.3	2/33.3
Amikacin	9/56.3	4/25.0	3/18.7	3/60.0	1/20.0	1/20.0	1/16.7	3/50.0	2/33.3

Notes: R – resistant; IR – intermediately resistant; S – sensitive; n – number of strains.

Among cephalosporin antibiotics, cefotaxime and ceftriaxone revealed the lowest activity against ESBL-producing strains of *E. coli*; 87.4±8.3% and (68.7±1.6)% of the tested cultures, respectively, were resistant to them. Ceftazidime and cefepime were a little more active – the number of strains of *E. coli*, resistant to them, did not exceed 37.4±2.1% and 25.0±1.8% of the total number of producing ESBL, respectively.

As for the ESBL-synthesizing strains of *P. mirabilis*, it was found that these bacteria were most

resistant to cefotaxime 60.0±1.9%, and slightly less resistant to ceftazidime and cefepime 40.0±1.2%. *K. pneumoniae* strains were resistant to these three cephalosporins in 50.0±2.4% of cases.

As for the rest spectrum of tested antibiotics in respect to ESBL-producing enterobacteria, it is worth paying attention the fact that all representatives of this microbial group have a high degree of resistance to antibiotics of the macrolides series. 83.3±0.9% of cultures showed resistance to erythromycin and azithromycin. 75.0±3.8% of the tested isolates of *E. coli* were also resistant to co-trimoxazole. The most effective preparations were nitroxoline and imipenem, inhibiting the growth of 81.1±2.8% and 93.7±1.0% of the cultures, respectively. 60.0±1.9% of *P. mirabilis* ESBL-producing strains were resistant to amikacin, fosfomicin and nitroxoline. Resistance to co-trimoxazole and fosfomicin was observed among the strains of *K.pneumoniae* 50.0±0.4% of them.

According to a number of scientists [6, 7], prevalence of ESBL among clinical strains of enterobacteria, resistant to cephalosporins of the third generation, varies widely, depends on a variety of factors and can reach 85%. In our research, the frequency of detection of such strains was 26.7±4.4%. Despite this relatively low percentage of isolation of ESBL-producers, the selected strains were characterized by a high degree of resistance to antibiotics of other pharmaceutical groups, and primarily to macrolides – erythromycin and azithromycin, as well as to co-trimoxazole and fosfomicin. The results, obtained in the present research, prove the data of other authors, who showed that the ESBL-producing strains of enterobacteria, isolated from the clinical material of the patients with various infectious-inflammatory diseases of the urogenital tract, are characterized by multi-resistance [2, 5, 6]. Thus, it was shown by P. Aminul et al. [2] that in addition to resistance to β-lactams, clinical bacteria strains of family *Enterobacteriaceae* showed co-resistance to fluoroquinolones and aminoglycosides, according to the data of A. Ben Ashur with the co-authors [4] – to nitrofurans and tetracyclines. It was shown by Y. Caron et al. [5] that the multi-resistant clinical strains of enterobacteria showed nonsusceptibility to fluoroquinolones and co-trimoxazole.

As a result of numerous monitoring researches, in modern clinical practice, the provision was stated that enterobacteria strains with the proved presence of ESBL must be regarded as resistant to all penicillins, cephalosporins (except cefamicyn) and monobactams irrespective of absolute values of MIC and diameters of the growth suppression zones around the discs with cephalosporins of III generation [9]. This, in turn, imposes a significant restriction on the spectrum of the possible use of antibiotic preparations for treatment of infectious-inflammatory diseases, caused by ESBL-producing representatives of family *Enterobacteriaceae*. Even greater difficulties in therapy are created by multi-resistant strains of enterobacteria, capable to synthesize ESBL.

Therefore, in order to select effective antibiotic preparations and administration of optimal treatment of these infections, it is necessary to conduct constant monitoring of ambulatory strains of ESBL-producing enterobacteria and take measures to prevent subsequent extension of multi-resistant variants.

CONCLUSIONS

1. According to the results of research with the use of the test-system "Androflor", it was found that out of 257 samples of biomaterial from the urogenital tract of males with genitourinary pathology, obligate pathogens of *C. trachomatis, M. genitalium, N. gonorrhoeae, T. vaginalis* were found in 37 samples 14.4±2.2%. The frequency of detection of *C. trachomatis* was 10.1±1.9%, the percentage of detection of the rest of them did not exceed the value of 1.6±0.2%.
2. Dysbiotic disruptions, caused by opportunistic pathogenic resident microflora, were found in 31.9±2.9% and by the transient – in 53.7±3.1% of patients. The main etiological agent of infectious-inflammatory diseases of UGT in males was the representatives of transient microflora – bacteria of family Enterobacteriaceae, identified as *E. coli*, *P. vulgaris, P. mirabilis, K. pneumoniae and K. oxytoca*. From 101 enterobacteria strains, 27 representatives of this family (26.7±4.4)%, in particular 16 isolates of *E. coli,* 5 isolates – *P. mirabilis* and 6 isolates – *K. pneumoniae*, revealed the ability to synthesize ESBL.
3. The isolated strains of ESBL-producing enterobacteria proved to be resistant to at least 6 tested antibiotics. All of ESBL-producing cultures showed resistance to preparations of the penicillin group – ampicillin and amoxiclav. In this case, resistance to at least one of the antibiotics of the cephalosporin group of III generation was noted. In addition, 83.3±2.1% of the examined isolates were characterized by resistance to macrolides – erythromycin and azithromycin, as well as to co-trimoxazole and fosfomicin, which makes it possible to refer them to the category of the multi-resistant.

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