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APPROACHES TO ANTIBIOTIC THERAPY IN PATIENTS WITH CALCULOUS PYELONEPHRITIS, UNDERGOING IN-PATIENT TREATMENT IN THE DEPARTMENT OF UROLOGY

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Abstract. Urolithiasis is one of the most common urologic diseases and it is found more than 3% of the population of Russia, which is complicated by calculous pyelonephritis from 43-81% up to 100% of cases. The knowledge of the main bacteria usually involved in patients with calculous pyelonephritis and their antimicrobial susceptibility is necessary for appropriate empirical therapy and prevention of the emergence of antibiotic resistance. The main pathogens in patients with calculous pyelonephritis undergoing treatment in the department of urology of St. Joseph Belgorod Regional Clinical Hospital in 2013-2015 was Escherichia coli, was presented in 36.8% of the isolates, followed by Klebsiella species in 18.1% of the isolates, Enterobacter species in 16.9% of the isolates, and Proteus species in 8.8% of the isolates. All isolates showed susceptibilities to carbapenems. Sensitivity to cephalosporins ranged from 48.5% of the cases to 41.8% of the cases, to fluoroquinolones from 32.4% of the cases to 24.5% of the cases, to co-trimoxazole ranged from 27.9% of the cases to 30.84% of the cases in 2013-2015. It was found increase of aminoglycosides activity: sensitive strains to amikacin were allocated 67.6% of the isolates, 86.1% of the isolates, 84.7% of the isolates, it was identified sensitive strains to gentamicin in 44.3% of the isolates, 53.5% of the isolates, 55.2% of the isolates in 2013, 2014, 2015, respectively. High effective agents was fosfomycin, which shown activity in 79.3% of the cases, 84.4% of the cases, 80.4% of the cases in 2013, 2014, 2015, respectively. The obtained data were shown, that amikacin, fosfomycin, piperacillin/tazobactam, cefoperazone/sulbactam, carbapenems can be used for empirical therapy in patients with calculous pyelonephritis undergoing treatment in the department of urology of St. Joseph Belgorod Regional Clinical Hospital.

Keywords: urolithiasis, calculous pyelonephritis, urinary tract infections, antibiotic sensitivity, extended-spectrum β-lactamase-producing strains of Enterobacteriacae

Urolithiasis is one of the most common urologic diseases and it is found more than 3% of the population of Russia [1], which is complicated by calculous pyelonephritis from 43-81% up to 100% of cases [2]. Currently, despite the relatively well-studied etiological structure of causative agents of pyelonephritis, issues of treatment of this disease is still actual, which is associated with the rapid growth of pathogens resistant to antimicrobial agents. It has transformed rational treatment regimens in the past to ineffective [3, 4, 5].

Irrational choice of antibacterial agents in patients with urinary tract infections not only leads to serious medical (increased incidence, recurrence, complications) and economic (growth of health care costs, increasing the duration of temporary disability), but also to the social (the deterioration of quality of life) and environmental (growth antibiotic resistance of microorganisms) effects [6]. This makes it necessary to conduct epidemiological studies to the definition of the structure of allocated

microorganisms and to determine their sensitivity in patients with calculous pyelonephritis.

Objectives of the study:

1. To study the structure of pathogens and their sensitivity to antibiotics in patients with calculous pyelonephritis undergoing treatment in the department of urology of St. Joseph Belgorod Regional Clinical Hospital in 2013-2015.

2. To determine the antibacterial chemotherapeutic agents for initial and etiological antibiotic therapy of patients with calculous pyelonephritis in the department of urology of St. Joseph Belgorod Regional Clinical Hospital.

Materials and methods:

It was a retrospective pharmacoepidemiological analysis of medical records. It were included medical history of male and female over 18 years with a diagnosis "calculous pyelonephritis" in case samples showing significant growth according to criteria recommendations of Russian society of urology [7].

It was analyzed medical history of 736 patients (42.2%, of them were men and 57.8% – women; mean age of patients was 56.38 ± 6.8 years old) with calculous pyelonephritis, who were treated in department of urology of St. Joseph Belgorod Regional Clinical Hospital in 2013-2015.

All patients underwent standard clinical examination, with mandatory bacteriological urine analysis, ultrasound study of kidneys. The clinical material for the study was an average portion of the morning urine or urine was obtained after drainage of the catheter-stent, or the draining ureteral catheter / nephrostomy drainage. Samples that were shown growth more than one types of organism, or had evidence of perineal contamination were not included for analysis.

The identification of microorganisms were obtained from the urine of patients with calculous pyelonephritis were treated in the department of urology of Saint Joseph Belgorod Regional Clinical Hospital in 2013-2015. Susceptibility testing was done by disk diffusion method and interpreted according to the EUCAST criteria. Statistical analyses were performed using "Statistica 10.0" applied statistical software package.

Results and discussion.

During the period of 2013-2015 total 497 strains were detected in urine of patients with calculous pyelonephritis have being treated in the department of urology of Saint Joseph Belgorod Regional Clinical Hospital in 2013-2015 (Table 1).

It was found that the most frequently isolated Gram-negative bacteria, were presented by strains of Enterobacteriacae. The most common uropathogen was Escherichia coli, which was presented in 36.8% of the cases, followed by Klebsiella species in 18.1% patient of the cases, and Enterobacter species in 16.9% of the cases. Also it was detected Proteus species in 8.8% of the cases, Citrobacter species in 5.1% of the cases. Pseudomonas species was detected in 5.1% of the cases, and Acinetobacter species in 2.6% of the cases (Table 1).

Table 1

Frequency of isolated bacterial pathogens isolated from patients with calculous pyelonephritis in 2013-2015

Pathogens	Number of isolated strains			
	2013	2014	2015	Total
Acinetobacter spp.	3	2	8	13
Citrobacter diversus	7	4	14	25
Escherichia coli.	68	55	60	183
Enterobacter spp	34	15	35	84
Klebsiella spp.	47	28	15	90
Proteus spp.	14	11	19	44
Pseudomonas aeruginoza	6	10	9	25
Enterococcus spp.	8	13	12	33
Total	**187**	**138**	**172**	**497**

Among Gram-positive bacteria the most frequent Gram-positive pathogen was Enterococcus spp. It was identified in 6.5% of the total number of strains isolated from urine of patients undergoing treatment in with calculous pyelonephritis have being treated in the department of urology of Saint Joseph Belgorod Regional Clinical Hospital in 2013-2015, which is less than the level was obtained by the data of other Russian researchers [8].

Due to the dominance of E. coli and other strains of Enterobacteria in the etiological structure of pathogens in calculous pyelonephritis the greatest interest is the data on the total sensitivity of all selected agents Enterobacteriacae and separate data sensitivity of E. coli, Klebsiella spp., Enterobacter spp.

Large proportions of E. coli were found to be resistant to ampicillin and amoxicillin-clavulanate in 2013-2015 (Table 2). It amounted 13.6%-18.5% susceptible strains and 27.2-33.3% susceptible strains to ampicillin and amoxicillin-clavulanate, respectively. It was shown high levels of level

extended-spectrum beta-lactamase-producing Escherichia coli, which reached 40.7% of the isolates, 45.5% of the isolates and 45.8% of the isolates in 2013, 2014 and 2015, respectively. All detected strains have shown their sensitivity to carbapenems.

It was revealed an increase in sensitivity to aminoglycosides: in 2013 the sensitivity to amikacin and gentamicin amounted to 55.6% of cases and 51.8% of cases, respectively. In 2014 and 2015, the susceptibility to amikacin amounted to 86.4% of the cases and 87.5% of the cases, respectively. Activity of gentamicin was slightly lower: it was identified in 63.6% of the strains and 70.8% of the strains in 2014 and 2015, respectively.

It was registered the low level of susceptibility to fluoroquinolones, which ranged from 31.8% of the cases to 37.1% of the cases to ciprofloxacin, from 29.1% of the cases to 37.1% of cases to levofloxacin in 2013-2015. The sensitivity of E. coli to co-trimoxazole amounted to 37.1% of the isolates, 36.4% of the isolates, 33.3% of the isolates in 2013, 2014, 2015, respectively. Fosfomycin showed a high level of activity, which was reached to 81.5% of the isolates, 86.3% of the isolates and 79.2% of the isolates in 2013, 2014 and 2015, respectively.

The findings suggest about the rise in the level of resistance of E. coli to penicillins, cephalosporins, fluoroquinolones, which is consistent with domestic authors obtained for the years 2009-2013. However, the sensitivity E. coli, in patients, who were treated at the department of urology of Saint Joseph Belgorod Regional Clinical Hospital in 2014-2015, to these antibacterial agents retained at substantially high sensitivity to amikacin, carbapenems, fosfomycin [8]. By comparison the result was obtained in National Multicenter Surveillance Study «MARATHON» with data of susceptibility to antibiotics in the department of urology of St. Joseph Belgorod Regional Clinical Hospital revealed higher susceptibility to ampicillin, amoxicillin/clavulanate, cephalosporins, carbapenems, aminoglycosides, a slightly higher susceptibility to fluoroquinolones, co-trimoxazole and lower sensitivity to fosfomycin [9].

As compared with the data of foreign researchers, the level of resistance strains of E. coli, which were registered in patients with urinary tract infections during inpatient treatment, below the level of resistance, identified by researchers at the Veterans Hospital in Boston (USA), and researchers at the hospital of Al Zahra (Iran), but exceeds the level of resistance reported in the clinical hospital in Dublin (Ireland) [10, 11, 12].

Table 2

Susceptibility of E. coli, Klebsiella spp., Enterobacter spp. to antibiotics isolated from patients with calculous pyelonephritis in 2013-2015

Pathogens	***E. coli***			***Klebsiella spp.***			***Enterobacter spp.***		
	2013	**2014**	**2015**	**2013**	**2014**	**2015**	**2013**	**2014**	**2015**
Total (%)	29.4	45.9	32	23.53	18.9	10.6	27.45	13.5	21.3
Ampicillin	18.5	13.6	16.6	0	0	0	0	0	0
amoxicillin / clavulanate	33.3	27.2	29.1	26.3	18.2	0	0	0	0
Cefotaxime	59.3	54.5	54.2	36.8	27.3	28.5	46.6	16.6	21.4
Ceftriaxone	59.3	54.5	54.2	36.8	27.3	28.5	46.6	16.6	21.4
Ceftazidime	59.3	54.5	54.2	36.8	27.3	28.5	46.6	16.6	21.4
Cefepime	59.3	59.1	58.3	36.8	36.4	28.5	46.6	16.6	21.4
Meropenem	100	100	100	100	100	100	100	100	100
Imipenem	100	100	100	100	100	100	100	100	100
Ertapenem	100	100	100	100	100	100	100	100	100
Gentamicin	51.8	63.6	70.8	36.8	45.5	42.8	33.3	33.3	28.5
Amikacin	55.6	86.4	87.5	73.7	90.9	85.7	73.3	66.6	71.4
Ciprofloxacin	37.1	31.8	33.3	26.3	18.2	28.5	26.2	16.6	0
Levofloxacin	37.1	31.8	29.1	26.3	18.2	28.5	20.0	16.6	0
Co-trimoxazole	37.1	36.4	33.3	21.1	18.2	28.5	26.2	16.6	35.7
Fosfomycin	81.5	86.3	79.2	73.7	81.8	71.4	86.6	66.6	83.3

Analysis of susceptibility of extended-spectrum β-lactamase-producing E.coli were isolated from the urine of patients with calculous pyelonephritis which were treated in the department of urology of the St. Joseph Belgorod Regional Clinical Hospital in 2015 was registered sensitivity isolates to carbapenem in 100% of the cases, gentamicin – in 40% of the cases, amikacin – in 90% of the cases, to ciprofloxacin – in 10% of the cases, to levofloxacin – in 10% of the cases, to co-trimoxazole – in 10% of the cases, to

fosfomycin – in 70% of the cases. The data is consistent with British researchers [13].

Korean researchers have identified slightly higher sensitivity of E. coli to the antibiotics: sensitivity to ciprofloxacin was identified in 20.7% of the strains, levofloxacin – in 22.7% of the strains, amikacin – in 94.1% of the strains, co-trimoxazole – in 34.3% of the strains, fosfomycin – in 87.7% of the strains [14].

Isolates of Klebsiella spp. was revealed a high level of resistance to penicillins, cephalosporins. All of the isolates were found to be resistant to ampicillin. The sensitivity to amoxicillin/clavulanate was reduced from 26.3% in 2013 to 0% of susceptible strains in 2015. Number of strains of Klebsiella spp., sensitive to cephalosporins was 36.8% in 2013. In 2014-2015 it was noted a decrease in their sensitivity to 27.3-28.5%. All isolates of Klebsiella spp. showed its sensitivity to carbapenems. It was registered low sensitivity to fluoroquinolones, co-trimoxazole. It was allocated 26.3% of the strains, 18.2% of the strains, 28.5% of the strains to ciprofloxacin and levofloxacin in 2013, 2014, 2015, respectively. The level of sensitivity to co-trimoxazole was 16.6-28.5% of susceptible strains in 2013-2015, unlike sensitivity to fosfomycin, which was 73.7%, 81.8%, 71.4% in 2013, 2014, 2015, respectively. It was shown low sensitivity to gentamicin, which varied from 36.8% to 45.5%, in contrast to amikacin, to which sensitivity was 73.7%, 90.9%, 85.7% in 2013, 2014, 2015, respectively. This is consistent with the data of researchers from the United States [15], but below the level of resistance was identified by Indian researchers. It has been shown, that the susceptibility of Klebsiella spp. which were isolated from sample of urine of patients who were hospitalized in a medical college hospital of Bangalore (India) in 2012, were registered a lower sensitivity to ampicillin, cephalosporins, aminoglycosides, fluoroquinolones. The level of sensitivity of strains Klebsiella spp. to carbapenems was 67.9% [16].

In comparison with the result obtained in National Multicenter Surveillance Study «MARATHON», we found higher sensitivity selected strains of Klebsiella spp. to cefotaxime, ceftazidime, cefepime, gentamicin, amikacin, with comparable susceptibility to carbapenems, fluoroquinolones, fosfomycin in the department of urology of the Belgorod Regional Clinical Hospital of St. Joasaph [9].

Frequency of the isolated strains of extended-spectrum β-lactamase-producing Klebsiella spp. isolated from the urine of patients with calculous pyelonephritis in the urology department of the St. Joseph Belgorod Regional Clinical Hospital in 2015 was reached 71.4% and the isolated strains showed a low susceptibility to the test antibiotic compared with the registered strains of extended-spectrum β-lactamase-producing E. coli. It was registered sensitivity of isolates Klebsiella spp. to carbapenem in 100% of the cases, gentamicin – in 40% of the cases, amikacin – 90% of the cases, to ciprofloxacin – in 10% of the cases, to levofloxacin – in 10% of the cases, to co-trimoxazole – in 10% of the cases, to fosfomycin – in 70% of the cases. The data is consistent with Korean researchers. [14].

Large proportions of the isolates were found to be resistant to penicillins and cephalosporins isolated strains. All strains of Enterobacter spp. isolated in 2013-2015 showed their resistance to ampicillin, amoxicillin/clavulanate. It was registered increase in the level of resistance of Enterobacter spp.: sensitivity to cephalosporins was recorded in 46.6% of the isolates, 16.6% strains 21.4% of strains in 2013, 2014, 2015, respectively. Strains of Enterobacter spp., which were isolated in 2013-2015, have been showed a higher level of resistance to cephalosporins as compared with the isolated strains of E. coli and Klebsiella spp. All isolates were susceptible to carbapenems. Analysis of the sensitivity of Enterobacter spp. was established low sensitivity to fluoroquinolones, co-trimoxazole. Amikacin was active in 73.3% of the cases, 66.6% of the cases, 73.3% of the cases; gentamicin in 33.3% of the cases, 33.3% of the cases, 28.5% of the cases in 2013, 2014, 2015, respectively. Susceptibility to ciprofloxacin does not exceed 26.2% of the strains to levofloxacin – 20.0% of the strains. Selected strains of Enterobacter spp. were susceptible to co-trimoxazole in 26.2% of the cases, 16.6% of the cases, 35.7% of the cases in 2013, 2014, 2015, respectively. High activity to fosfomycin was showed in 86.6% of the isolates, 66.6% of the isolates, 83.3% of the isolates in 2013, 2014, 2015, respectively.

The findings of the high level of resistance Enterobacter spp. were consistent with those of Russian and foreign authors [9, 17].

The identified strains of Enterobacter spp. showed the highest level of resistance among Enterobacteriaceae. Out of all strains of Enterobacter spp. it was registered 78.6% extended-spectrum β-lactamase-producing strains of Enterobacter spp. in patients with calculous pyelonephritis in the department of urology of the St. Joseph Belgorod Regional Clinical Hospital in 2015. The most active antibacterial agents were carbapenems, which sensitivity were 100% of the cases. Susceptibility to amoxicillin/clavulanate in 0% of the cases, gentamicin – in 27.2% of the cases, amikacin – in 63.6% of the cases, ciprofloxacin in 18.2% of the cases, levofloxacin – in 9.1% of the cases, co-trimoxazole – in 0% of the cases, fosfomycin – in 72.7% of the cases. This data exceeds the level of resistance, identified by researchers in the study of the spectrum of pathogens and their sensitivity to one of the

smaller hospitals in Bo (Sierra Leone) in 2013-2014. [18].

The most effective agents to all strains of isolated Enterobacteriaceae were carbapenems: all isolates showed sensitivity to carbapenems. In general, the total susceptibilities for all strains of Enterobacteriacae were higher compared to strains of E. coli and below compared to strains of Klebsiella spp. and Enterobacter spp. Sensitivity to ampicillin was 7.5% of the cases, 9.3% of the cases, 11.3% of the cases; amoxicillin/clavulanate – 23.0% of the cases, 23.2% of the cases, 17.0% of cases, cefotaxime, ceftriaxone, and ceftazidime – 48.5% of the cases, 41.8% of the cases, 41.9% of the cases, to the cefepime – 48.5% of the cases, 46.5% of the cases, 43.8% of the cases in 2013, 2014, 2015, respectively. Fluoroquinolones activity was as follows: 32.4% of the cases, 30.2% of the cases, 26.4% of the cases to ciprofloxacin, 31.1% of the cases, 30.2% of the cases, 24.5% for the cases to levofloxacin; in 2013, 2014, 2015, respectively. Sensitivity to co-trimoxazole ranged from 27.9% of the cases to 30.84% of the cases in 2013-2015. Aminoglycosides showed an increase of its activity: sensitive strains to amikacin were allocated 67.6% of the isolates, 86.1% of the isolates, 84.7% of the isolates in 2013, 2014, 2015, respectively. It was registered lower sensitivity to gentamicin compared to amikacin. It identified 44.3% of the isolates, 53.5% of the isolates, 55.2% of the isolates sensitive to gentamicin in 2013, 2014, 2015, respectively. High effective agents was fosfomycin, which was active in 79.3% of the cases, 84.4% of the cases, 80.4% of the cases in 2013, 2014, 2015, respectively.

Summary:

1. The main pathogens in patients with calculous pyelonephritis undergoing in-patient treatment in the department of urology of St. Joseph Belgorod Regional Clinical Hospital in 2013-2015 was Escherichia coli, was presented in 36.8% of the isolates, followed by Klebsiella species in 18.1% of the isolates, Enterobacter species in 16.9% of the isolates, and Proteus species in 8.8% of the isolates. All isolates showed susceptibilities to carbapenems. Sensitivity to cephalosporins ranged from 48.5% of the cases to 41.8% of the cases, to fluoroquinolones from 32.4% of the cases to 24.5% of the cases, to co-trimoxazole ranged from 27.9% of the cases to 30.84% of the cases in 2013-2015. It was found increase of aminoglycosides activity: sensitive strains to amikacin was allocated 67.6% of the isolates, 86.1% of the isolates, 84.7% of the isolates, it were identified sensitive strains to gentamicin in 44.3% of the isolates, 53.5% of the isolates, 55.2% of the isolates in 2013, 2014, 2015, respectively. High effective agents was fosfomycin, which shown activity in 79.3% of cases, 84.4% of cases, 80.4% of cases in 2013, 2014, 2015, respectively.

2. For initial antibiotic therapy of calculous pyelonephritis patients in patients undergoing treatment in the department of urology of St. Joseph Belgorod Regional Clinical Hospital is recommended amikacin, fosfomycin, piperacillin/tazobactam, cefoperazone/sulbactam, carbapenems.

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