THE SENSITIVITY OF PATHOGENS OF COMMUNITY-ACQUIRED URINARY TRACT INFECTIONS IN KARAGANDA

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Summary
As part of multicenter study DARMIS (SRI AC, Smolensk, Russia) it was conducted the determination of sensitivity to antimicrobial agents of 25 urinary strains of Escherichia coli, isolated at community-acquired urinary tract infections in patients living in Karaganda, Kazakhstan. It was revealed the low part of strains sensitive to the inhibitor-protected and unprotected aminopenicillins, gentamicin, trimethoprim/sulfamethoxazole, as well as fluorinated and non-fluorinated quinolones. In 12.0% of cases Escherichia coli, the pathogens of community-acquired urinary tract infections were the producers of extended spectrum β-lactamase (ESBL).

Key words: Escherichia coli, community-acquired urinary tract infections, antibiotic sensitivity, ESBL

Introduction
One of the most common groups of diseases that occur in outpatient practice, are the urinary tract infection. The therapy of outpatient urinary tract infections is often prescribed empirically, based on the recommendations on urinary tract infections treatment (Belousov et.al., 2007; Hooton et.al., 2005). It is known that such recommendations are developed on the basis of the sensitivity of uropathogens obtained in individual countries or regions, and reflect the situation characteristic for them (Kulakov et.al., 2004; Naber et.al., 2008). It is important to understand that the use of such recommendations in other regions can not be used a priory, as the susceptibility of pathogens to antimicrobial agents has the specific for every region, which is confirmed by several studies (Kahlmeter et.al., 2003; Schito et.al., 2009; Rafalskiy et.al., 2006).

There is no evidence base for the development of recommendations for the treatment of community-acquired urinary tract infections to date in Kazakhstan, which was the rationale for this study (Karlowsky et.al., 2002; Warren et.al., 1999).

Material and methods
As a part of multicenter study to evaluate the sensitivity to antimicrobial agents of community-acquired urinary pathogens in Karaganda.

This study is part of a prospective multicenter clinical and microbiological study «Multicenter study of the dynamics of antimicrobial resistance of urinary tract infections in different subpopulations of patients» («DARMIS»), carried out on the basis of scientific research institute of antimicrobial chemotherapy (SRI AC, Smolensk, Russia). We can mention inclusion and exclusion criteria of the patients to this study. From this point of view, criteria for inclusion of patients to the study are patients of both genders from all age groups, including pregnant women, the presence of clinical picture of one of the following community-acquired infections as acute cystitis, acute exacerbations of chronic cystitis, acute pyelonephritis, acute exacerbations of chronic pyelonephritis, asymptomatic bacteriuria during pregnancy.
and isolation of the pathogen in the diagnostically significant titer.

Criteria for exclusion of patients from the study are the absence of any of the criteria for inclusion; the indications of a history of hospitalization of any type for any indication in the last two months before the development of this episode of infection; an indication of the invasive urologic surgery within last three months, as catheter insertion endourological surgery; inability to realize the bacteriological analysis of urine; inability to collect the full medical history of the patient; laboratory-documented infection of the reproductive system in men as prostatitis, orchitis, or epididymitis; isolated urethritis without symptoms of cystitis or pyelonephritis and treatment with antibiotics for ≥24 h before the urine collection for bacteriological examination.

Isolation of microorganisms was carried out by conventional methods. The identification was performed using the time-flight mass spectrometry (MALDI-TOFF). Determination of antimicrobial susceptibility was performed by serial dilution in Mueller-Hinton agar (BBL, USA) and evaluated in accordance with the recommendations of EUCAST. Phenotypic definition of extended spectrum β-lactamase production was performed by double discs method. Quality control was realized using the control strain of E. coli ATCC 25922. Statistical processing was performed using the program Microsoft Office Excel 2007.

Results and discussions

There are clinical characteristics of the subjects from this study. From this point of view, in total, the work includes the results of the survey of 28 patients at the age from 3 to 82 years. The mean age was (M±SD) 37±23 years. Of these, 92,9% were female and 7,1% – male. In 46,4% of cases the diagnosis, about which the patients referred for bacteriological urine analysis, was «chronic pyelonephritis», in 21,4% – «acute cystitis», in 10,7% – «recurrent cystitis», in 7,1 % – «chronic pyelonephritis, chronic cystitis», 3,6% – «acute cystitis, chronic pyelonephritis», «asymptomatic bacteriuria», «chronic renal failure I-II», «diabetic nephropathy II».

In addition to the main diagnosis, it was evaluated the presence or absence of complicating factors. In most of the cases (60,7%), the presence of confounding factors were observed. In 7,1% of cases it was noted the presence of urolithiasis (UL). In a few cases (by 3,6%) it was revealed nephroptosis, enuresis, hysteroptosis, diabetes mellitus (DM). In addition, in a few cases (also by 3,6%) it was revealed the presence of associated complicating factors – diabetes mellitus and congestive heart failure, diabetes mellitus and hypertension, diabetes mellitus and nephroptosis, UL and nephroptosis.

Earlier it was repeatedly shown that pregnancy can be considered as a factor contributing to the development of UTI. Analysis of the incidence of bacteriurias in pregnant women revealed their presence in 32,1% (Figure 1), 50,0% of examined were not pregnant, some of them (32,1%) were in menopause. In some of the patients as children and male patients, the possibility of pregnancy as a risk factor was absent in principle, their part was 17,9%.

Figure 1. The presence of pregnancy as a factor, evaluative the development of UTI
The previous hospitalization was observed in 17.86% of surveyed persons, and the period from discharge to the development of the UTI was more than 2 months, met the inclusion criteria.

The results showed that in the majority of cases of community-acquired UTI pathogens were Enterobacteriaceae (Figure 2).

![Figure 2](image_url)

**Figure 2.** The composition of agents of community-acquired UTIs in the studied group

In 89.3% of cases the pathogens of community-acquired UTI was Escherichia coli, which corresponds to data presented by other researchers. Significantly less it was revealed the other Enterobacteriaceae – *Proteus mirabilis* and *Klebsiella pneumoniae* (by 3.6%). In a few cases it was identified the coagulase-negative staphylococci as *Staphylococcus epidermidis*.

To characterize the resistance to antimicrobial drugs, we selected the data obtained by testing only Escherichia coli, which was due to two reasons. First, Escherichia coli were isolated in dominant majority (89.3%). Secondly, other isolated of family Enterobacteriaceae have natural resistance to certain antimicrobial, which makes it impossible to evaluate the sensitivity of bacteria to antibiotics of different kinds in combination.

The results of determination of susceptibility of Escherichia coli to β-lactam antibiotics are presented in Figure 3.

![Figure 3](image_url)

**Figure 3.** the susceptibility of *E.coli* urostrains (n=25) to β-lactam antibiotics

Less than a half (48.0%) of the strains were sensitive to ampicillin. A similar pattern of sensitivity to aminopenicillins is not unique for our region. Our data are consistent with those obtained in other studies. Thus, according to multicenter studies UTIAP I-III (1998-2006), carried out in Russia, the proportion of strains that are insensitive to ampicillin ranged from 33.1 to 37.1% . According to the results of the study ARESC (IX 2003 - VI 2006), conducted in Europe and Brazil, the proportion of strains susceptible to ampicillin also did not exceed an average of 42.0%.

In addition, the proportion of strains that are sensitive to inhibitor-protected aminopenicillins as amoxicillin/clavulanate and ampicillin/subactam, also was low and amounted to 60.0% and 52.0%, respectively.

At determining the sensitivity to cephalosporins attracted attention decreased sensitivity to third-generation cephalosporins: the proportion of strains susceptible to cefixime, cefotaxime and cefoperazone did not exceed 80.0-88.0%, which is a prerequisite for limiting their use as drugs of choice. So, 92.0% and 96.0% of strains were sensitive to ceftazidime and cefituben and 92.0% strains were susceptible to cephalosporin of IV generation – cefepime. All isolated strains were susceptible to carbapenems as imipenem, meropenem and ertapenem.

In 12.0% of cases the resistance to cephalosporin was due by extended spectrum β-lactamase (ESBL) production.
At the same time, the level of gene expression of ESBL production remained low, which is reflected in the sensitivity to the inhibitor-protected ureido-penicillins. While the comparing of the proportion of insensitive strains (I% + R%) to ampicillin and ampicillin/sulbactam revealed no significant differences (52,0% vs 40,0%, p=0,19), the adding tazobactam to piperacillin manifested by significant reduction of the proportion of non-susceptible strains (8% vs 52,0%, p=0,0014), and the proportion of strains with effectively inhibited growth reached 92%.

At determining of the sensitivity to aminoglycosides it was observed that all the isolates are susceptible to amikacin and only 80,0% of strains susceptible to gentamicin (Figure 4), which is clearly is the reflection of inappropriate policies of use of gentamicin in Central Kazakhstan for a long time.

**Figure 4.** Sensitivity to antibiotics of different groups of Escherichia coli urostrains (n = 25)

Recently, in some recommendations for therapy of UTI fluoroquinolones considered as drugs of choice. However, last years, some number of reports showed the increasing of the part of community-acquired Escherichia coli urostrains, which resistant to fluoroquinolones in Korea and Europe. Results of the study ARESC showed that in some countries there is an increase of the level of Escherichia coli resistance to fluoroquinolones, which allowed the authors to state that fluoroquinolones should not be recommended as first choice for the empirical treatment of uncomplicated infections of the lower urinary tract. Also, there are studies that show a steady increase of resistance to fluoroquinolones of uropathogenic Escherichia coli, isolated from patients with acute uncomplicated cystitis in some Russian cities, particularly in Smolensk in the period 1998-2008.

In our study, the proportion of strains that are sensitive to quinolones as nalidixic acid and fluoroquinolones as ciprofloxacin and levofloxacin, was 72,0%, which is consistent with the global trend and points to the inappropriateness of the use of these drugs for empirical treatment of community-acquired urinary tract infections.

There is a tendency in many countries to a significant increase of the stability of the microflora to trimethoprim-sulfamethoxazole. According to the results of multicenter studies SENTRY more than 45% of Escherichia coli urostrains were resistant to trimethoprim-sulfamethoxazole, ARESC – 29,4% , UTIAP I-III – 17,7% -21,0%. Our findings showed that 64,0% of strains were susceptible to trimethoprim-sulfamethoxazole, in 36,0% of cases there has been steady.

The recommendations of the Infectious Diseases American Society (IDSA) nitrofurantoin is regarded as the drug of choice for treatment of acute uncomplicated cystitis. According to the ARESC study the proportion of strains that are sensitive to nitrofurantoin was 95,2% . In UTIAP I-II studies the fraction of strains resistant to nitrofurantoin was 1,2-1,4%. The results of our study showed no significant differences in sensitivity to nitrofurantoin: urinary isolates of Escherichia coli strains at 92% were sensitive to this drug.

The high activity against Escherichia coli strains, pathogens of community-acquired urinary tract infection was
detected in fosfomycin, 100.0% of isolates were susceptible.

Conclusions

In most cases the predominant causative agent of community-acquired urinary tract infection are Escherichia coli (89.3%). Also it was showed the low proportion of strains sensitive to inhibitor-protected and non-protected aminopenicillins, fluorinated and non-fluorinated quinolones, and trimethoprim/sulfamethoxazole. Finally, in 12.0% of cases Escherichia coli, the pathogens of community-acquired urinary tract infections were ESBL producers.

ACKNOWLEDGMENTS

The authors are grateful to the research workers of SRI AC (Smolensk, Russia), in particular to Palagin I.S., Sukhorukova M.V. and Edelstein M. V. for their help at this work implementation.

References