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RESISTANCE of *E.coli* ISOLATED FROM CHILDREN WITH COMMUNITY-ACQUIRED URINARY TRACT INFECTIONS (CAUTIs) IN RUSSIA: Results of multicenter study "ARMID".

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ABSTRACT

Background: UTIs are one of the most frequent bacterial infections in children. *E.coli* is the primary pathogen causing CAUTIs. **Methods:** During the 2000-01 years 8 centers from European and Asian part of Russia took part in the study. The MICs of 16 antimicrobials were determined by agar dilution method according to the current NCCLS guidelines. **Results:** A total of 635 consecutive urine isolates from 607 children aged 1 month to 18 years with CAUTIs were collected. The most frequently isolated species from children with CAUTIs was *E.coli* (53.0%) followed by *Klebsiella* spp. (9.7%), *Proteus* spp. (8.5%), *Enterococcus* spp. (8.5%), *Enterobacter* spp. (5.7%) and *P.aeruginosa* (5.4%). Antimicrobial resistance rates of *E.coli* were as follows: ampicillin - 51.5%; co-amoxiclav - 3.9%; cefuroxime - 3.9%; ceftriaxone - 2.4%; ceftazidime - 0%; ceftibuten - 0%; cefepime - 0.9%; imipenem - 0%; gentamicin - 9.7%; netilmicin - 5.4%; amikacin - 0%; nalidixic acid - 7.0%; ciprofloxacin - 2.7%; fosfomycin - 0%; nitrofurantoin - 2.1% and co-trimoxazole - 35.5%. **Conclusions:** The main problem with uropathogens in Russia is a high level of *E.coli* resistance to aminopenicillins and co-trimoxazole. They can not be recommended as a drugs of choise for CAUTIs.

INTRODUCTION

UTIs are one of the most frequent infections in children. These infections are usually caused by Gram-negative bacteria most of which belong to the family *Enterobacteriaceae. E.coli* is a major bacterial pathogen causing CAUTIs. Therapy for these infections is usually begun before results of microbiological tests are known. In most cases, the choice of antibiotics for the treatment of UTIs is made empirically and should be based on the local antibiotic susceptibility data.

MATERIALS AND METHODS

Bacterial isolates. A total of 635 consecutive urine isolates from 607 children aged 1 month to 18 years with CAUTI were collected at 8 medical centers in 2000-2001 (Fig. 1).

Figure 1. Geographical location of centers, participating in the study "ARMID".

All isolates were initially identified in local laboratories using standard biochemical tests, then transferred to the central laboratory of the Institute of Antimicrobial Chemotherapy, where they were reidentified and stored in trypticase-soy/glycerol broth at -70°C until analysis. **Susceptibility testing.** MICs of ampicillin, co-amoxiclav, cefuroxime, ceftriaxone, ceftazidime, ceftibuten, cefepime, imipenem, gentamicin, netilmicin, amikacin, nalidixic acid, ciprofloxacin, fosfomycin, nitrofurantoin and co-trimoxazole were determined by agar dilution method and interpreted according to the current NCCLS guidelines. *E.coli* strains ATCC 25922 and ATCC 35218 were used for quality control of susceptibility testing. Data managent and statistical analysis were performed using the M-lab software (Institute of Antimicrobial Chemotherapy, Smolensk, Russia).

RESULTS AND DISCUSSION

Table 1. Susceptibility *E.coli* to antimicrobials

Antimicrobial	MIC breakpoints S	MIC breakpoints I	MIC breakpoints R	S, %	I, %	R, %	MIC50, mg/L	MIC90, mg/L	MIC ranges
Ampicillin	≤8	16	≤32	47.3	1.2	51.5	64	64	1-64
Co-amoxiclav	≤8	16	>32	79.4	16.7	3.9	8	16	0.25-64
Cefuroxime	≤4	8	>16	95.5	0.6	3.9	4	8	0.5-128
Ceftriaxone	≤8	16-32	64	96.7	0.9	2.4	0.06	0.06	0.06-128
Ceftazidime	≤8	16	>32	99.7	0.3	0	0.125	0.25	0.06-64
Ceftibuten	≤8	16	>32	100	0	0	0.125	0.25	0.03-64
Cefepime	≤8	16	>32	98.2	0.9	0.9	0.06	0.125	0.06-128
Imipenem	≤4	8	>16	99.5	0.5	0	0.5	0.5	0.5-8
Gentamicin	≤4	8	>16	90.3	0	9.7	1	4	0.5-32
Netilmicin	≤8	16	>32	91.6	3.0	5.4	1	4	0.5-64
Amikacin	≤8	32	>64	100	0	0	2	4	1-16
Nalidixic acid	≤16	-	32	93	0	7.0	2	4	0.5-32
Ciprofloxacin	≤1	2	>4	96.7	0.6	2.7	0.03	0.03	0.03-8
Fosfomycin	≤64	128	>256	99.7	0.3	0	0.25	2	0.5-128
Nitrofurantoin	≤32	64	>128	95.5	2.4	2.1	16	16	4-256
Co-trimoxazole	≤2	-	>4	64.5	0	35.5	0.25	16	0.06-16

Table 2. Resistance *E.coli* to antimicrobials in centers

Antimicrobial	Moscow-1 n=41	Moscow-2 n=44	St-Petersburg n=35	Smolensk n=73	Kazan n=45	Orenburg n=26	N. Novgorod n=29	Irkutsk n=37
Ampicillin	56.1	43.2	50	57.2	48.9	50	31	67.6
Co-amoxiclav	2.4	0	8.6	5.5	4.4	0	0	8.1
Cefuroxime	0	0	8.6	5.5	13.3	0	0	0
Ceftriaxone	0	0	2.9	2.7	11.1	0	0	0
Ceftazidime	0	0	0	0	0	0	0	0
Ceftibuten	0	0	0	0	0	0	0	0
Cefepime	0	0	2.9	1.4	2.2	0	0	0
Imipenem	0	0	0	0	0	0	0	0
Gentamicin	4.9	4.5	8.6	11	17.8	3.8	0	13.5
Netilmicin	2,4	2.3	5.7	2.7	2.2	3.8	0	2.7
Amikacin	0	0	0	0	0	0	0	0
Nalidixic acid	4.9	13.6	2.9	6.8	8.9	0	17.2	0
Ciprofloxacin	0	0	0	2.7	4.4	0	13.8	0
Fosfomycin	0	0	0	0	0	0	0	0
Nitrofurantoin	4.9	6.8	0	1,4	2,2	0	0	0
Co-trimoxazole	41.5	25	34.3	39.7	35.6	38.5	17.2	45,9

The most frequently isolated species from children with CAUTIs was *E.coli* (53.0%), followed by *Klebsiella* spp. (9.7%), *Proteus* spp. (8.5%), *Enterococcus* spp. (8.5%), *Enterobacter* spp. (5.7%) and *P.aeruginosa* (5.4%). (Fig. 2).

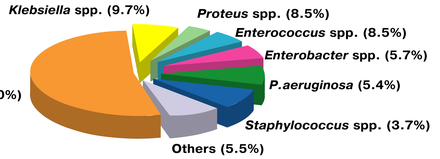

Figure 2. Distribution of microorganisms.

Results of the in vitro susceptibility testing of *E.coli* isolates are summarized in Table 1.

Beta-lactams. This study revealed an extremely high level of resistance to ampicillin (51.5%). The activity of co-amoxiclav varied from 91.4 to 100% in different centers (average: 96.1%).

Imipenem and newer cephalosporins were highly active. However, the appearence of several isolates resistant to third and fourth generation cephalosporins, especially to ceftriaxone, is alarming.

Aminoglycosides. Amikacin was the most active aminoglycoside tested. No isolates resistant to this compound were detected. Resistance rates to gentamicin and netilmicin were 9.7% and 5.4%, respectively.

Quinolones. Seven percent of *E.coli* were resistant to nalidixic acid, whereas only 2.7% - to ciprofloxacin.

Antibiotics of other groups. Resistance to co-trimoxazole was observed for 35.5% of isolates. There were no strains resistant to fosfomycin and only 2.1% - were resistant to nitrofurantoin.

As shown in Table 2 resistance rates of different antimicrobial agents were generally similar in geographically distant centers. Nevertheless, an exceptional situation was observed in N.Novgorod where all the *E.coli* strains were susceptible to co-amoxiclav, cephalosporins, imipenem, aminoglycosides, fosfomycin and nitrofurantoin, but more frequently resistant to nalidixic acid and ciprofloxacin.

Isolates resistant to extended-spectrum cephalosporins were found only in Kazan, Smolensk and St.-Petersburg.

Table 3 . Frequency of isolates with multiple resistance

No. of resistance markers	Resistance phenotype	No. (%) of isolates
2	Am-Tsx	70 (21.2)
	Am-Q	3 (0.9)
	Am-Amc	2 (0.6)
	Am-Ag	1 (0.3)
	Am-Nf	1 (0.3)
3	Am-Ag-Tsx	11 (3.3)
	Am-Q-Tsx	6 (1.8)
	Am-Amc-Tsx	4 (1.2)
	Am-Amc-Cs	2 (0.6)
	Am-Amc-Ag	1 (0.3)
	Am-Ag-Q	1 (0.3)
4	Am-Cs-Ag-Tsx	6 (1.8)
	Am-Ag-Q-Tsx	3 (0.9)
	Am-Cs-Ag-Q	1 (0.3)
	Am-Cs-Q-Tsx	1 (0.3)
	Am-Q-Tsx-Nf	1 (0.3)
5	Am-Amc-Cs-Ag-Tsx	3 (0.9)
	Am-Ag-Q-Tsx-Nf	2 (0.6)
	Am-Amc-Cs-Tsx-Nf	1 (0.3)
	Am-Amc-Cs-Q-Tsx	1 (0.3)

Resistance markers: Am - ampicillin, Amc - co-amoxiclav, Cs - cephalosporins (cefuroxime or ceftriaxone or ceftazidime or ceftibuten or cefepime); Ag - aminoglycosides (gentamicin or netilmicin or amikacin); Q - quinolones (nalidixic acid or ciprofloxacin); Tsx - co-trimoxazole; Nf - nitrofurantoin

Analysis of multiple resistance. Table 3 shows the frequencies of co-resistance to antimicrobials of different classes in *E.coli* isolates. The most frequently observed pattern was co-resistance to amoxicillin and co-trimoxazole (found in 21.2% of isolates). It was accompanied by co-resistance to either one of the aminoglycosides or quinolones in 3.3% or 1.8% of the cases, respectively. Simultaneous resistance to amoxicillin, co-trimoxazole, aminoglycosides and at least one of the cephalosporins was found in 1.8% of the isolates. Other combinations of resistance markers were less frequent, however single isolates non-susceptible to 4 or even 5 different antibiotics were seen.

CONCLUSIONS

1. *E.coli* is the primary bacterial pathogen causing CAUTIs in children.
2. Resistance of outpatients urinary *E.coli* isolates to aminopenicilins and co-trimoxazole is common in Russia.
3. The most active antimicrobials were co-amoxiclav, III-IV generation cephalosporins, carbapenems, ciprofloxacin, amikacin, fosfomycin and nitrofurantoin.
4. Multiple resistance becomes increasingly common among *E.coli* strains causing CAUTIs in children in Russia.