PROFILE AND PHENOTYPES OF RESISTANCE OF MICROORGANISMS FROM PREGNANT WOMEN WITH ASYMPTOMATIC BACTERIURIA IN RUSSIA

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POSTER Nr. 724

REVISED ABSTRACT

Objective: Asymptomatic bacteriuria (ASB) is common during pregnancy. Its adequate empirical antimicrobial treatment is possible only if resistance of the UTI pathogens in region is well established.

Methods: During the 2002-2003 prospective epidemiological study involved 132 pregnant women aged 16 to 43 years with ASB ($\geq 10^5$ CFU/ml) at 6 Russian community health-care centers in Moscow, Smolensk, Volgograd and St-Petersburg. After re-identification, MICs for 8 of antimicrobials (ampicillin - AMP, amoxicillin/clavulanate - AMC, cefuroxime -CFR, cefotaxime - CFT, gentamicin - GNT, co-trimoxazole - CTZ, nitrofurantoin - NTF, fosfomycin - FSF) were determined by agar dilution method and interpreted using NCCLS/CLSI 2003 guidelines. Quality control was performed using reference strains including *E. coli* ATCC 25922, *E. coli* ATCC 35218 and *P. aeruginosa* ATCC 27853.

Results: A total of 129 urine isolates from women with ASB were collected. *E.coli* was the predominant pathogen (84/65.1%), followed by *Klebsiella* spp. (12/9.3%), *Enterobacter* spp. (11/8.5%), *P.mirabilis* (8/6.2%), *Staphylococcus* spp. (4/3.1%) and *Enterococcus* spp. (3/2.3%). Antimicrobial resistance rates of *E.coli* were as follows: AMP - 29.8%; CTZ - 12.0%; GNT - 6.0%; CFR - 4.8%; AMC - 3.6%; NTF - 3.6%; CFT - 2.4% and FSF - 0%. The most active antimicrobials (sensitivity 91-100%) against *Klebsiella* spp. and *P.mirabilis* were AMC, CFR, CFT, GNT and FSF; against *Enterobacter* spp. - CFT, GNT and FSF.

Conclusions: The main problem with uropathogens in Russia is a high level of *E.coli* resistance to aminopenicillins and CTZ. These antimicrobials should no longer be used as drugs of choice in the treatment of ASB. The most active antimicrobials against non-*E.coli Enterobacteriaceae* isolates were CFT, GNT and FSF.

INTRODUCTION

Women with ASB in early pregnancy have a 20-30-fold increased risk of developing pyelonephritis during pregnancy, compared with women without bacteriuria. Also these women are more likely to experience premature delivery and to have infants of low birth weight. Prospective, comparative clinical trials have consistently reported that antimicrobial treatment of ASB during pregnancy decreases the risk of subsequent pyelonephritis from 20-35% to 1-4% (Smaill F., Cochrane Database Syst Rev, 2001). Therefore, due to the possibility of serious complication for both the mother and the foetus antimicrobials should be given to pregnant women with ASB.

ASB is usually caused by Gram-negative bacteria most of which belong to the family *Enterobacteriaceae. E.coli* is a major bacterial pathogen causing ASB. In most cases the choice of antibiotics for the treatment of ASB is made empirically and should be based on the local antibiotic susceptibility data.

MATERIALS AND METHODS

Study population. One hundred and thirty two pregnant women with ASB were enrolled in multicenter prospective epidemiological study (Fig. 1).

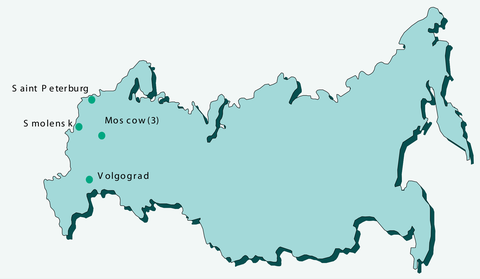

Figure 1. Geographical location of centers participating in the study

Bacterial strains. A total of 129 consecutive urine isolates from the patients with ASB were included in the microbiological analysis. All isolates were initially identified in local laboratories using standard biochemical tests and then transferred to the central laboratory of the Institute of Antimicrobial Chemotherapy (Smolensk, Russia), where they were re-identified and stored in trypticase-soy/glycerol broth at -70^{0}C until further analysis.

Susceptibility testing. The MICs of 8 antibiotics were determined by the agar dilution method and interpreted according to the current NCCLS/ CLSI guidelines. Quality control was performed using reference strains including *E.coli* ATCC 25922, *E.coli* ATCC 35218 and *P.aeruginosa* ATCC 27853.

Data management and statistical analysis were performed using the M-Lab software (Institute of Antimicrobial Chemotherapy, Smolensk, Russia).

RESULTS AND DISCUSSION

E.coli was the most frequently isolated microorganism from pregnant women with ASB (84/65.1%), followed by *Klebsiella* spp. (12/9.3%), *Enterobacter* spp. (11/8.5%), *P.mirabilis* (8/6.2%), *Staphylococcus* spp. (4/3.1%) and *Enterococcus* spp. (3/2.3%) (Fig. 2).

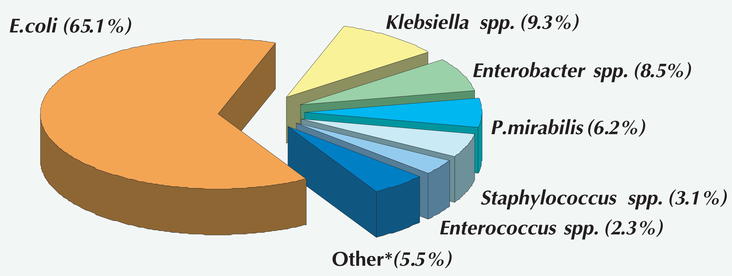

Figure 2. Distribution of microorganisms

Results of the in vitro susceptibility testing of *E.coli* and other *Enterobacteriaceae* are summarized in Table 1.

The study revealed a high level of *E.coli* resistance to APM (29.8%) and CTZ (12.0%).

Table 1. Susceptibility of *Enterobacteriaceae* to antimicrobials and MICs distribution.

Antibiotic	Germ name	S*, %	I*, %	R*, %	MIC_{50}, mg/l	MIC_{90}, mg/l	MICs distribution, mg/l: 0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256
AMP	*E.coli*	70.2	0	29.8	4	256						5	25	25	4				1	24
	Klebsiella spp.	0	33.3	66.7	32	64										4	4	4		
	P.mirabilis	6	0	2	2	256						2	4							2
	Enterobacter spp.	0	27.3	72.7	32	256										3	4	2		2
AMC	*E.coli*	82.1	14.3	3.6	4	16							16	30	23	12	3			
	Klebsiella spp.	100.0	0	0	2	4						1	6	5						
	P.mirabilis	8	0	0	1	8						4	1	2	1					
	Enterobacter spp.	0	18.2	81.8	128	128										2	1	2	5	1
CFR	*E.coli*	95.2	0	4.8	4	8						1	20	48	11		1			3
	Klebsiella spp.	100.0	0	0	2	8						2	4	4	2					
	P.mirabilis	8	0	0	1	4						1	6	1						
	Enterobacter spp.	54.5	27.3	18.2	8	32								1	5	3	1	1		
CFT	*E.coli*	97.6	0	2.4	0.06	0.125	14	60	8										1	1
	Klebsiella spp.	100.0	0	0	0.06	0.125	3	7	2											
	P.mirabilis	8	0	0	0.06	0.06		8												
	Enterobacter spp.	100.0	0	0	0.25	0.5			4	4	3									
GNT	*E.coli*	94.0	0	6.0	1	2				2	10	61	4	2				3	2	
	Klebsiella spp.	100.0	0	0	1	1				1	3	8								
	P.mirabilis	8	0	0	1	2				1		6	1							
	Enterobacter spp.	100.0	0	0	1	1					1	10								
CTZ	*E.coli*	88.0	-	12.0	0.125	64		42	14	11	4	3						10		
	Klebsiella spp.	91.7	-	8.3	0.25	2			3	6			2		1					
	P.mirabilis	6	-	2	0.25	64		3		3				1				1		
	Enterobacter spp.	81.8	-	18.2	0.125	4		5	4					1				1		
NTF	*E.coli*	94.0	3.6	2.4	16	32									1	61	17	3	1	1
	Klebsiella spp.	41.7	8.3	50.0	64	256										2	3	1	4	2
	P.mirabilis	1	7	0	64	64								1				7		
	Enterobacter spp.	0	63.6	36.4	64	256												7		4
FSF	*E.coli*	100.0	0	0	0.5	2					60	11	9	1	1	2				
	Klebsiella spp.	100.0	0	0	16	32								2	2	5	2	1		
	P.mirabilis	8	0	0	8	64					1		1	1	4			1		
	Enterobacter spp.	90.9	0	9.1	16	32							1		3	4	1	1		1

* - S, I and R for *P.mirabilis* have been rounded.

The most potent antimicrobials tested against all frequently isolated *Enterobacteriaceae* were CFT, GNT and FSF. Resistance rates to these compounds ranged from 0% to 2.4%, from 0% to 6.0% and from 0% to 9.1% respectively. No *E.coli* were resistant to FSF.

CFR and AMC were the most active compounds against *E.coli, Klebsiella* spp. and *P.mirabilis* with resistance rates ranging from 0% for *Klebsiella* spp. and *P.mirabilis* to 4.8/3.6% for *E.coli* respectively. With exception of *E.coli* (94.0% of the isolates were susceptible), NTF had low susceptibility rates for non-*E.coli Enterobacteriaceae* tested.

Analysis of multiple resistance in *E.coli* isolates displayed the most frequently observed patterns were co-resistance to AMP and CTZ as well as co-resistance to AMP and GNT (found in 6/7.1% and 4/4.8% of isolates respectively). Other combinations of resistance markers were less frequent; however two isolates were non-susceptible to four antimicrobials of different classes. All these multiple resistance strains were susceptible to FSF.

CONCLUSIONS

- *E.coli* is increasingly resistant to commonly prescribed antimicrobials in Russia, especially to ampicillin and co-trimoxazole.
- The most active antimicrobials tested against *E.coli* were fosfomycin, cefuroxime, cefotaxime, amoxicillin/clavulanate, gentamicin and nitrofurantoin.
- The most potent compounds against non-*E.coli Enterobacteriaceae* were cefotaxime, gentamicin and fosfomycin.
- Multiple resistance occurs sometimes among *E.coli* strains causing ASB in pregnant women in Russia.