A NTIMICROBIAL RESISTANCE OF NOSOCOMIAL GRAM-NEGATIVE BACTERIA IN RUSSIAN INTENSIVE CARE UNITS (ICUS) **Poster # 1539**

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Background: resistance to antimicrobials in gram-negative nosocomial pathogens presents an obstacle for efficient therapy being of especial concern in ICUs patients. The objective of the study was to evaluate antimicrobial resistance of nosocomial gram-negatives in Russian ICUs.

Methods: Antimicrobial susceptibility testing of nosocomial gram-negative organisms isolated from Russian ICU patients with nosocomial infections was performed by agar dilution method (NCCLS, 2004).

Results: A total of 3042 non-duplicate gram-negative isolates were isolated from patients in 33 Russian ICUs during 2002-2004. Dominant pathogens were: *P. aeruginosa* (35%), *A. baumannii* (15%), *K. pneumoniae* (14%), *E. coli* (13%), *Enterobacter* spp. (5%), *Proteus* spp. (5%). Resistance rates (intermediate + resistant strains, %) for key pathogens were as follows:

Antimicrobials	P. aeruginosa	A. baumannii	K. pneumoniae	E. coli
Amikacin	42	66	31	20
Amoxicillin/ clavulanic acid	-	-	74	57
Cefepime	59	64	61	35
Cefoperazone	73	98	78	51
Cefoperazone/ sulbactam	61	2	30	15
Cefotaxime	-	_	76	46
Ceftazidime	48	76	57	33
Ciprofloxacin	65	74	38	52
Ertapenem	-	_	3	1
Gentamicin	75	89	75	54
Imipenem	39	2	0	0
Levofloxacin	66	62	27	51
Meropenem	41	3	0	0
Piperacillin/ tazobactam	42	75	42	16
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Based on phenotypic ESBL detection tests 81% *K. pneumoniae* and 50% *E. coli* strains were found to be ESBL-producers. **Conclusions:** *P. aeruginosa* displayed high level resistance to all agents tested except polymyxin B. Carbapenems and cefoperazone/sulbactam showed excellent activity against *A. baumannii*. ESBL-production is widespread among *K. pneumoniae* and *E. coli* with carbapenems possessing the highest activity against these pathogens.

INTRODUCTION

National surveillance studies are essential tools for combating antimicrobial resistance in nosocomial pathogens. Data obtained in such studies shed the light on to the current resistance state and serve as a barometer for emerging problems [1].

Despite there is a shift in the spectrum of nosocomial pathogens towards gram-positive bacteria, gram-negative pathogens still are responsible for a large number of nosocomial infection in Intensive Care Units (ICUs). Thus in our study we have concentrated on the prevalence and resistance patterns of nosocomial gram-negative bacteria in ICUs throughout Russia, as well as on the dynamic of these parameters.

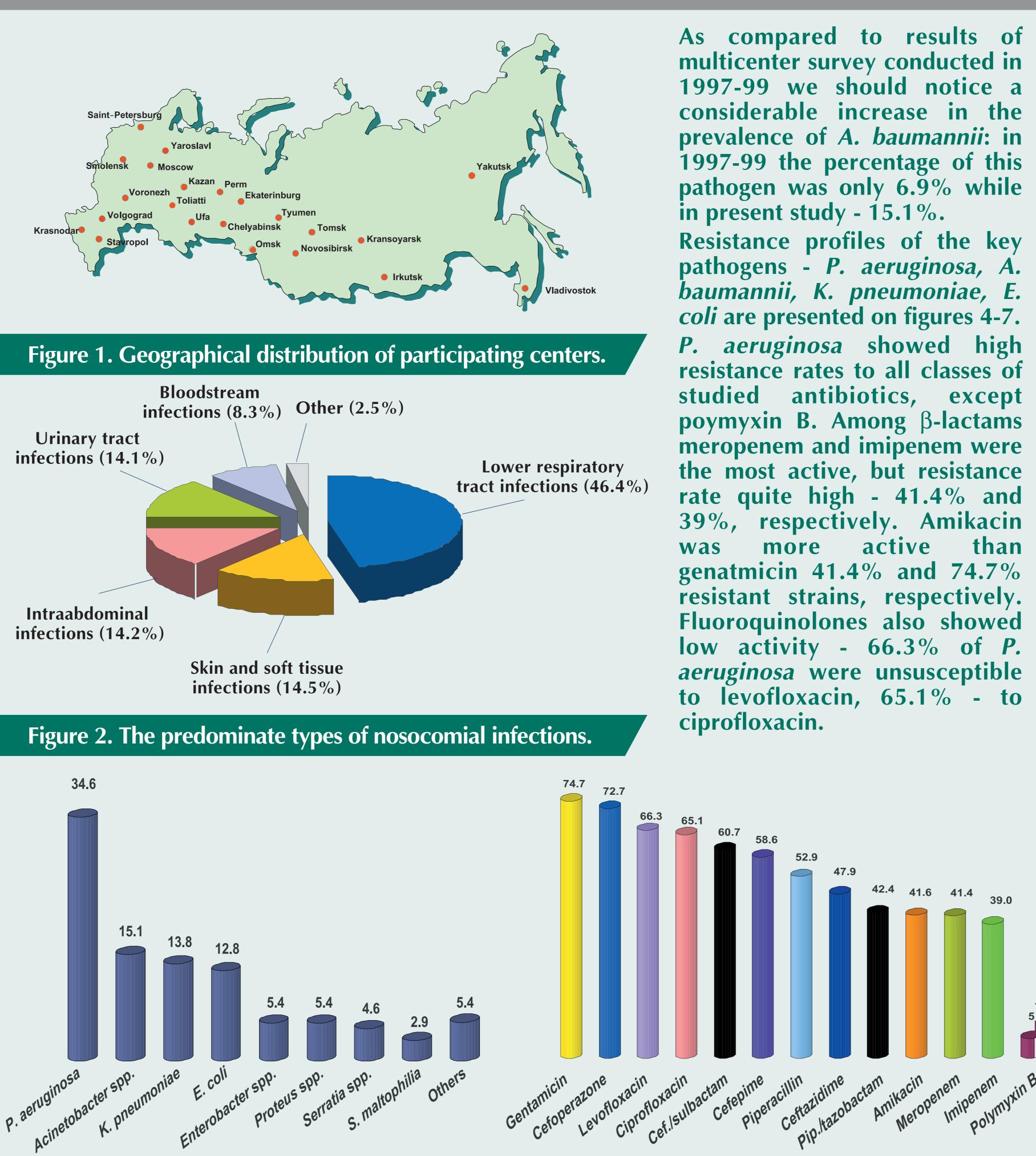
METHODS

Prospective multicenter microbiology study participating centers was conducted during 2002-2004. Participating centers collected consecutive gram-negative bacteria from ICU patients with documented nosocomial infections. Duplicate isolates were excluded from the study. Strains were transferred to central laboratory in Smolensk. Before antimicrobial susceptibility testing strains were stored at -70°C. In central laboratory minimal inhibitory concentrations (MICs) of amikacin, amoxicillin/clavulanic acid, ampicillin, cefepime, cefoperazone, cefoperazone/sulbactam, cefotaxime, cefotaxime, cefotaxime/clavulanic acid, ceftazidime, ceftazidime/clavulanic acid, ceftriaxone, ciprofloxacin, ertapenem, gentamicin, imipenem, levofloxacin, meropenem, moxifloxacin, piperacillin, piperacillin/tazobactam, polymyxin (for *P. aeruginosa*) were determined by agar dilution in accordance with NCCLS guidelines, 2004. Cefoperazone breakpoints were used to interpret results of cefoperazone/sulbactam testing; for polymyxin susceptibility testing results SFM, 2003 guideline was applied. Intermediate strains were included into the resistant category. E. coli ATCC 25922, E. coli ATCC 35218 and P. aeruginosa ATCC 27853 were used as quality control strains. Data management and statistical analysis were performed with Mlab software (Institute of Antimicrobial Chemotherapy, Smolensk, Russia).

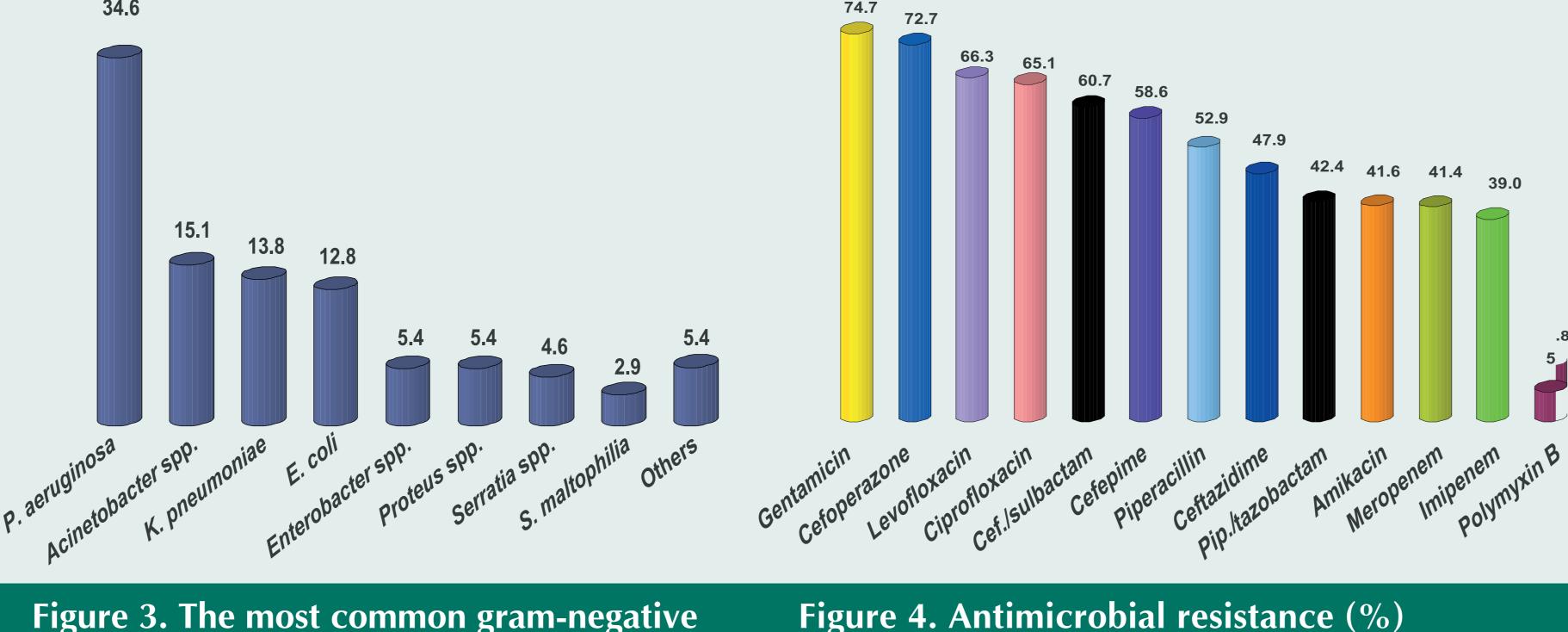
RESULTS AND DISCUSSION

A total of 33 hospitals from 22 cities took part in the study. Centers-participants are shown on the picture 1. Among them 5 hospitals were pediatric. A total of 2296 patients with nosocomial infections were examined.

The majority of strains (46.4%) were collected from patients with nosocomial lower respiratory tract infections. The distribution of infection types studied is presented on figure 2. A total of 3042 gram-negative pathogens were isolated. The most common pathogens were Pseudomonas aeruginosa (34.6%), Acinetobacter baumannii (15.1%), Klebsiella pneumoniae (13.8%), Escherichia coli (12.8%), Proteus spp. (5.4%), Enterobacter spp. (5.4%), Serratia marcescens (4.6%), Stenotrophomonas maltophilia (2.9%) (fig. 3). Klebsiella oxytoca, Citrobacter freundii, Morganella morganii, Burkholderia cepacia, Chryseobacterium *meningosepticum* were among rarely isolated pathogens.



multicenter survey conducted in 1997-99 we should notice a considerable increase in the prevalence of A. baumannii: in **1997-99** the percentage of this pathogen was only 6.9% while in present study - 15.1%. Resistance profiles of the key pathogens - P. aeruginosa, baumannii, K. pneumoniae, E. *coli* are presented on figures 4-7. P. aeruginosa showed high resistance rates to all classes of studied antibiotics, except poymyxin B. Among β -lactams meropenem and imipenem were the most active, but resistance rate quite high - 41.4% and 39%, respectively. Amikacin was more active than genatmicin 41.4% and 74.7% resistant strains, respectively. Fluoroquinolones also showed low activity - 66.3% of P. aeruginosa were unsusceptible



pathogens of nosocomial infections in Russian ICUs, 2002-04 (n=3042), %. of nosocomial *P. aeruginosa* isolated in Russian ICUs, 2002-04 (n=1053).

Cefoperazone/sulbactam, imipenem, meropenem exhibited the highest activity among both ?lactams and all antibiotics. Resistance rates were 3.5%, 2.2% and 2.2% for meropenem, imipenem and cefoperazone/sulbactam, respectively. Levofloxacin showed higher activity than ciprofloxacin: 62.3% and 73.9% unsusceptible strains, respectively; MIC₅₀ and MIC₉₀ -8 and 16 mg/l and 64 and 128 mg/l, respectively. Resistance to amikacin was lower as compared to gentamicin: 65.6% vs 89.1% unsusceptible strains, respectively.

Our results show that carbapenems retain their high activity against nosocomial K. *pneumoniae*: all strains were susceptible to imipenem and meropenem. Data about ertapenem activity are of special interest as far as the agent was studied at first time against such substantial number of *K. pneumoniae* from different geographical sites of Russia. Only 2.6% K. pneumoniae were resistant to ertapenem. The rest antibiotics showed lower activity against K. pneumoniae. Gentamicin resistant rate was high - 75.2%, amikacin also showed low activity - 31.4% of resistant strains. About 38% K. pneumoniae were unsusceptible to ciprofloxacin, while moxifloxacin and levofloxacin were more active - 26.7 and 28.3% unsusceptible strains, respectively. Quite low activity (>50% unsusceptible strains) of III-IV generation cephalosporins is likely due to high prevalence of ESBL-producers among nosocomial *K. pneumoniae*.

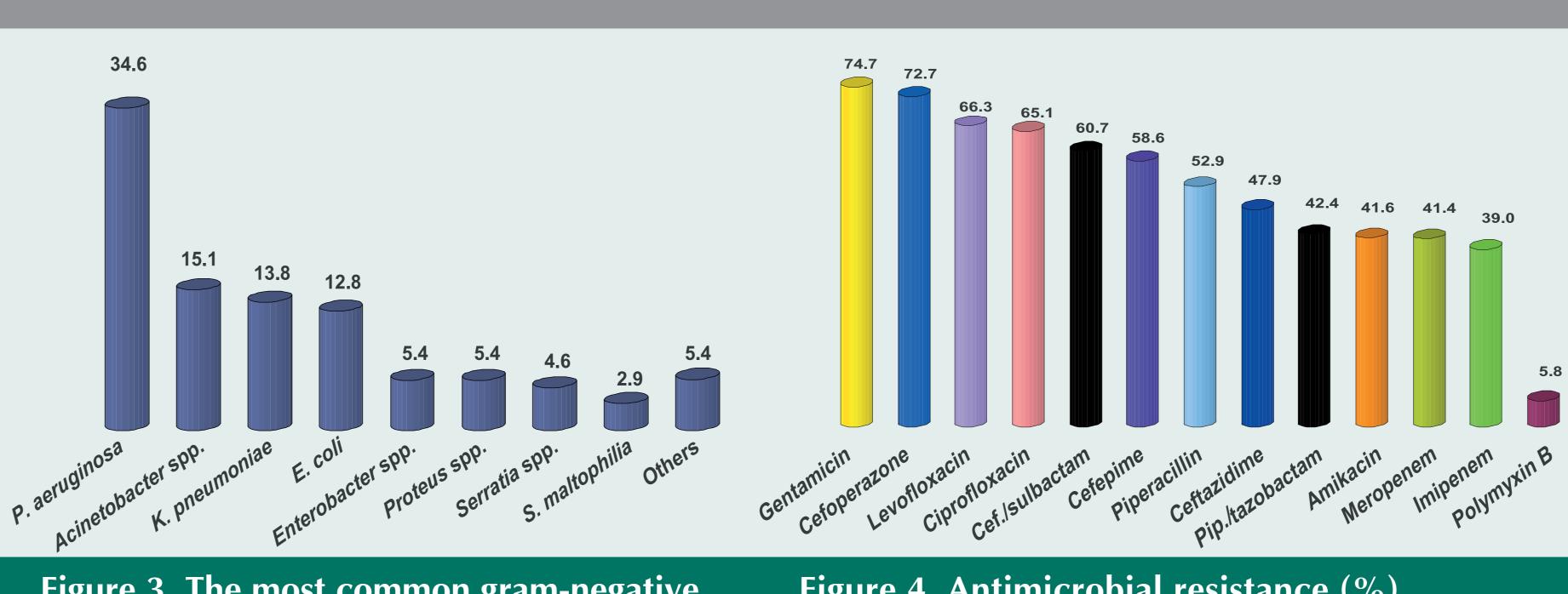


Figure 3. The most common gram-negative pathogens of nosocomial infections in Russian ICUs, 2002-04 (n=3042), %.

Figure 4. Antimicrobial resistance (%) of nosocomial *P. aeruginosa* isolated in Russian ICUs, 2002-04 (n=1053).

Studied *E. coli* showed low susceptibility to piperacillin, amoxicillin/clavulanate - more than 55% strains were unsusceptible. Flouroquinolones showed low activity as well - 51-51.5% strains were unsusceptible to ciprofloxacin, levofloxacin, moxifloxacin. Among cephalosporins the highest activity was seen for ceftazidime - 33.2% of unsusceptible strains. Cefoperazone/sulbactam and piperacillin/tazobactam demonstrated high activity -15.5% and 15.7% unsusceptible strains, respectively.

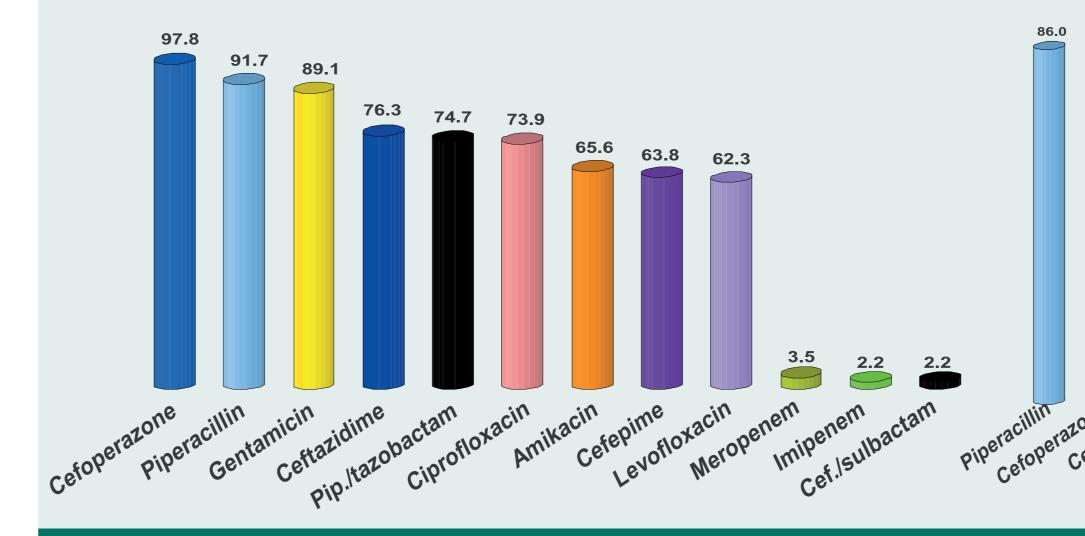


Figure 5. Antimicrobial resistance (%) of nosocomial Acinetobacter spp. isolated in Russian ICUs, 2002-04 (n=459).

Figure 6. Antimicrobial resistance (%) of nosocomial K. pneumoniae isolated in Russian ICUs, 2002-04 (n=420).

Carbapenems were the most active antibiotics tested: 0.5% isolates were unsusceptible to ertapenem, imipenem and meropenem were active against all strains. According to phenotypic methods 81.4% and 49.7% strains of K. pneumoniae and E coli, respectively were found to be ESBL-producers (fig. 8).

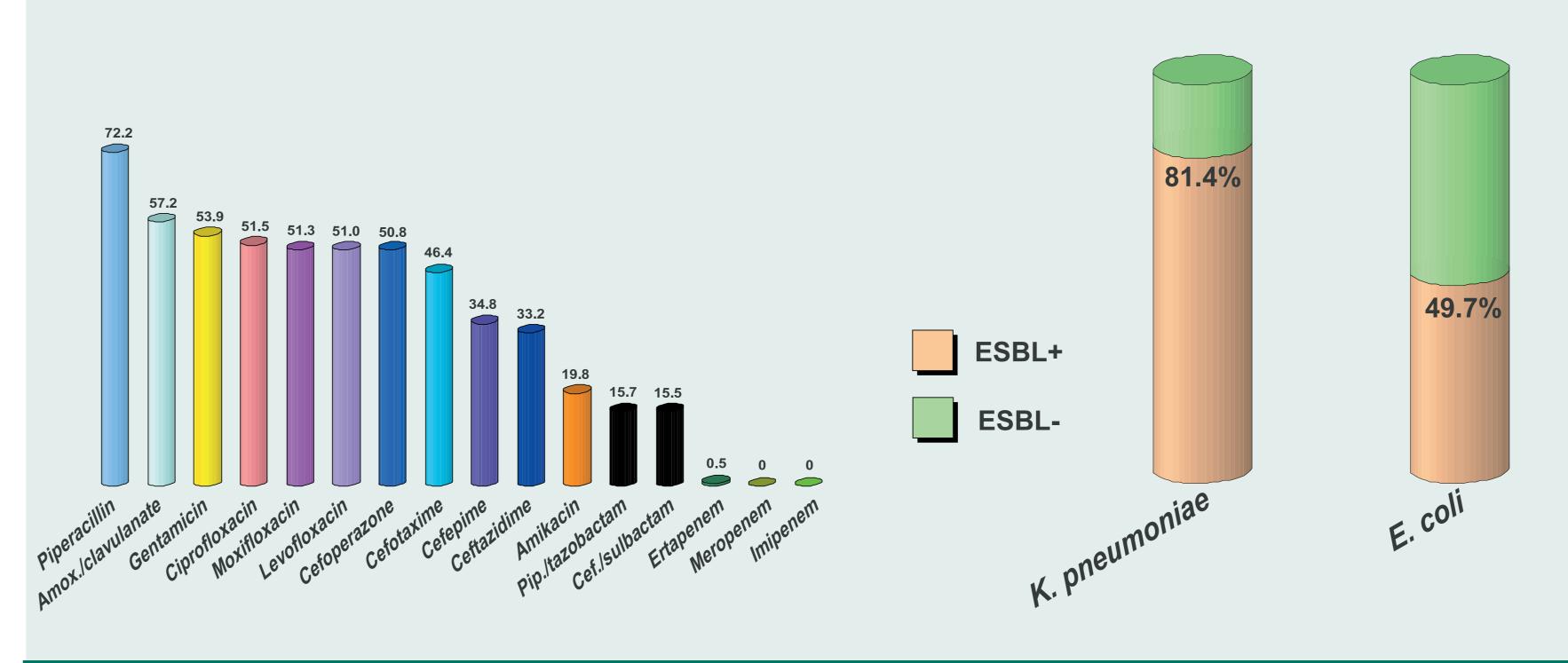


Figure 7. Antimicrobial resistance (%) of nosocomial *E. coli* isolated in Russian ICUs, 2002-04 (n=388).

Figure 8. Prevalence of ESBL-producers (%) among nosocomial *K. pneumoniae* and E. coli in Russian ICUs, 2002-04.

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In the light of growing threat of increasing of antimicrobial resistance of nosocomial pathogens we would like to make an insight in the temporal tendencies in Russian ICUs. We compare our data with previous results of multicenter study conducted in Russia 1997-99 [2, 3] Resistance dynamics of *P. aeruginosa* and *A. baumannii* are presented on figures 9-10. High increase of resistance to antipseudomonal cephalosporins was seen along with increase of resistance rates to ciprofloxacin, amikacin. But the most dramatical increase (from 3 up to 41%) was seen in resistance rate to meropenem.

As for A. baumannii data to less antimicrobial were available from the previous study. More than two-fold increase of resistance to ciprofloxacin was observed. Resistance to amikacin increased more than sevenfold. The emergence of carbapenems resistance was observed, but 2.2% of imipenem resistance strains look quite consoling in contrast to high imipenem resistance of *P. aeruginosa*.

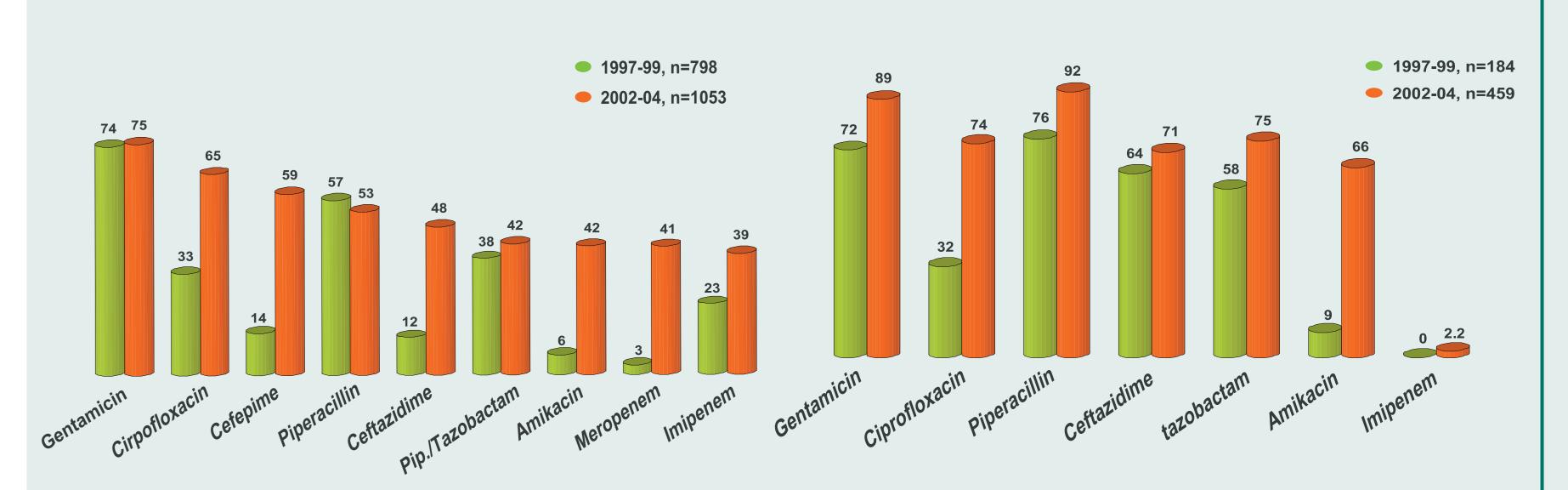


Figure 9. Resistance dynamic in nosocomial P. aeruginosa, 2002-04 vs 1997-99 (%).

Figure 10. Resistance dynamic in nosocomial A. baumannii, 2002-04 vs 1997-99 (%).

CONCLUSIONS

1. P. aeruginosa (34.6%), A. baumannii (15.1%), K. pneumoniae (13.8%), E. coli (12.8%), were the most common gram-negative nosocomial pathogens in Russian ICUs.

2. Considerable increase in A. baumannii prevalence among nosocomial gram-negative bacteria was found (from 6.9% in 1997-99 to 15.1% in present study)

3. P. aeruginosa (%), A. baumannii (%), K. pneumoniae (%), E. coli (%) showed different antibiotic resistance profiles:

- *P. aeruginosa* expressed high resistance rates (>30% unsusceptible strains) to all antibiotics studied with the exception of polymyxin B (only 5.8% unsusceptible strains); - cefoperazone/sulbactam, imipenem, meropenem were the most active against A. baumannii

- carbapenems (imipenem, meropenem, ertapenem) were the most active against K. pneumoniae

- imipenem, meropenem, ertapenem, cefoperazone/sulbactam, piperacillin/tazobactam, amikacin retained high activity against *E. coli*.

4. High levels of ESBL production were found in *K. pneumoniae* and *E. coli* (81.4% and 49.7%, respectively).

5. Dramatical increase of resistance rates on example of key pathogens *P. aerginosa* and A. baumannii underlines the need for continuous efforts in the field of antibiotic policy and resistance monitoring in Russian ICUs.

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