THE CHARACTERISTICS OF AMINOGLYCOSIDES RESISTANCE IN NOSOCOMIAL GRAM-NEGATIVE STRAINS IN RUSSIA

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Objectives: To determine phenotypes and mechanisms of resistance to aminoglycosides in nosocomial gram-negative strains in ICUs in Russia.

Methods: A total of 648 nosocomial gram-negative aminoglycoside-resistant strains isolated in ICUs of 14 Russian hospitals were examined. The samples were sputum, wound samples, abdominal drains, urine and blood. The mechanisms of aminoglycoside resistance were determined by Aminoglycoside Resistant Pattern (AGRP) method. The following aminoglycosides were used: kanamycin, neomycin, gentamicin, tobramycin, netilmicin, isepamicin, amikacin, 5-epi-sisomicin, 2′-N-ethyl-netilmicin, 6′-N-ethyl-netilmicin, fortimicin, apramycin, lividomycin and butirosin.

Results: The predominant phenotypes of aminoglycosides resistance were: gentamicin-tobramycin-netilmicin (44,9%), gentamicin-tobramycin (22,2%), gentamicin-tobramycin-netilmicin-amikacin (13,8%). The gentamicin-tobramycin-amikacin-isepamicin phenotype was determined only in 4,2% of examined strains and gentamicin-tobramycin-netilmicin-amikacin-isepamicin phenotype was found in 4% of strains.

The most frequent mechanism of resistance was the production of aminoglycoside modifying enzymes. The prevalent enzymes were AAC(3)-V – 46,9%, ANT(2″) – 27,9%, APH(3′)-VI – 11,9%, AAC(6′)-I – 11,4%. The rare enzymes were AAC(3)-I – 2,5%, AAC(3)-IV – 1,2%, AAC(2′)-I – 1,1%, AAC(3)-III – 0,6%. The majority of tested strains produced 2-4 enzymes simultaneously (83,5%), including the APH(3′)-I enzyme, causing resistance to kanamycin and neomycin.

Conclusions: the leading mechanism of aminoglycoside resistance in Russian gram-negative nosocomial strains was the production of aminoglycoside modifying enzymes. According to the obtained data determination of aminoglycoside resistance mechanisms in given hospital is essential for the rational choice of aminoglycoside for empirical therapy of nosocomial infections.

Introduction and Purpose

Aminoglycosides are considered as those of the drugs of choice for empirical therapy of gram-negative nosocomial infections. Rates of cross-resistance to aminoglycosides are very high. It results from production of enzymes modifying several drugs of this class of antimicrobials simultaneously. Rational choice of antimicrobial therapy should be based on aminoglycoside resistance patterns in a given hospital. Aim of this study was to determine phenotypes and mechanisms of resistance to aminoglycosides in nosocomial gram-negative bacilli in ICUs of different Russian regions.

Methods

Gram-negative strains were collected from ICUs patients with nosocomial infections in 14 Russian hospitals during 1997-1999. The infections were pneumonia, skin and soft tissue infections, peritonitis, urinary tract infections. The samples for culture were sputum, wound samples, abdominal drains, urine and blood. A total of 648 nosocomial gram-negative gentamicin-resistant strains were isolated and tested. The mechanisms of aminoglycosides resistance were determined by Aminoglycoside Resistant Pattern (AGRP) method - the examination of phenotypes of resistance to 12 aminoglycosides: kanamycin, neomycin, gentamicin, tobramycin, netilmicin, isepamicin, amikacin, 5-epi-sisomicin, 2′-N-ethyl-netilmicin, 6′-N-ethyl-netilmicin, fortimicin and apramicin. Susceptibility testing to the listed antimicrobials was performed by disk diffusion method on Mueller-Hinton II agar. Additionally, susceptibility to lividomycin and butirosin was performed using agar dilution method.

Results

The predominant aminoglycoside-resistance mechanism was the production of aminoglycoside-modifying enzymes.

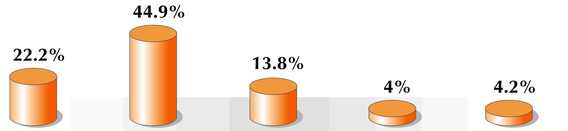
The predominant phenotypes of resistance to aminoglycosides were gentamicin-tobramicin-netilmicin (44,9%), caused by production of one of the modifying enzymes AAC(3)-V (94,8%), AAC(3)-IV (2,7%), AAC(2′)-I (2,4%). Simultaneous resistance to gentamicin and tobramycin was the second (22,2%) common phenotype of aminoglycoside resistance associated with ANT(2″). Cross-resistance to second- and third-generation aminoglycosides was infrequent in Russian isolates. The 13,8% of tested strains were resistant to gentamicin-tobramycin-netilmicin-amikacin. The latter phenotype was caused by simultaneous production of the AAC(6′)-I with the one of the following enzymes or enzymes combination: AAC(3)-V, ANT(2″), AAC(3)-I, or ANT(2″) + AAC(3)-I. Such phenotype of resistance, as gentamicin-tobramycin-amikacin-isepamicin was found much more rarely (4,2%) and was due to APH(3′)-VI + ANT(2″). Similarly, rare phenotype of resistance (4%) was simultaneous resistance to all clinically significant second- and third-generation aminoglycosides (gentamicin, tobramycin, netilmicin, amikacin, isepamicin), that was associated with the enzyme combinations, such as APH(3′)-VI + AAC(3)-V, APH(3′)-VI + AAC(6′)-I + AAC(3)-I, APH(3′)-VI + AAC(6′)-II, APH(3′)-VI + AAC(3)-IV or impermeability.

Therefore, the most prevalent aminoglycoside modifying enzymes detected in nosocomial gram-negative microorganisms in Russia were AAC(3)-V (46,9%), ANT(2″) (27,9%), APH(3′)-VI (11,9%), AAC(6′)-I (11,4%). Rates of occurrence of AAC(3)-V and ANT(2″) in different Russian hospitals were similar. However, rate of occurrence of APH(3′)-VI varied significantly in different regions and hospitals. For example, no strains with APH(3′)-VI were found in Krasnodar, Krasnojarsk, Kazan, whereas in Moscow hospitals from 0% to 32,5% of strains had this resistance mechanism. The less frequently found aminoglycoside-modifying enzymes were AAC(3)-I (2,5%), AAC(3)-IV (1,2%), AAC(2′)-I (1,1%), and AAC(3)-III (0,6%).

Most of the tested strains (83,5%) produced simultaneously 2 – 4 enzymes, including APH(3′)-I, conferring resistance to kanamycin and neomycin.

Fig. 1. Centres participating in the study

Fig 2. Main phenotypes of aminoglycoside resistance



G, T	G, T, Nt	G, T, Nt, A	G, T, Nt, A. Is	G, T, A, Is
ANT(2″)	AAC(3)-V	AAC(6′)-I+	APH(3′)-VI+	APH(3′)-VI+
		AAC(3)-V	AAC(3)-V	ANT(2″)
	or AAC(3)-IV			
		or AAC(6′)-I+	or APH(3′)-VI+	
	or AAC(2′)-I	ANT(2″)	AAC(6′)-I+	
	or AAC(6′)-II	or AAC(6′)-I+	or AAC(3)-I	
		AAC(3)-I	APH(3′)-VI+	
			AAC(6′)-II	
		or AAC(6′)-I+		
		ANT(2″)+	or APH(3′)-VI+	
		AAC(3)-I	AAC(3)-IV	

Conclusion

- The leading mechanism of aminoglycoside resistance in nosocomial gram-negative bacteria In Russia is production of aminoglycoside-modifying enzymes.
- The most common enzymes are AAC(3)-V and ANT(2″), conferring resistance to gentamicin-tobramycin-netilmicin and gentamicin-tobramycin, respectively.
- Production of enzymes leading to the resistance to amikacin and isepamicin is not common in Russia.
- Rate of occurrence and profiles of aminoglycoside-modifying enzymes varied significantly in different regions and hospitals.
- Results of this study highlight the need for obtaining local data on aminoglycoside resistance mechanisms in gram-negative bacteria that should serve as a basis for rational empirical choice of antimicrobials for the treatment of nosocomial infections.