ANTIMICROBIAL RESISTANCE IN *STAPHYLOCOCCUS AUREUS* ISOLATED FROM PATIENTS WITH NOSOCOMIAL PNEUMONIA

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A. Dekhnich, L. Stratchounski, I. Edelstain
Institute of Antimicrobial Chemotherapy, Smolensk, Russia

Andrey V Dekhnich
Institute on Antimicrobial Chemotherapy
Smolensk State Medical Academy
214019, Smolensk, Russian Federation
Tel.: +7 0812 611301
E-mail: andrei@antibiotic.ru

Abstract

■ Background: *S. aureus* is one of the leading causes of nosocomial pneumonia that accounts for more than 20% of cases. Resistance of *S. aureus* to antimicrobials has increased recently and its rate varies among regions and countries. The objective of the study was to evaluate antimicrobial resistance in *S. aureus* isolated from patients with nosocomial pneumonia in Russia.

■ Methods: A total of 74 strains of *S. aureus* isolated from patients in 11 hospitals in different parts of Russia were studied. Susceptibility to 16 antimicrobials (ciprofloxacin, chloramphenicol, clindamycin, erythromycin, fusidic acid, gentamicin, levofloxacin, linezolid, moxifloxacin, oxacillin, quinupristin/dalfopristin, rifampicin, teicoplanin, tetracycline, trimethoprim/sulfamethoxazole, vancomycin) was determined by agar dilution (NCCLS, 2003).

■ Results: The prevalence of MRSA among tested strains was 37.8%. The most active antimicrobials were linezolid, vancomycin, teicoplanin, fusidic acid and trimethoprim/sulfamethoxazole to which no resistance was found. Antimicrobials with low frequency of resistance were quinupristin/dalfopristin and rifampicin (1.4% of nonsusceptible strains). The rates of non-susceptibility to other antimicrobials were as follows: levofloxacin - 12.2%, ciprofloxacin - 14.9%, clindamycin - 25.7%, erythromycin - 33.8%, gentamicin - 33.8%, chloramphenicol - 32.4%, tetracycline - 43.2%.

■ Conclusions:

1) Concerning the high prevalence of MRSA the use of beta-lactams monotherapy in patients with nosocomial pneumonia is unjustified.

2) In patients with nosocomial pneumonia in units with high prevalence of MRSA linezolid should be preferred.

3) Vancomycin, fusidic acid, co-trimoxazole and quinupristin/dalfopristin could be considered as possible alternative.

Introduction

Staphylococcus aureus is very important human pathogen that is associated with a broad range of clinical syndromes including nosocomial pneumonia. Depending on the study, *S. aureus* accounts for 13-25% of all cases of nosocomial pneumonia [1, 2].

It is well understood that the most problematic issue in the treatment of staphylococcal pneumonia is versatility of the pathogen related to development of resistance to all antimicrobials available in clinical practice. There are only 2 agents active against almost all strains - vancomycin and linezolid. But at the same time vancomycin has unsatisfactory clinical efficacy in the treatment of pneumonia due to suboptimal lung PK/PD parameters [3]. So, to guide the therapy of nosocomial staphylococcal pneumonia it is very important to have the recent local data on antimicrobial susceptibility [4]. At the same time the published information on this matter is limited with no such studies performed in Russia.

According to the above the objective of the study was to evaluate antimicrobial resistance in *S. aureus* isolated from patients with nosocomial pneumonia in Russia.

Materials and Methods

A total of 74 strains of *S. aureus* isolated from 74 patients in 11 hospitals in different parts of Russia (Fig. 1) - 3 in Central region (Moscow, Smolensk), 1 in North-West region (St.-Petersburg), 2 in South region (Krasnodar, Stavropol), 2 in Volga region (N. Novgorod, Kazan), 1 in Ural region (Ekaterinburg), 2 in Siberia (Krasnoyarsk, Tomsk), were included in the study.

Majority of patients (54, 73.0%) included in the study were hospitalised in ICUs. Ten patients (13.5%) were hospitalised in general surgical, 7 (9.5%) - in neonatal, 3 (4.1%) - in general medical units, respectively.

Susceptibility testing was performed by agar dilution method according to NCCLS recommendations. Double series dilutions in Muller-Hinton agar (Beckton Dickinson, USA) of the following antimicrobials were used: chloramphenicol (Fluka, Germany), ciprofloxacin (Sigma, Germany), clindamycin (Sigma, Germany), erythromycin (Sigma, Germany), fusidic acid (Leo Pharmaceutical, Denmark), gentamicin (Sigma, Germany), levofloxacin (Aventis Pharma, France), linezolid (Pharmacia, USA), moxifloxacin (Bayer, Germany), oxacillin (Sigma, Germany), quinupristin/dalfopristin (Aventis Pharma, France), rifampicin (Fluka, Germany), teicoplanin (Sigma, Germany), tetracycline (Sigma, Germany), trimethoprim/sulfamethoxazole (Sigma, Germany), vancomycin (Eli Lilly, USA). Susceptibility testing results were interpreted in accordance with NCCLS recommendations (2003) with the exception of fusidic acid, moxifloxacin and lincomycin. Recommendations of Antibiotic Committee of French Microbiological Society (Comite de l'Antibiogramme de la Societe Francaise de Microbiologie) were used for fusidic acid. There where no available interpretation criteria for moxifloxacin. *S. aureus* ATCC 29213 was used as a control strain for susceptibility testing.

Results and Discussion

The prevalence of MRSA among tested strains was 37.8% that is comparable to the previously published data [5, 6]. Prevalence of MRSA differs from 0% to 85.7%, depending on the centre participating in the study.

Among all tested antimicrobials the most potent were glycopeptides (vancomycin and teicoplanin), linezolid, fusidic acid and trimethoprim/sulfamethoxazole with all strains susceptible to these agents. MIC_{50}, MIC_{90}, MIC ranges are shown in the Tables 1 and 2. High activity of glycopeptides and linezolid corresponds to the data from all other studies available in the literature. At the same time very limited data on susceptibility of respiratory isolates of *S. aureus* to fusidic acid and trimethoprim/sulfamethoxazole could be found.

Table 1. Results of susceptibility testing

	I+R, %	MIC_{50}/MIC_{90}, mg/L	MIC ranges, mg/L
Vancomycin	0	1/1	0.5-2
Teicoplanin	0	1/2	0.5-2
Linezolid	0	2/2	1-4
Fusidic acid	0	0.125/0.125	0.03-0.25
Trim./Sulfa.	0	0.125/0.5	0.06-2.0
Quinu./Dalfo.	1.4	0.5/1	0.125-2
Rifampicin	1.4	0.03/0.03	0.03-128
Levofloxacin	12.2	0.25/8	0.125-8
Ciprofloxacin	14.9	0.5/16	0.25-64
Clindamycin	25.7	0.125/256	0.06->256
Gentamicin	33.8	1/256	0.25->256
Oxacillin	37.8	0.5/256	0.06->256
Tetracycline	43.2	0.5/128	0.125-256
Erythromycin	33.8	0.5/256	0.125->256
Chloramphenicol	32.4	8/128	4-128
Moxifloxacin	NA	0.06/2	0.015-2

Only 1 strain (1.4%) isolated in Moscow was intermediately resistant (MIC - 2 mg/L) to quinupristin/dalfopristin; one isolate (1.4%) from Krasnodar was resistant to rifampicin with MIC 128 mg/L.

Activity of fluoroquinolones varied among different members of the class. Among all tested strains 12.2% of isolates were non-susceptible to levofloxacin compared to 14.9% of strains non-susceptible to ciprofloxacin. Levofloxacin had lower MIC_{50} and MIC_{90} (0.25 and 0.5 mg/L, respectively) than ciprofloxacin (0.5 and 4.0 mg/L, respectively). Moxifloxacin was the most active fluoroquinolone with MIC_{50}=0.06 mg/L, MIC_{90}=0.125 mg/L.

High resistance rates were detected to clindamycin (25.7%), chloramphenicol (32.4%), gentamicin (33.8%), erythromycin (33.8%), and tetracycline (43.2%).

Table 2. MICs distribution (%) of antibiotics tested

Antibiotic	MIC, mg/L														
	<0.015	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	>256
Oxacillin			1.4	2.7	16.2	29.7	12.2		2.7	2.7		12.2	1.4	6.8	12.2
Vancomycin					8.1	86.5	5.4								
Teicoplanin						1.4	73	25.6							
Linezolid							17.5	81.1	1.4						
Fusidic acid		2.7	21.6	66.2	9.5										
Co-trimoxazole			47.3	37.8	1.4	5.4		8.1							
Erythromycin				1.4	29.7	35.1									33.8
Clindamycin			1.4	66.2	4.1	2.7			5.4						24.3
Gentamicin					1.4	40.5	22.9	1.4					1.4	16.2	16.2
Rifampicin		98.6												1.4	
Tetracycline				1.4	8.1	43.1	2.7	1.4				2.7	18.9	20.3	1.4
Chloramphenicol									5.4	62.1			12.2	20.3	
Quinupristin/dalfopristin				2.7	17.6	50	28.3	1.4							
Ciprofloxacin					14.9	63.4	6.8		2.7		10.8		1.4		
Levofloxacin				24.3	52.7	10.8			1.4	10.8					
Moxifloxacin*	1.4	29.7	44.5	9.5	2.7	1.4		10.8							

* No recommendations for interpretation of susceptibility testing results available

Susceptible Intermediate Resistant

Conclusions

The overall rate of methicillin-resistance in nosocomial respiratory isolates of *S. aureus* was 37.8% which makes beta-lactams an inappropriate option for the first choice therapy of nosocomial pneumonia in majority of medical institutions.

The most potent antimicrobial for the empiric therapy of nosocomial staphylococcal pneumonia was linezolid, to which no resistant strains were found.

In spite that no resistance have been detected for vancomycin, fusidic acid and trimethoprim/sulfamethoxazole, these agents could be considered only as an alternative to linezolid because of suboptimal lung pharmacokinetic of vancomycin, and the lack of adequate clinical data concerning fusidic acid and trimethoprim/sulfamethoxazole.

The low rate of resistance (1.4%) to quinupristin/dalfopristin and rifampicin can theoretically advise the use of this agent as an alternative to linezolid, but the unsatisfactory safety profile of both drugs and easiness of development of resistance to rifampicin during therapy make their usefulness doubtful.

Macrolides, lincosamydes, tetracyclines and chloramphenicol should not be used in the therapy of nosocomial pneumonia caused by *S. aureus.*

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