

CURRENT STATE OF ANTIMICROBIAL RESISTANCE OF *S. PYOGENES* (GAS) IN RUSSIA: RESULTS OF PROSPECTIVE MULTICENTER STUDY (PeHASus-I, PHASE «B»)

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Revised abstract

The study was conducted in 16 cities (Chelyabinsk, Ekaterinburg, Irkutsk, Yakutsk, Yaroslavl, Kazan, Krasnodar, Moscow, Novokuznetsk, Saint Petersburg, Smolensk, Stavropol, Tyumen, Tomsk, Ryazan, Voronezh) in Russia in 2000-2002. A total of 683 non-duplicate clinical isolates of *Streptococcus pyogenes* (GAS) were included in this study. Identification of the strains was done on the basis of colony morphology, Gram stain, bacitracin (0.02 IU) susceptibility and latex agglutination tests. Susceptibility testing to penicillin G (PEN), ceftriaxone (CTR), erythromycin (ERY), azithromycin (AZI), clarithromycin (CLA), midecamycin (MID), spiramycin (SPI), telithromycin (TEL), clindamycin (CLI), ciprofloxacin (CIP), levofloxacin (LEV), tetracycline (TET), chloramphenicol (CHL), vancomycin (VAN) and linezolid (LIN) was performed centrally by broth microdilution method. Breakpoints were those of NCCLS (2002), except for TEL (≤ 0.5 ; $1 > 2$ mg/L), SPI (< 1 ; > 4 mg/L) and MID (< 1 ; > 4 mg/L). There were no resistance detected to PEN, TEL, LEV, VAN and LIN. Percentage of non-susceptible (intermediate and highly resistant) to macrolides and lincosamides isolates was as follows: ERY – 8%, AZI – 8%, CLA – 7%, MID – 2%, SPI – 2% and CLI – 1%. The highest non-susceptibility was observed to TET (47%) and CHL (14%). PEN remains 100% active against all GAS isolates. 16-membered macrolides (spiramycin and midecamycin) and lincosamides possessed the high *in vitro* activity against all tested strains. No resistance was observed to LEV, VAN and LIN. High resistance to TET and CHL compromises their usage for the treatment of streptococcal infections.

Introduction

S. pyogenes is a very important bacterial pathogen in children and adults causing community-acquired upper respiratory tract infections (tonsillitis), skin and soft tissue infections which are among the most frequent reasons for seeking of medical advice. Currently the prevalence of antibiotic resistance is increasing globally. Fortunately, for the time being the resistance to β -lactams in *S. pyogenes* seems not to be a problem. But at the same time situation with resistance to number of other agents is not uniform and there are substantial differences in patterns of resistance do exist between countries and regions. Thus, regional and local data on resistance are of extreme importance.

Purpose

To determine the antimicrobial resistance of clinical strains *S. pyogenes* isolated in adults and children in different regions of Russia.

Methods

This study was conducted in 16 cities in different Russian regions in 2000-2002: Central (Moscow, Kazan, Ryazan, Voronezh, Yaroslavl), North-Western (Saint-Petersburg, Smolensk), Ural (Chelyabinsk, Ekaterinburg), Southern (Krasnodar, Stavropol), Siberia (Irkutsk, Novokuznetsk, Tyumen, Tomsk, Yakutsk) (Fig. 1).

► Fig. 1. Centers participating in the study



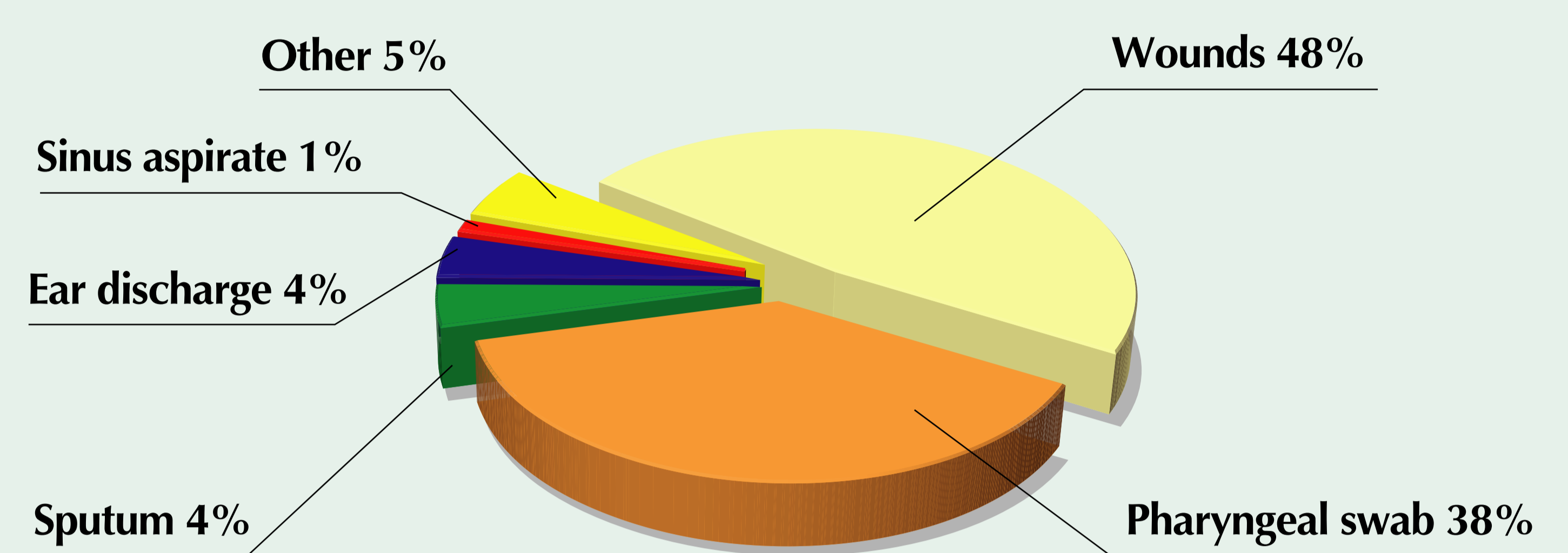
Identification of the strains was done on the basis of colony morphology, Gram stain, bacitracin (0.02 IU) susceptibility and latex agglutination tests. Susceptibility testing was performed using cation-adjusted Mueller-Hinton broth (BBL, USA) with 2-5% lysed horse blood. Microtiter plates were incubated for 24 h at 35°C at ambient air. *S. pneumoniae* ATCC 49619 was used for quality control. Interpretation of results was done according to NCCLS guidelines (2002).



Results and discussion

A total of 683 non-duplicate clinical strains of *S. pyogenes*, isolated from children and adults were included in this study. Clinical specimens from which the tested strains of *S. pyogenes* have been isolated are presented in Fig. 2.

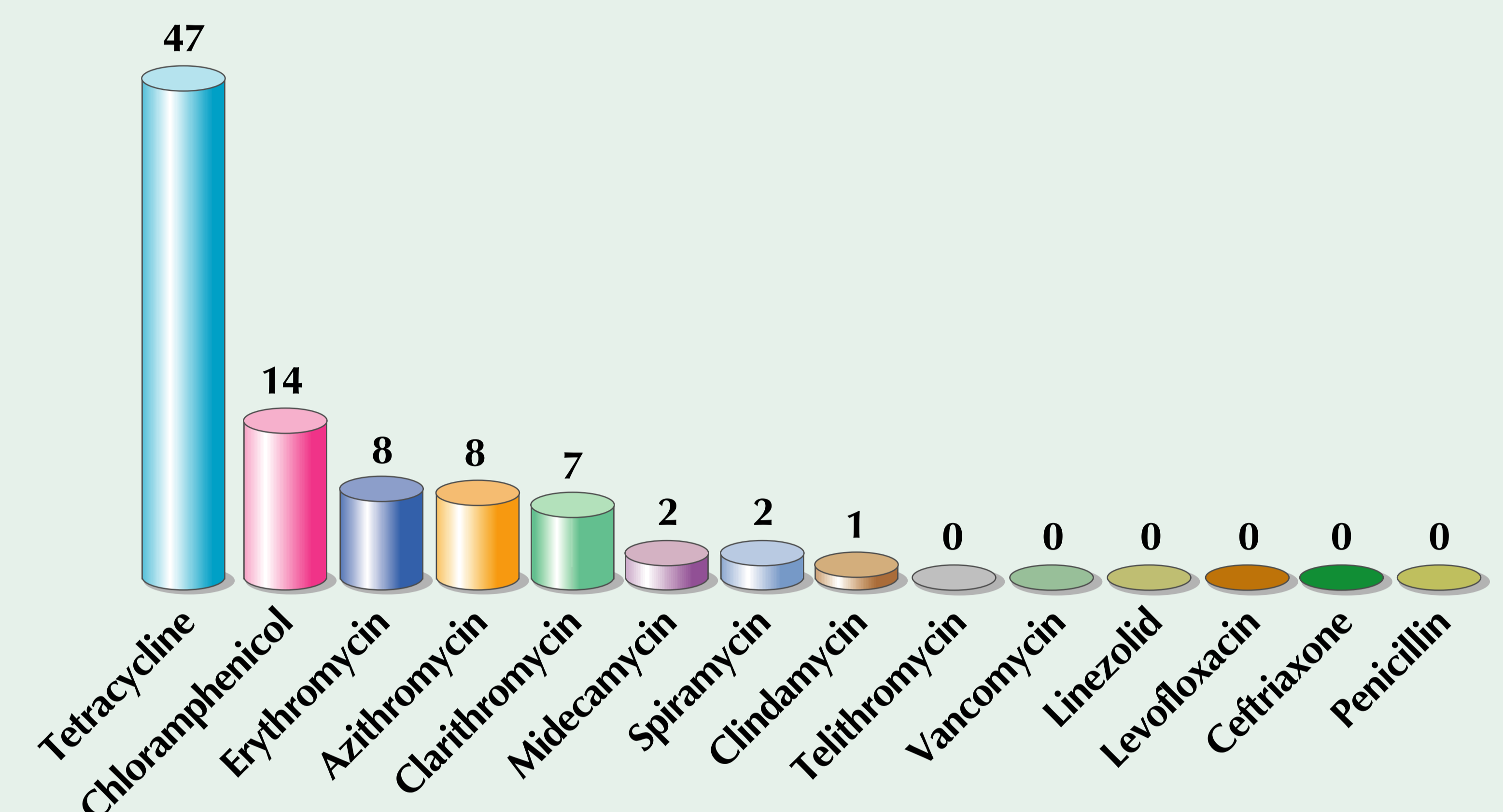
► Fig. 2. Clinical specimens from which the tested strains were isolated



The majority of strains were isolated from wounds (48%) and pharyngeal swabs (38%).

The percentages of non-susceptible (intermediately resistant plus resistant) to tested antimicrobials isolates are presented in Fig. 3.

► Fig. 3. Non-susceptibility to antimicrobials in *S. pyogenes*



The overall results of the susceptibility testing are presented in the Table.

► Table. Results of susceptibility testing of *S. pyogenes*

Antibiotic	S, %	I/R, %	R, %	MIC ₅₀ , mg/L	MIC ₉₀ , mg/L	MIC ranges, mg/L
Penicillin G	100	0	0	0.06	0.06	0.008-1
Ceftriaxone	100	0	0	0.015	0.015	0.004-0.06
Erythromycin	92	3	5	0.03	0.06	0.015-4
Azithromycin	92	0	8	0.03	0.06	0.015-4
Clarithromycin	93	3	4	0.03	0.125	0.015-4
Midecamycin	98	1	1	0.25	0.5	0.03-8
Spiramycin	98	1	1	0.25	0.5	0.015-4
Telithromycin	100	0	0	0.015	0.03	0.002-0.5
Clindamycin	99	0	1	0.015	0.03	0.015-4
Tetracycline	53	2	45	0.25	32	0.125-32
Ciprofloxacin	-	-	-	0.5	1	0.125-4
Levofloxacin	100	0	0	0.5	0.5	0.125-2
Chloramphenicol	86	1	13	2	16	0.06-16
Vancomycin	100	0	0	0.5	0.5	0.03-1
Linezolid	100	0	0	1	1	0.03-2

Not surprisingly, no strains non-susceptible to penicillin were found.

Low frequencies of resistance to macrolides was detected: from 0.3-2% to 16-membered macrolides (midecamycin and spiramycin) to 7-8% to 14- and 15-members macrolides (erythromycin, azithromycin and clarithromycin). It is probably due to the presence of the *mef* gene (M-phenotype).

Among 56 erythromycin-resistant strains, only 5 were resistant to 16-membered macrolides and lincosamides, that could be explained by the MLS_B-phenotype (*erm*-gene). No strains non-susceptible to telithromycin were found.

Glycopeptides (vancomycin) as well as respiratory fluoroquinolones (levofloxacin) and oxazolidinones (linezolid) were active against all tested strains.

Conclusions

► No resistance to penicillin G and ceftriaxone was found, thus allowing β -lactams to retain their positions as the drugs of choice for the treatment of infections caused by *S. pyogenes*.

► The relatively low rates of non-susceptibility to macrolides indicate that these antimicrobials can be considered as alternatives to β -lactams in non-severe infections and in patients with β -lactam allergy.

► Other possible options for the therapy of *S. pyogenes* infections are ketolides (telithromycin), glycopeptides (vancomycin), oxazolidinones (linezolid) and respiratory fluoroquinolones (levofloxacin) to which no resistances were found.

► High rate of resistance to tetracycline (47%) does not allow to use this antimicrobial for the empiric treatment of infections caused by group A streptococci.