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EPIDEMIOLOGY AND ANTIMICROBIAL RESISTANCE OF *STREPTOCOCCUS PNEUMONIAE* STRAINS ISOLATED IN NIŠ DISTRICT DURING 1999-2003

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Summary. *Streptococcus pneumoniae, a frequent cause of infections of the respiratory tract, the middle ear and the central nervous system has shown an increase in resistance to antimicrobial drugs, which significantly hinders therapy. The aim of the study was to determine the frequency of occurrence of S.pneumoniae and to determine the level of resistance to the most frequently used antimicrobial drugs and to study it in relation to resistance in other European countries. In a five-year period 2,185 isolates of S.pneumoniae of various origins were studied, identified by means of morphological, cultural and antigen characteristics, and tested by disc diffusion method for recommended antimicrobial drugs. These isolates were viewed from the aspect of sex, patient's age, type of the sample, and their seasonal character. The experimental group consisted of 320 isolates tested by means of the disc diffusion and agar dilution method, to indicate their susceptibility to penicillin, cephtriaxon, erythromycin, and trimetoprim-sulphametoxasol, according to the recommendation of the American National Committee for Clinical Laboratory Standards (NCCLS), now called Clinical and Laboratory Standards Institute (CLSI). From 2,185 S. pneumoniae obtained from various clinical materials, the highest percentage was found in the population under the age of 15 (84.07%). The nose swab (81.4%) and the transtracheal aspirate (7.51%) were the most frequent positive. The isolates which were obtained from outpatients were more frequent than those obtained from hospitalized patients. The occurrence of seasonal variation can also be detected (82.05% in the winter period). From the multi-resistant isolates, the most frequent are the phenotypes resistant to penicillin, erythromycin, and trimetoprim-sulphametoxasol (11.85%). Examinations were performed on 320 isolates of S.pneumoniae and gave the following results: 68.2% of the isolates showed a reduced sensitivity to penicillin, 33.7% to erythromycin, 19.4% to cephtriaxon and 66.5% to trimetoprim-sulphametoxasol. The level of resistance and percentage of highly resistant isolates (21.3%) rank us among the European countries with the highest rate of resistance of S.pneumoniae to penicillin. The level of resistance to penicillin, erythromycin, and trimetoprim–sulphametoxasol is the highest among the isolates obtained from carriers (38%, 33.7% and 46%). In the case of cephtriaxon, the level of resistance is highest among the hospital isolates (8%), while the percentage of isolates resistant (10%) and intermediary (9.4%) to cephtriaxon is at the level of the Mediterranean and Eastern European countries. There is a significantly high level of resistance to trimetoprim–sulphametoxasol (59%).*

Key words: *Streptococcus pneumoniae, antimicrobial resistance, surveillance*

Introduction

Streptococcus pneumoniae (*S. pneumoniae*) is a microorganism with a high rate of incidence. It is foremost among the colonizers of the nasopharyngeal mycosis where it persists as part of the microbial flora without causing illness. In addition, it holds a prominent place among the causes of infections of the respiratory tract, along with those of the middle ear and central nervous system. *S. pneumoniae* has been isolated in around 30% of the etiologically verified acute respiratory infections (ARI) and is combined with the significantly high number of terminal cases, unlike the viral ARI (1). Globally speaking, *S. pneumoniae* is annually connected with the death of one million children under the age of 5 (2).

Regarding therapy, a special problem is the resistance of certain strains of *S. pneumoniae,* which aggravates treatment and makes the prognosis uncertain. Recent research indicates an increase in a number of penicillin resistant strains of *S. pneumoniae* (PRSP), but also in the occurrence of resistance to other antibiotics as well.

In Europe, the focus of resistance is on the countries of the Mediterranean (Spain, France), as well as the countries of Eastern Europe (Romania, Hungary, Bulgaria) (3). In our area, the occurrence of strains resistant to penicillin was registered for the first time in 1977 (4). The data from 1995 indicate a decreased sensitivity to penicillin and a high sensitivity to cephalosporin of the third generation (5). During 1996 an increase was noted

in the resistance of hospital strains as compared to strains from the nose swab, as well as the existence of a higher rate of multi-drug resistant isolates (MDR) obtained from hospital materials (6,7).

The occurrence of carriers is very high: 5-10% in the adult population and 20-40% in the case of healthy children; but it also indicates variation in regards to patients' age, the seasons and geographic location. The seasonal character is manifested in the occurrence of the largest number of carriers in mid-winter, with the number of people infected peaking in February (8).

Aim of the Study

The aim of the study was to determine the frequency of the occurrence of *S. pneumoniae* isolates in regards to age, the sort of samples, its origin, and seasonal variations and to determine the level of resistance to recommended antimicrobial drugs by disc diffusion method. Within the experimental group, the aim was to determine the level of resistance to penicillin, cephtriaxon, erythromycin, and trimetoprim-sulphametoxasol by disc diffusion and agar dilution method and to study it in relation to the resistance in other European countries.

Material and Methods

Group I. In the period from January 1999 until May 2003 at the Department for Microbiology and Parasitology of the Institute of Public Health in Niš, 2,185 isolates of *S. pneumoniae* were studied, all identified by means of cultural and morphological characteristics and an optochin test, with a coagglutination test to verify the findings. The study incorporated 1,786 nose swabs, 65 throat and nose swabs, as well as 94 sputums, 164 endotracheal aspirates, 50 swabs of the conjunctive, 8 swabs of the outer canal of the ear, 7 liquors, 5 blood samples and 6 tracheostomy swabs. These isolates were studied from the viewpoint of sex, age, type of the sample, origin of the isolate, along with their seasonal character which was taken into consideration by means of distribution over the months. Testing sensitivity to antimicrobial drugs by disc-diffusion included: penicillin (by oxacillin), cephtriaxon, erythromycin, trimetoprim-sulphametoxasol, tetracycline, lincocin, azithromicin, rifampicin, ofloxacin and chloramphenicol.

Group II. A total of 320 isolates for the experimental group were obtained (170 from outpatients, 100 from samples obtained from hospitalized patients, and 50 isolates from healthy individuals-carriers) and isolated in the period from 2001 to 2003. These isolates were tested by means of disc diffusion and agar dilution method. Sensitivity testing to antimicrobial drugs included: penicillin, cephtriaxon, erythromycin, and trimetoprim-sulphametoxasol.

Two hours at the latest after being obtained, all the samples were processed by means of standard bacteriological methods. The sowing was carried out on a blood agar plate which contained 5% sheep blood. After an incubation period of 18-20 hours at a temperature of 37 ± 1^0C, identification on the basis of microscopic, cultural, biochemical and antigen characteristics of bacteria was carried out. The isolates which were obtained were conserved in horse serum with 7% glucose and were frozen at a temperature of -20^0C. Testing sensitivity to antimicrobial drugs was carried out according to the recommendations of the American National Committee for Clinical Laboratory Standards (NCCLS), now called Clinical and Laboratory Standards Institute (CLSI) (9). The standard disc diffusion test was carried out by means of antibiogram tablets of the Institute for Immunology and Virology "Torlak" in Belgrade. The testing included the following discs: oxacillin (5μg), penicillin (6 μg) cephtriaxon (30 μg), trimetoprim-sulphametoxasol (1.25+23.75 μg), and erythromycin (15 μg). The agar dilution method was carried out using clean penicillin drugs (activity of 1280 IJ/ml) and cephtriaxon drugs (activity of 160 mg/L, diluted in distilled water), trimetoprim-sulphametoxasol (activity of 160/3040 mg/L, diluted by means of 0.1M NaOH in water) and erythromycin (activity of 640 mg/ml diluted in 95% ethanol). The disc diffusion and the Minimal Inhibitory Concentration (MIC) of penicillin, cephtriaxon, erythromycin and trimetoprim- sulphametoxasol was determined on the Müeller-Hinton agar (Difco, Detroit, Mich.) with an additional 5% sheep blood.

Break points for tested antimicrobial drugs

Tested antibiotic/ sensitivity (μg/ ml)	S	I	R
Penicillin	0.006	0.125 /l-1.0	2.0
Cephtriaxon (for nonmeningeal isolates)	1.0	2.0	4.0
Cephtriaxon (for meningeal isolates)	0.5	1.0	2.0
Erythromycin	0.25	0.5	1.0
Trimetoprim-Sulfametoxasol	0.5	1.0-2.0	4.0

Results

Group I. In the five-year period, a total of 2,185 *S. pneumoniae* were obtained from various clinical materials. *S. pneumoniae* was analyzed from the viewpoint of the frequency of occurrence in relation to age groups. On the basis of the obtained data, it can be concluded that its isolation is most frequent in the age group under 15 years of age, where the percentage of isolates for this group is 84.07% of the total number (Table 1).

Table 1. Distribution of pneumococcal isolates in a view of ages

Age (years)	Number of isolates	Percent
0	92	4.21%
1	317	14.51%
2	381	17.44%
3	233	10.66%
4	196	8.97%
5	178	8.15%
6	146	6.68%
7 – 14	294	13.46%
15 – 19	39	1.78%
20 – 60	261	11.95%
>60	48	2.20%
Total	2184	100.00%

By testing the frequency of occurrence of the isolates of hospitalized and outpatient origin, we concluded that the percentage of isolates of outpatient origin was significantly higher (87%).

In relation to the sample from which *S. pneumoniae* was isolated, we can single out the nose smear with 81.4% as the most frequent, and the endotracheal aspirate with 7.51% of occurrence. Liquor, blood and tracheostomy made up 1% of all the matter. By further analyzing the sort of the sample, it was determined that the nose swab, conjunctive swab and the sputum were most often outpatient in origin, while the aspirates were to a great degree obtained from hospital samples (Table 2).

Table 2. Distribution of pneumococcal isolates in a view of material and origin

Clinical material	Origin		Total
	Outpatients	Hospital	
Nose smears	1,706	80	1,786
Throat and nose smears	59	6	65
Smears of the conjunctive	46	4	50
Smears of the ear	6	2	8
Sputum	76	17	93
Aspirate	6	158	164
Liquor	0	7	7
Blood	0	5	5
Smear tracheostomy	2	4	6
Total	1,901	283	2,184

A significant deviation can be noted in the number of isolates in the period from October until May, in the sense of there being a statistically significant difference between the winter and summer period, which is also indicated by a χ^2 (47.32) and $p \leq 0.01$. The percentage of isolates obtained in the winter period is as high as 82.05% (Figure 1).

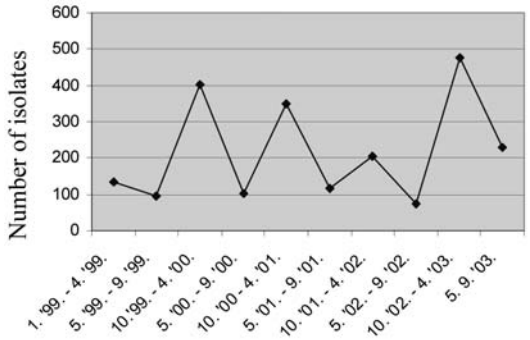

Fig. 1. An outline of the seasonal variation of *S. pneumoniae*

The occurrence of resistance of *S. pneumoniae* to antibiotics is not limited solely to one of them or a particular class, but is often found combined with the resistance to several kinds of antimicrobial drugs. Resistance to three or more different groups of antibiotics is known as a multiple resistance.

From our data, as shown in Table 3 it can be noted that the phenotype PEN^R TS^R (penicillin and trimetoprim-sulphametoxasol) was the one most frequently isolated, along with the PEN^R ER^R (penicillin-erythromycin).

From among the multi-drug resistant isolates the most common are the phenotypes PEN^R ER^R TS^R (penicillin, erythromycin and sulphametoxasol), PEN^R ER^R T^R (penicillin, erythromycin, tetracycline), and PEN^R ER^R TS^R T^R (penicillin, erythromycin, trimetoprim-sulphametoxasol and tetracycline). The part of the isolates resistant to more than four groups of antibiotics was less than one percent (Table 3).

Table 3. Distribution of the resistance and multi-drug resistance phenotypes of *S. pneumoniae*

Antibiotics	R	%
PEN + TS	683	31.26
PEN + ER	398	18.22
PEN +AZ	381	17.44
PEN + T	361	16.52
PEN + ER + TS	259	11.85
PEN +AZ + TS	253	11.58
PEN +AZ + T	214	9.79
PEN + ER + T	213	9.75
PEN + ER + TS + T	149	6.82
PEN +AZ + TS +T	147	6.73
PEN + ER + TS +L	121	5.54
PEN + ER + T + L	60	2.75
PEN + ER + T + OF	25	1.14
PEN + ER + TS + T +OF	17	0.78
PEN+ER+TS+OF+T+H+RIF	17	0.78
PEN+ER+TS+OF+T+H+RIF+LI	3	0.14

Group II. The experimental group was made up of 320 isolates of *S. pneumoniae* obtained from various clinical materials, isolated in the period from 2001 to 2003. By means of the agar dilution method, the percentage of occurrence of the sensitive (S), resistant (R) and intermediate (I) isolates in regards to penicillin, cephtriaxon, erythromycin and trimetoprim- sulphametoxasol was determined.

A high percentage of intermediary isolates in relation to the sensitive and resistant ones, as well as a generally high percentage of isolates with a diminished sensitivity to penicillin (68.2%), was noted. The percent of resistant isolates (MIC >1 μg/ml) was 21.3% (Figure 2).

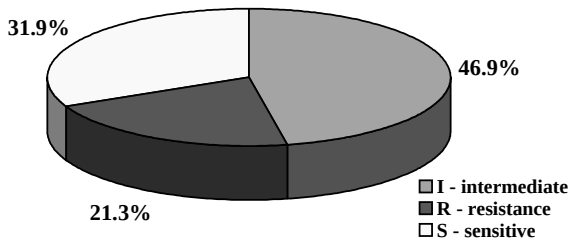

Fig. 2. Sensitivity of *S. pneumoniae* to penicillin by means of the agar dilution method

Testing sensitivity to erythromycin has shown that, unlike in the case of penicillin, the percentage of intermediary isolates in relation to the other two categories, is very low and only has a value of 5.9%. The overall share of isolates with decreased sensitivity to erythromycin is 33.7% (Figure 3).

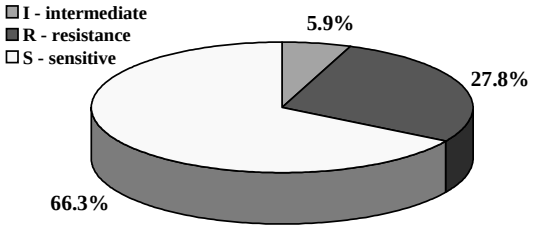

Fig. 3. Sensitivity of *S. pneumoniae* to erythromycin by means of the agar dilution method

Of all the isolates tested for cephtriaxon, 19.4% showed a diminished sensitivity to this antibiotic. The occurrence rate of the intermediate and resistant categories is very balanced (9.4% and 10.0%, respectively) (Figure 4).

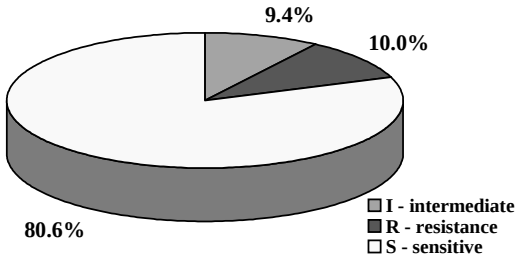

Fig. 4. Sensitivity of *S. pneumoniae* to ceftriaxon by means of the agar dilution method

By analyzing the sensitivity to trimetoprim-sulphametoxasol, a high percentage of isolates with a reduced sensitivity (66.5%) was noted to exist, as well as a high percentage of intermediate isolates (Figure 5).

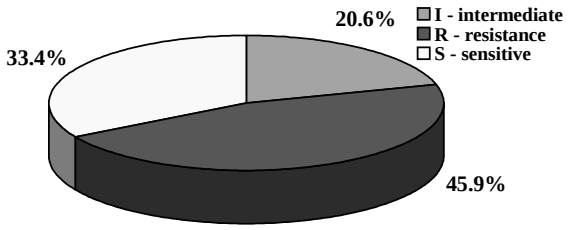

Fig. 5. Sensitivity of the isolates to trimetoprim-sulphametoxasol by means of the agar dilution method

By testing the level of resistance of the isolates of hospitalized, outpatients and carriers to penicillin, erythromycin, and trimetoprim–sulphametoxasol, we concluded that the percentage of isolates of carriers (38%, 33.7% and 46%) was the highest.

Discussion

Antimicrobial resistance over the last few years has reached alarmingly great proportions, in the case of hospitalized and outpatients alike. The problem occurs locally, and slowly becomes a global problem, to which no country of this region is immune. This phenomenon knows neither geographical barriers nor species barriers (10). Resistant strains are found more and more frequently to be the cause of infections of the respiratory system. Among the causes, we find *S. pneumoniae*, which is growing increasingly resistant to antibiotics, by means of various mechanisms.

The resistance of *S. pneumoniae* to penicillin. A few of the more recent international studies (SENTRY, the Alexander Project, PROTEKT) present the data on the progress of the strain of *S. pneumoniae* resistant to penicillin (PRSP) in European countries and the USA.

Data from Western Europe present us with less than 5% occurrence of PRSP in Holland, Great Britain and Sweden. Unlike this region, the prevalence of PRSP is significantly greater in the countries of the Mediterranean, especially in France and Spain, where it is over 50%. It is of significant importance to emphasize that in these countries, the strains with a high level of resistance are dominant (11,12). In Great Britain, PRSP has increased from 0% in 1988 to 3.3% in 1995 (11). In the year 2000, this percentage, according to the data obtained by the PROTEKT study, is already 14.3% (8.8% intermediary and 5.5% resistant). Northern Ireland has around 25% PRSP. Strains highly resistant to *S. pneumoniae* penicillin have occurred in Germany, with an increase from 0.3-3.9% during the period between 1992 and 1995 (11,12).

In Scandinavian countries, this percentage is smaller than in other European countries. In Finland, no resistant strain was detected until 1990, and in 1995 there were 1.2% of resistant and 4.2% of intermediary isolates (13). In Sweden, in the period from 1994 until 1997 the prevalence of PRSP was around 3-4% (14).

Central and Eastern Europe differ in the prevalence of PRSP in certain countries. The latest data obtained by Bozdogan (15) during the course of their research in 2001 indicate the following for this region: Romania and Croatia more than 50%, Slovakia 50%, Bulgaria 48.6%, Hungary 46%, Letonia 6%, Slovenia 4.4%. The lowest prevalence was noted in the Czech Republic (less than 5%). Russian data vary between 9 and 24% (15).

The fact that the percentage of highly resistant isolates is 21.3% puts us in the category of countries with the highest rate of resistance in Europe (Spain, France, Hungary, Romania).

The resistance of *S. pneumoniae* to expanded-spectrum cephalosporins. For a long time, expanded-spectrum cephalosporins of a wide specter were the drugs of choice for treatment of severe pneumonia-related illnesses, such as meningitis and sepsis. The reason for this approach to therapy is the fact that *S. pneumoniae* up until the mid-eighties was uniformly sensitive to these antibiotics (16).

Their widespread use in clinical practice has, unfortunately, brought about the occurrence of resistance, which can be seen in the failure of therapy in the case of pneumonia-related meningitis (17). At the beginning of the nineties of the past century, only isolates of an intermediary resistance were isolated, while newer data indicate that there has been the occurrence of *S. pneumoniae* highly resistant to cephalosporins of the third generation among the invasive and non-invasive isolates (18,19). Generally speaking, the resistance is greater in the countries of the Mediterranean countries (17%) and is greater in the case of non-invasive isolates (20,21).

Testing has shown a low level of resistance, where the percentage of the resistant isolates is 10%, and the percentage of intermediary isolates 9.4%. This piece of information indicates that the sensitivity to this antibiotic has been reduced to an alarmingly low level, in the range of European countries with the highest level of resistance.

The resistance of *S. pneumoniae* to erythromycin. At the point when macrolidic antibiotics were being introduced into the treatment of infectious diseases, *S. pneumoniae* was highly sensitive to this drug. Over time, resistant strains came into being, and the level of resistance has reached great heights over the past 25 years.

The greatest level of resistance to macrolide antibiotics is noted in the countries of the Mediterranean. Over the past five years, resistance has increased for the following values in the following countries: Spain 29-47%, Italy 32-35%, Greece 25-36%, and France 50-58% (22,23,24,25).

Unlike this region, the data obtained by many authors indicate that Northern Europe, especially the Scandinavian countries, is an area with the least prevalence of resistant strains. Finland, Norway and Sweden have 7-19.6% strains resistant to erythromycin (23). In Germany, there are 10% of such strains, in Great Britain 9.1%, Austria 3%, Belgium 25%, Switzerland 9% (22,23,26).

Central and Eastern Europe also have a relatively high percentage of resistance to erythromycin – in Croatia, Romania, Hungary, Bulgaria, Poland, Slovakia and Slovenia that percentage has reached 14-49%, while the Czech Republic has a significantly lower level of resistance - 5% (15,23,27). Over the last 10 years an increase in resistance to erythromycin has been detected in Macedonia - in 1991 there were 9% resistant ones, and in 2001 there were 19% (28,15).

The data regarding our country from 1995 report 27% strains resistant to erythromycin. Our study of the sensitivity to erythromycin has yielded the number of 28% of resistant strains.

The resistance of *S. pneumoniae* to trimetoprim-sulphametoxasol. The prevalence of the resistance of *S. pneumoniae* to trimetoprim-sulphametoxasol has been rapidly increasing, and in many of the countries of Eastern and Central Europe now exceeds 50% (15). This trend is the consequence of a very high rate of use of this antibiotic for the treatment of infections of the respiratory tract, due to the low cost of its production. Jones *et al.* present the latest data from 2003 which refer to several European countries. Resistance to trimetoprim-sulphametoxasol is 29.9% in France, 9.9% in Italy, 45.5% in Spain, 27.3% in Greece, 7.9% in Germany and 5.4% in Great Britain (23), and in Slovenia 28% (27).

The resistance to trimetoprim-sulphametoxasol within the scope of our research also indicates a high level. The percentage of resistant isolates was 45.5%. A high level of resistance of *S. pneumoniae* to trimetoprim-sulphametoxasol in our area can be brought into connection with the widely occurring use of this antibiotic, which is clearly noticeable in Eastern European countries (15).

Multi-drug resistant *S. pneumoniae*. One of the most significant aspects of antimicrobial resistance of *S. pneumoniae* is the appearance and spreading of multi-resistant strains through the world (25). Its presence is registered all over Europe, Asia, North and South America (29).

Data originating from the Alexander Project from 1996 to 1997 offer the following information regarding the co-resistance of *S. pneumoniae* highly resistant to penicillin, along with other antibiotics: Slovakia (tetracycline 30%, chloramphenicol 50%, cotrimoxasol 100%), Hungary (tetracycline 60%, chloramphenicol 53%, cotrimoxasol 100%) and Poland (tetracycline 62%, chloramphenicol 39%, cotrimoxasol 77%) (26).

In Romania 11.3% *S. pneumoniae* resistant to erythromycin, penicillin, chloramphenicol and rifampicin was registered (26). In Greece 13% of these isolates were noted (30), and in Italy more than 2% *S. pneumoniae* are resistant to more than five antibiotics. A high percentage of isolates resistant to tetracycline, chloramphenicol, penicillin and cotrimoxasol was registered in Croatia in the period between 1991 and 1999 and is 40% (31).

In our country, of all the resistant isolates the most common is penicillin-cotrimoxasol resistance with 31.26%, penicillin-erythromycin resistance with 18.22%, and of the multi-resistant, resistance to penicillin-erythromycin-cotrimoxasol with 11.85%, and penicillin-erythromycin-tetracycline (9.75%).

Conclusion

The percentage of resistant isolates classifies our region among those areas with the highest level of resistance. The level of resistance and the percentage of highly resistant isolates (21.3%) classify us among the countries with the highest rate of resistance to penicillin in Europe (Spain, France, Hungary, Romania). Resistance to trimetoprim-sulphametoxasol indicates a significantly high level of resistance (45.9%), as well as erythromycin (27.8%). In the case of cephtriaxon, the level of resistance is greatest in hospital isolates (8%), most probably due to the existence of a selective antibiotic pressure among hospitalized patients. The percentage of isolates resistant to cephtriaxon is 10%, and the percentage of intermediary isolates is 9.4%. This kind of

resistance level is highly comparable to most European countries, except those of the Mediterranean and Eastern European countries.

The level of resistance to penicillin, erythromycin, and trimetoprim- sulphametoxasol in the case of isolates obtained from carriers (38%, 33.7% and 46%, respectively) is significantly higher than in the case of isolates obtained from outpatient and hospitalized patients.

In relation to the type of material from which *S. pneumoniae* was isolated, a significantly higher level of resistance to penicillin was detected in the case of outpatient isolates (67% resistant and intermediary) and isolates from carriers in relation to the invasive isolates (blood, liquor - 23%).

From among the multi-drug resistant isolates the most common are the phenotypes PEN^R ER^R TS^R (penicillin, erythromycin and sulphametoxasol) 11.8%, PEN^R ER^R T^R (penicillin, erythromycin, tetracycline) 9.7%, and PEN^R ER^R TS^R T^R (penicillin, erythromycin, trimetoprim- sulphametoxasol and tetracycline) 6.8%.

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EPIDEMIOLOGIJA I ANTIMIKROBNA REZISTENCIJA SOJEVA STREPTOKOKUS PNEUMONIAE IZOLOVANIH U NIŠKOM REGIONU TOKOM 1999-2003.

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Kratak sadržaj: *S. pneumoniae, čest uzročnik infekcija respiratornog trakta, srednjeg uha i centralnog nervnog sistema poslednjih godina pokazuje porast rezistencije na antimikrobna sredstva što otežava terapijski pristup. Cilj rada bio je utvrđivanje učestalosti pojave S.pneumoniae i određivanje nivoa rezistencije na penicilin, ceftriakson, eritromicin i trimetoprim- sulfametoksazol, kao i njegovo upoređivanje sa rezistencijom u ostalim zemljama Evrope. U petogodišnjem periodu ispitano je 2185 izolata S.pneumoniae različitog porekla, identifikovanih pomoću morfoloških, kulturelnih i antigenih osobina. Ovi izolati sagledani su sa aspekta pola, uzrasta, vrste bolesničkog materijala, porekla izolata i sezonskog karaktera i testirani disk-difuzionom metodom na preporučene antimikrobne lekove. Eksperimentalnu grupu činilo je 320 izolata testiranih disk-difuzionom i agar- dilucionom metodom na penicilin, ceftriakson, eritromicin i trimetoprim-sulfametoksazol, prema preporukama Američkog nacionalnog komiteta za kliničke laboratorijske standarde (NCCLS), sada Instituta za kliničke laboratorijske standarde (CLSI). Od 2185 S.pneumoniae iz različitog kliničkog materijala, najveći procenat bio je u uzrastu do 15 godina (84,07%) i to iz brisa nosa (81,4%) i aspirata (7,51%). Izolati ambulantnog porekla zastupljeniji su od bolničkih (87%). Uočava se pojava sezonskih varijacija (82,05% u zimskom periodu). Od multirezistentnih izolata najčešći su fenotipovi rezistentni na penicilin, eritromicin i sulfametoksazol. Ispitivanje osetljivosti eksperimentalne grupe od 320 izolata S.pneumoniae, dalo je sledeće podatke: 68,2% izolata sa smanjenom osetljivošću prema penicilinu, 33,7% prema eritromicinu, 19,4% prema ceftriaksonu. Rezistencija na trimetoprim-sulfametoksazol je 66,5%. Nivo rezistencije i procenat visoko rezistentnih izolata (21,3%) svrstavaju nas u red zemalja sa najvišom stopom rezistencije na penicilin u Evropi. Nivo rezistencije na penicilin, eritromicin i trimetoprim-sulfametoksazol najviši je kod izolata iz nosilaštva (38%, 33,7% i 46%). Kod ceftriaksona je nivo rezistencije najviši kod bolničkih izolata (8%), a procenat rezistentnih (10%) i intermedijarnih (9,4%) izolata je na nivou mediteranskih i istočnoevropskih zemalja. Postoji značajno visok nivo rezistencije na trimetoprim-sulfametoksazol (59%).*

Ključne reči: *Streptococcus pneumoniae, antimikrobna rezistencija, pregled*