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# BACTERIOLOGICAL STUDY OF STAPHYLOCOCCAL STRAINS ISOLATED FROM PATIENTS WITH PRIMARY AND SECONDARY COMMUNITY-ACQUIRED MENINGITIS

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**Abstract.** *Staphylococcus* spp. susceptibility to antibacterial chemotherapeutics is changing and the incidence of resistant strains is growing. The **aim** of this study was to identify the characteristics and the susceptibility of the staphylococcal strains determining community-acquired meningitis in order to be able to choose the correct treatment. **Materials and methods.** There have been tested 220 strains isolated from at least two blood cultures in patients with primary and secondary meningitis, from cerebrospinal fluid (CSF) (the first, the second and the third intrathecal puncture) and from other pathological products. The strains have been isolated from 87 patients at Clinical Hospital of Infectious Disease Iaşi from January 1st, 1977 through March 1st, 2007. Classical methods of isolation and identification have been used (bacterioscopy, cultures from pathological products). Blood cultures were performed on heart-brain broth and thioglycolate medium and evaluated for 14 days. CSF cultures were performed on enriched solid and liquid broth and evaluated for 3-5 days. The other pathological products were cultured on selective media with sodium chlorinate salt. Identification was based on morphology Gram positive cocci and metabolic characteristics and coagulase test. Susceptibility of the isolated strains was tested using standard disc diffusion method on Müeller-Hinton agar. Minimum inhibitory concentrations (MIC) of some antibacterial chemotherapeutics (fluoroquinolones, ceftriaxone, vancomycin) were also determined using method of dilution antimicrobial susceptibility test on Müeller-Hinton broth. The *Staphylococcus aureus* ATCC 25923 strain was used as control. **Results and discussion.** The analyzed period was split into three smaller periods: 1977-1987, 1988-1998 and 1999-2007. During the first period, 45 staphylococcal strains have been identified (35 strains of *S. aureus* and 10 coagulase negative staphylococci). These strains were highly sensitive to classic antistaphylococcal therapy. However, *S. aureus* was found more sensitive to some antibacterial drugs compared to coagulase negative staphylococci. During 1988-1998, 19 staphylococcal strains have been isolated (13 strains of *S. aureus* and 6 coagulase negative staphylococci). Susceptibility to oxacillin, rifampin, lincomycin decreased under 73% and to trimethoprim-sulfamethoxazole – under 40%. During the last period, the 23 strains isolated (17 strains of *S. aureus* and 6 coagulase negative staphylococci) have been tested with 16 antibacterial drugs (including ciprofloxacin, imipenem, amoxicillin-clavulanic acid and vancomycin). Susceptibility to classic antistaphylococcal drugs decreased dramatically: oxacillin – 65.2%, gentamycin – 78%, lincomycin – 47.8%, erythromycin – 30.4%. Susceptibility to ceftriaxone, ofloxacin and sulbactam-ampicillin varies between 87-83%. The susceptibility to vancomycin and ciprofloxacin was 100%. **Conclusions.** During the analyzed period, staphylococcal resistance to classic antibacterial chemotherapeutics increased from 5% to 50% and, soon after that, resistance to systemic quinolones have been discovered.

**Key words: *Staphylococcus aureus*, coagulase negative staphylococci, susceptibility, resistance**

**Rezumat.** Sensibilitatea stafilococilor la terapia cu antibiotice s-a modificat, iar incidența tulpinilor rezistente a crescut. **Scopul** acestui studiu a fost identificarea spectrului sensibilității la substanțele antibacteriene, creşterea incidenței rezistenței stafilococilor a impus necesitatea cunoaşterii caracteristicilor şi a comportării față de antibiotice a tulpinilor incriminate în meningita stafilococică comunitară, în vederea aplicării unui tratament corect. **Material şi metodă**. Au fost testate 220 tulpini, izolate din cel puțin două hemoculturi de la bolnavii cu meningite primare sau secundare, LCR (din prima, a doua şi a treia puncție rahidiană) şi alte produse patologice. Tulpinile aparțin celor 87 de bolnavi cu meningită stafilococică primară sau secundară internați în Spitalul Clinic de Boli Infecțioase Iaşi, în perioada 1.01.1977 – 1.03.2007. Metodele de izolare şi de identificare au fost cele clasice. S-au efectuat examene bacterioscopice pentru prelevatele care se pretează la acest examen. În paralel s-a executat cultivarea produselor patologice conform metodologiei folosite în laboratorul clinic. Hemoculturile s-au efectuat pe bulion cord-creier şi bulion tioglicolat şi s-au supravegheat timp de 14 zile. LCR s-a cultivat pe medii de cultură solide şi lichide îmbogățite, cu incubare 3-5 zile. Alte produse patologice au fost cultivate pe medii selective cu sare. Identificarea culturii obținute s-a bazat pe studiul caracterelor de cultură, morfotinctoriale, de metabolism şi testul coagulazei. Testarea sensibilității stafilococilor s-a efectuat prin metoda difuzimetrică standard pe geloza Müeller-Hinton, iar pentru unele antibiotice ca fluorochinolonele, ceftriaxona, vancomicina s-a determinat şi concentrația minimă inhibitorie (CMI) prin metoda diluțiilor în bulion Müeller-Hinton. S-a folosit ca tulpină de referință *Staphylococcus aureus* ATCC 25923. **Rezultate şi discuții.** Perioada analizată a fost separată în 3 decade pentru a avea o perspectivă asupra caracteristicilor stafilococilor şi a sensibilității acestora la antibiotice. În perioada, 1977-1987 au fost testate 45 de tulpini de stafilococ (35 de tulpini *S. aureus* şi 10 tulpini stafilococi coagulază negativi), constatându-se că acestea aveau o marcată sensibilitate față de antibioticele antistafilococice clasice. Totuşi, *S. aureus* s-a dovedit a fi mai sensibil la unele antibiotice comparativ cu stafilococii coagulază negativi. În perioada 1988-1998 au fost izolate 19 tulpini de stafilococ: 13 tulpini *S. aureus* şi 6 tulpini de stafilococ coagulază negativ. S-a evidențiat o scădere a sensibilității stafilococilor față de oxacilină, rifampicină, lincomicină (sub 73%), iar față de trimetoprim-sulfametoxazol sub 40% (antibiotice antistafilococice clasice). În ultima perioadă, 1999-2007 cele 23 de tulpini: 17 tulpini *S. aureus* şi 6 tulpini de stafilococ coagulază negativ, au fost testate la un număr de 16 antibiotice (s-au adăugat în studiu: ciprofloxacina, imipenemul, amoxicilina+acidul clavulanic şi vancomicina). Analiza a arătat o scădere îngrijorătoare a sensibilității stafilococilor față de antibioticele clasice: oxacilină – 65,2%, gentamicină – 78%, lincomicină – 47,8%, eritromicină – 30,4%. Față de ceftriaxonă, ofloxacină şi sulbactam+ampicilină, sensibilitatea a variat între 87-83%. Sensibilitatea pentru vancomicină şi ciprofloxacină a fost de 100%. **Concluzii**. Evoluția în timp a rezistenței stafilococilor la antibioticele clasice a crescut de la 5% la 50%, ulterior semnalându-se rezistență şi la chinolonele cu administrare sistemică.

**Cuvinte cheie: *Staphylococcus aureus*, stafilococ coagulază negativ, sensibilitate, rezistență**

## INTRODUCTION

*Staphylococcus* spp. susceptibility to antibacterial drugs is changing and the incidence of resistant strains is growing. Therefore, identifying the characteristics and the susceptibility of the staphylococcal strains is necessary in order to be able to choose the right treatment.

## MATERIALS AND METHODS

### *Staphylococcal Strains Origin*

The staphylococcal strains have been isolated from 87 patients with primary or secondary community-acquired meningitis at Clinical Hospital of Infectious Disease Iaşi from January 1st, 1977 through March 1st, 2007.

There have been tested 220 strains isolated from at least two blood cultures, from cerebrospinal fluid (CSF) (the first, the second and the third intrathecal puncture) and from other pathological products (tab. 1).

**Table 1. Staphylococcal strains origin and the meningitis pathogeny in 87 patients**

| Meningitis type | | Patients number | Pathological products | Strains number |
|---|---|---|---|---|
| Primary | | 28 | CSF | 97 |
| Secondary | sepsis | 46 | blood cultures | 93 |
| | spinal abscess | 7 | epidural pus | 24 |
| | medium otitis | 1 | otic pus | 1 |
| | otomastoiditis | 3 | mastoideus pus | 3 |
| | sinusitis | 2 | sinusal secretion | 2 |
| ***Total*** | | ***87*** | | ***220*** |

*Methods of Isolation and Identification*

Classical methods of isolation and identification have been used (bacterioscopy, cultures from pathological products).

Blood cultures were performed on heart-brain broth and thioglycolate medium and evaluated daily, until positive cultures were obtained, with a maximum surveillance of 14 days.

CSF cultures were performed on enriched solid and liquid broth and evaluated for 3-5 days. The other pathological products were cultured on selective media with sodium chlorinate salt.

Identification was based on cultivation, microscopical and metabolic characteristics and and coagulase test, separating positive coagulase staphylococci (*S. aureus*) and negative coagulase staphylococci (*S. epidermidis* and other species).

*Testing the Susceptibility to Antibacterial Chemotherapeutics*

Staphylococcal susceptibility and resistance have been tested using standard disc diffusion method on Müeller-Hinton agar. MIC of some antibacterial drugs (fluoroquinolones, ceftriaxone, vancomycin) was also determined using dilutions method on Müeller-Hinton broth. Susceptibility testing to antibacterial chemotherapeutics was made with OXOID disks.

*Staphylococcus aureus* ATCC 25923 strain has been used as control.

RESULTS

In order to have a better view of staphylococcal characteristics and of their susceptibility, the analyzed period was split into three smaller periods: 1977-1987, 1988-1998 and 1999-2007 (tab. 2).

In the first period there have been isolated 132 strains from CSF, blood cultures and pus. In the second period there have been isolated 37 strains and in the third period there have been isolated 51 strains from the mentioned pathological products (tab. 2).

**Table 2. Staphylococcal strains repartition during the three periods**

| Period | Main strains number | Strains isolated from pathological products | | |
|---|---|---|---|---|
| | | CSF | Blood cultures | Pus |
| 1977-1987 | 45 | 50 | 66 | 16 |
| 1988-1998 | 19 | 20 | 11 | 6 |
| 1999-2007 | 23 | 27 | 16 | 8 |
| ***Total*** | ***87*** | ***97*** | ***93*** | ***30*** |

*Bacteriological Characteristics of The Isolated Staphylococcal Strains*

Analyzing cultural, morphology in Gram staining, metabolic and pathogenicity characteristics, the 87 main strains were separated into *S. aureus* (positive coagulase staphylococci) and negative coagulase staphylococci (mainly, *S. epidermidis*).

The main tests used for differentiation were: coagulase test, acid produced anaerobically from manitol (positive for *S. aureus* and negative for *S. epidermidis*), the hemolysins and pigments production which varied, but was mainly positive for *S. aureus*.

*The Incidence of S. aureus and Negative Coagulase Staphylococci Determining Meningitis*

Meningitis in 87 patients has been determined by positive coagulase staphylococci (*S. aureus*) in 65 cases (74.7%) and by negative coagulase staphylococci in 22 cases (25.3%) (fig. 1).

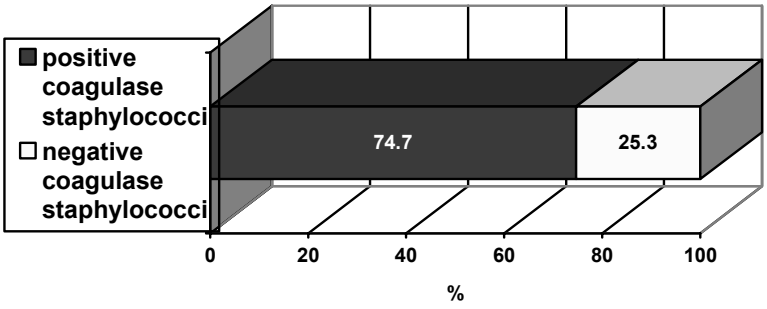


**Fig. 1. Staphylococcal species in meningitis etiology**

Positive and negative coagulase staphylococci proportions were nearly equally distributed both for primary and secondary staphylococcal meningitis (tab. 3).

**Table 3. The incidence of *S. aureus* and negative coagulase staphylococci isolated from CSF and from blood cultures**

| | | CSF and pus | Blood cultures | Total |
|---|---|---|---|---|
| **Total strains number** | | **87** | **46** | **133** |
| positive coagulase staphylococci | Strains number | 65 | 35 | 100 |
| | % | 74.7 | 76.1 | 75.2 |
| negative coagulase staphylococci | Strains number | 22 | 11 | 33 |
| | % | 25.3 | 23.9 | 24.8 |

The incidence of *S. aureus* and negative coagulase staphylococci determining meningitis during the three periods is presented in table 4.

**Table 4. The incidence of *S. aureus* and negative coagulase staphylococci in meningitis etiology during the three periods**

| Strains | Main strains number | Number of strains during | | |
|---|---|---|---|---|
| | | 1977-1987 | 1988-1998 | 1999-2007 |
| *S. aureus* | 65 | 35 | 13 | 17 |
| Negative coagulase staphylococci | 22 | 10 | 6 | 6 |
| ***Total strains number*** | ***87*** | ***45*** | ***19*** | ***23*** |

During the first period (1977-1987) the most cases of meningitis emerged and the most staphylococcal strains were isolated: 45 staphylococcal strains (35 strains of *S. aureus* and 10 coagulase negative staphylococci). During the next periods (1988-1998 and 1999-2007) the number of staphylococcal strains isolated from patients with meningitis decreased, being smaller or equal with half of the number of strains isolated during the first period: 19 and 23 strains, respectively..

*The Susceptibility of the Staphylococcal Strains Isolated from Meningitis Cases*

Due to the large period of the study, 29 years, there have been registered differences in staphylococcal strains susceptibility to antibacterial drugs and, therefore, differences in meningitis therapy.

As mentioned before, susceptibility and resistance of the isolated staphylococcal strains have been analyzed during the three selected periods.

*Staphylococcal Strains Susceptibility and Resistance to Antibacterial Drugs During 1977-1987*

During the first period, susceptibility and resistance to antibacterial drugs of the 45 staphylococcal strains isolated from the

same number of patients are presented in figure 2 and reveal the following aspects:

- more than 40 strains (>90%) were sensitive to pristinamycin, oxacillin, gentamycin, chloramphenicol and lincomycin;
- 37 strains (82%) were sensitive to rifampin and trimethoprim-sulfamethoxazole and 8 strains (18%) were resistant;
- susceptibility to kanamycin, streptomycin and erythromycin were discovered for 36, 34 and 33 strains, respectively (>70%);
- penicillin G was inactive for 41 strains, only 4 strains (9%) being sensitive to this drug.

Hence, during this period, the staphylococci had a great susceptibility to classic antistaphylococcal therapy.

Analyzing the susceptibility and the resistance to antimicrobial drugs of the 35 strains of *S. aureus* compared to those of the 10 coagulase negative staphylococci some differences were revealed in figures 2 and 3.

There were found differences between the coagulase negative staphylococci sensitivities compared to those of *S. aureus*. The biggest differences were discovered for chloramphenicol: 70% of coagulase negative staphylococcal strains were sensitive, and 30% - resistant, while all strains (100%) of *S. aureus* were sensitive to chloramphenicol.

50% of the coagulase negative staphylococcal strains were sensitive to erythromycin, while susceptibility to kanamycin and streptomycin had a level of 60%.

The levels of susceptibility to oxacillin, gentamycin, lincomycin and trimethoprim-sulfamethoxazole are only with 2-4% higher for coagulase negative staphylococci than for *S. aureus*.

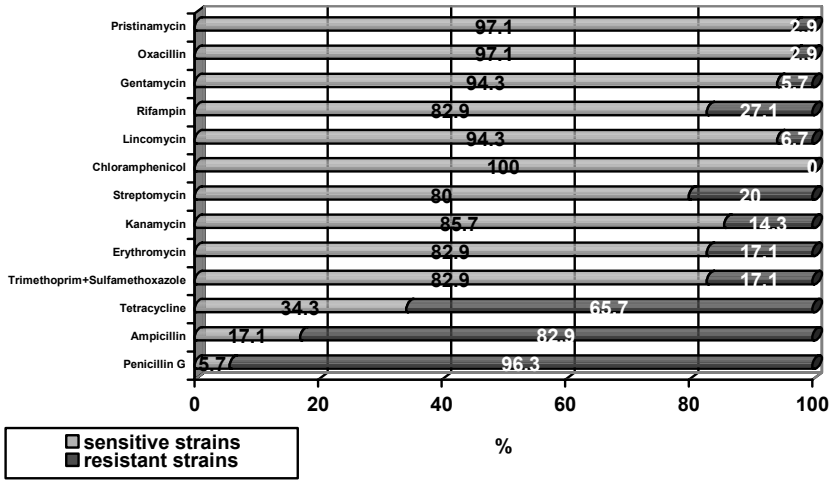


**Fig. 2. Susceptibility and resistance to antibacterial drugs of *S. aureus* strains (1977-1987)**

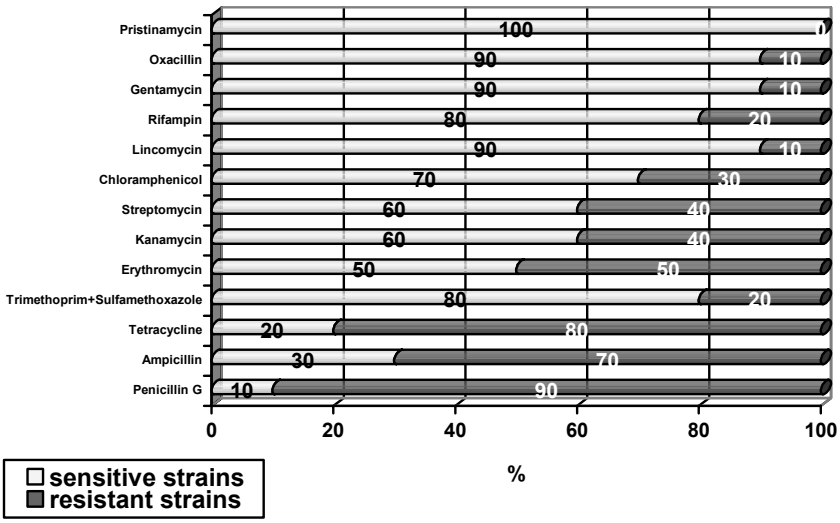


**Fig. 3. Susceptibility and resistance to antibacterial drugs of coagulase negative staphylococcal strains (1977-1987)**

*Staphylococcal Strains Susceptibility and Resistance to Antibacterial Drugs During 1988-1998*

The 19 staphylococcal strains susceptibility to antimicrobial drugs during the second period (1988-1998) revealed different aspects compared to the previous period. There was a decreasing susceptibility to classic antistaphylococcal drugs; susceptibility to oxacillin, rifampin, lincomycin dropped under 73% (with 14, 13 and 13 sensitive strains, respectively) (fig. 4).

In addition, sensitivities to erythromycin, chloramphenicol and kanamycin were around 40% (with 8, 8 and 7 sensitive strains, respectively).

During this period, staphylococcal susceptibility to trimethoprim-sulfamethoxazole was under 40% (7 sensitive strains from a total of 19 strains).

On the other hand, susceptibility to pristinamycin remained over 90% from 1977 through 1990.

During both first periods tetracycline and ampicillin were practically inactive, therefore no more susceptibility testing have been performed in the last period. However, since the '90, susceptibility testing to cephalosporins, fluoroquinolones and other anti-bacterial chemotherapeutics has been added.

18 staphylococcal strains were sensitive to ceftriaxone and only one had intermediary susceptibility, while all of the 19 strains were sensitive to ofloxacin.

The sulbactam-ampicillin mixture was active on more than 90% of the strains, while ampicillin was practically inactive (only 1 strain ampicillin-sensitive from a total of 19 strains).

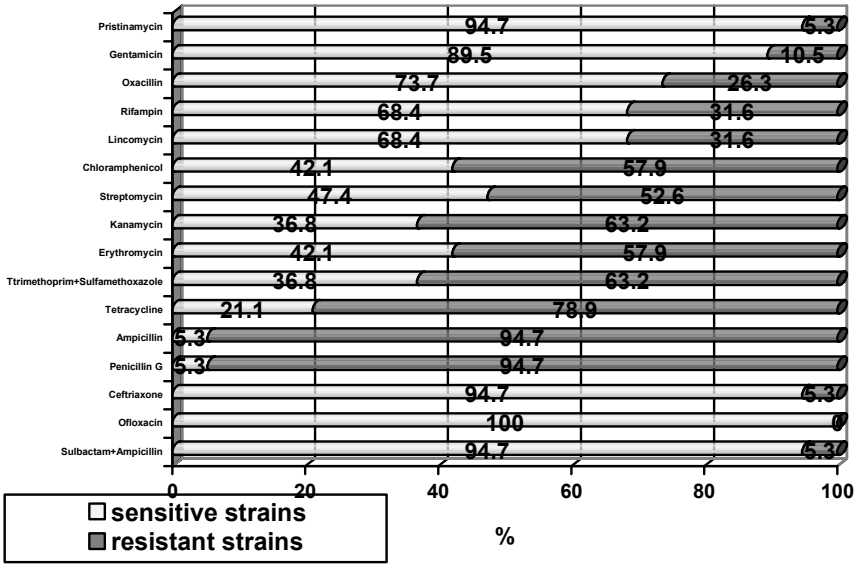


**Fig. 4. Susceptibility and resistance to antibacterial drugs of staphylococcal strains (1988-1998)**

Summarizing, during 1988-1998, the staphylococci determining primary and secondary meningitis were less sensitive to classic antibacterial chemotherapy with 10-20%. On the other hand, susceptibility to ceftriaxone, sulbactam-ampicillin and ofloxacin was close to 100%.

*Staphylococcal Strains Susceptibility and Resistance to Antibacterial Drugs During 1999-2007*

During the last period (1999-2007), 23 patients with meningitis were evaluated. From these patients, the same number of staphylococcal strains was isolated. These strains were tested to 16 antibacterial drugs, 4 of which were newly introduced: ciprofloxacin, imipenem, amoxicillin-clavulanic acid and vancomycin (fig. 5).

The results showed that:

- staphylococcal strains susceptibility to classic antibacterial chemotherapeutics like oxacillin, gentamycin, lincomycin or erythromycin is brutally decreasing;
- susceptibility levels to rifampin and chloramphenicol are close to the levels of susceptibility determined in the previous period;
- susceptibility levels to ceftriaxone, ofloxacin and sulbactam-ampicillin were of 87%, 87% and 83% respectively;
- ciprofloxacin and vancomycin were active on all strains (100% susceptibility), while imipenem was active on 91.3% of staphylococci.

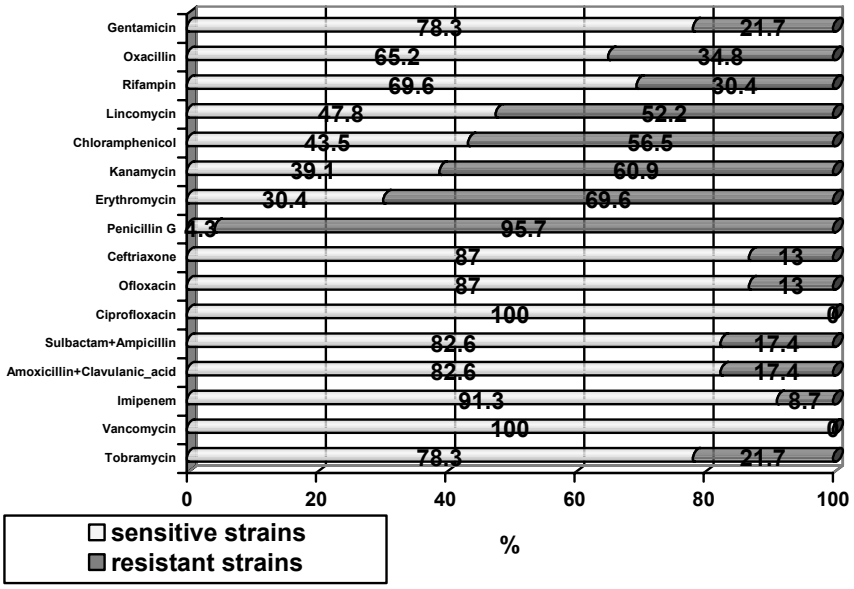


**Fig. 5. Susceptibility and resistance to antibacterial drugs of staphylococcal strains (1999-2007)**

*The Evolution of the Staphylococcal Strains Susceptibility and Resistance to Antibacterial Drugs*

*a. The Evolution of the Staphylococcal Strains Susceptibility to Antibacterial Drugs*

Analyzing susceptibility and resistance to some antimicrobial drugs over the whole period of 29 years, it can be observed a decrease of susceptibility of staphylococcal strains.

Investigating the evolution in time of the staphylococcal strains behavior over the three periods (1977-1987, 1988-1998 and 1999-2007) the following aspects can be exposed:

- staphylococcal strains susceptibility to oxacillin decreased from 95% to 74% and to 66%, respectively;
- the level of susceptibility to erythromycin fell from 73% to 30% in the third period;
- a lower decrease of activity was recorded for rifampin (from 80% to 70%);
- a severe reducing in activity was confirmed for lincomycin (from 93% to 48%);
- susceptibility to gentamycin decreased from 93% to 78% and to kanamycin – from 79% to 39%.

*b. The Evolution of the Staphylococcal Strains Resistance to Antibacterial Drugs*

Exploring the evolution in time of the staphylococcal resistance and grouping the behavior of the 87 staphylococcal strains in the selected

periods, the increasing resistance to classic antibacterial chemotherapy becomes obvious. The same phenomenon is observed for the other drugs introduced later into therapy.

Thus, the percentage of resistance to oxacillin increased from 4.4% to 26%, and later to 34%, the levels of resistance to gentamycin increased from 6% to 10%, and to 21.7%, respectively.

The resistance to erythromycin for the staphylococci isolated from CSF, increased progressively: 26%, 58%, 69% and the resistance to lincomycin was about 7% in the first period, while 52.2% – during the last period.

The staphylococcal strains resistance to rifampin is less spectacular (from 17% to 32%), but chloramphenicol was inactive for more than half of the strains (57%).

Even the resistance to the last introduced antibacterial drugs suffers slight increase for the staphylococci determining meningitis (tab 5).

**Table 5. The staphylococcal strains resistance to antibacterial drugs during 1977-2007**

| | ***Periods*** | | | | | |
|---|---|---|---|---|---|---|
| | ***1977-1987*** | | ***1988-1998*** | | ***1999-2007*** | |
| **Number of strains** | **45** | | **19** | | **23** | |
| **Antibacterial drug** | **Nr.** | **%** | **Nr.** | **%** | **Nr.** | **%** |
| Oxacillin | 2 | 4.4 | 5 | 26.3 | 8 | 34.8 |
| Penicillin G | 41 | 91.9 | 18 | 94.7 | 22 | 95.7 |
| Gentamycin | 3 | 6.7 | 2 | 10.5 | 5 | 21.7 |
| Kanamycin | 9 | 20.0 | 12 | 63.2 | 14 | 60.9 |
| Erythromycin | 12 | 26.7 | 11 | 57.9 | 16 | 69.6 |
| Rifampin | 8 | 17.8 | 6 | 31.6 | 7 | 30.4 |
| Lincomycin | 3 | 6.7 | 6 | 31.6 | 12 | 52.2 |
| Chloramphenicol | 3 | 6.7 | 11 | 57.9 | 13 | 56.5 |
| Trimethoprim+Sulfamethoxazole | 8 | 17.8 | 12 | 63.2 | - | - |
| Tetracycline | 31 | 68.9 | 15 | 78.9 | - | - |
| Ceftriaxone | - | - | 1 | 5.3 | 3 | 13.0 |
| Ofloxacin | - | - | - | - | 3 | 13.0 |
| Sulbactam+Ampicillin | - | - | 1 | 5.3 | 4 | 17.4 |

DISCUSSIONS

The high level of resistance to oxacillin for the staphylococcal strains was mentioned in some European countries (France, Great Britain, Italy and Greece) even before the period of our study began (1, 2, 3, 4). Comparing our research to other data from the literature, we found important variations between different regions regarding the staphylococcal strains susceptibility especially for *S. aureus,* to some antibacterial chemotherapeutics (e.g. rifampin, gentamycin). Therefore, every case of infection should be analyzed taking into consideration the region of provenience of the case and the antistaphylococcal therapy should be adapted accordingly.

For example, the *S. aureus* strains resistance to oxacillin, reported by Miftode et al., varied between 19% (in Bucureşti) and 39% (in Timişoara) (5), while for the staphylococcal strains isolated from patients with primary and secondary community-acquired meningitis, in Iaşi, during 1999-2007, the levels of resistance to oxacillin reached 34.8%.

Other important issues around staphylococcal monitoring are represented by the optimal therapeutic management achievable by utilizing "two tube coagulase" method for rapid identification of *S. aureus* from blood cultures and the efficient policies for methicillin-resistant *S. aureus* infection control in intensive care units (6, 7).

Pointed recently by Karabiber at al., the increase of staphylococcal strains resistance to erythromycin is also revealed in our study (8). On the other hand, the glycopeptide resistance reported by Goldstein et al. or Biavasco et al. was not identified in the present study (9, 10).

## CONCLUSIONS

The oxacillin-susceptibility of the staphylococci determining meningitis decreased progressively from 95% to 74% and, during the last years, to 66%. The erythromycin susceptibility fell from 73% to 30% during the past 7 years. The same situation was recorded for rifampin-susceptibility of the staphylococcal strains isolated (decreasing from 80% to 70%) but an even more dramatically change in susceptibility was outlined to lincomycin (decreasing from 93% to 48%). The susceptibility to gentamycin decreased from 93% to 78%, and that to kanamycin – from 79% to 39%.

During the past years, there could be observed slight increases in resistance to the last introduced antibacterial drugs for the staphylococci determining meningitis: ceftriaxone – 13%, ofloxacin – 13% and sulbactam-ampicillin mixture – 17.4%.

Identifying the characteristics and the susceptibility of the staphylococcal strains determining community-acquired meningitis remains an important issue in the treatment management and patient prognostic.

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