



ANTIMICROBIAL TREATMENT FOR INFECTIONS DUE TO BETA-HEMOLYTIC GROUP A STREPTOCOCCI

Gavriliu Liana-Cătălina, Popescu G. A., Popescu Cristina, Streinu-Cercel A.

National Institute of Infectious Diseases "Prof. Dr. Matei Balș", University of Medicine and Pharmacy "Carol Davila" Bucharest, Romania

Abstract. Group A beta-hemolytic streptococcus is responsible for a variety of infections in humans and is frequently involved in the etiology of bacterial tonsillitis. Its resistance to macrolides is a growing public health problem. **Objectives:** to analyse the antimicrobial susceptibility rate of group A beta-hemolytic streptococcus and to evaluate its temporal evolution, especially for macrolides. **Methods:** We analysed the antimicrobial susceptibility tests for group A beta-hemolytic streptococci isolated from patients hospitalized in the National Institute of Infectious Diseases "Prof. Dr. Matei Balș", during July 2009 -June 2010. The temporal evolution of the antimicrobial resistance was studied for the two semesters of the analyzed period, and the evolution of macrolide resistance was further analyzed for shorter periods (four quarters). **Results:** 172 bacterial strains were analyzed; most of them were isolated from pharyngeal swabs (88.37%). For five classes of antibiotics the susceptibility rate was 100%: penicillin, glycopeptides, linezolid, rifampin, trimethoprim-sulfamethoxazole. Lower rates of susceptibility were found to macrolides (86.47%), clindamycin (85%), fluoroquinolones (98.65%), cyclins (26.16%). The temporal evolution of the susceptibility had no statistical significance for any of the antibiotics that have shown activity under 100% (fluoroquinolones: $p = 0.38$, macrolides: $p = 0.30$, clindamycin: $p = 0.28$). **Conclusions:** Penicillin remains the antibiotic of choice for the treatment of beta-hemolytic group A streptococcal infections. The current resistance level of beta-hemolytic streptococci to macrolides and clindamycin requires the limitation of their use and, pending the regaining of their efficiency, other therapeutic solutions need to be defined. **Keywords:** antimicrobial resistance, macrolides, beta-hemolytic group A streptococci

Introduction

Beta-hemolytic group A streptococcus (BH-GAS) is responsible for a variety of infectious diseases with severity ranging from mild infections (skin and soft tissue infections, tonsillitis) to invasive life-threatening infections (necrotizing fasciitis, toxic shock syndrome). It is the most common bacterial etiology of tonsillitis, accounting for 15-30% of the cases in pediatric patients and 5-10% in adults [1]. Although it remains susceptible to penicillin, this being the first choice therapy for infections with this etiology, BHGAS resistance to macrolides, which

are the alternative therapeutic option, is a cause of concern for clinicians all over the world. High levels of resistance are mentioned in France (23%) [2], in Portugal (11%) [2], in Japan (16.2%) [3], peaking at over 95% in a recent study in China [4].

Objectives

This paper aims to analyze the antibiotic resistance of BHGAS strains isolated from varied septic foci. A particular objective was to evaluate the proportion and temporal evolution of resistance to macrolides.

Methods

We conducted a non-interventional, cross-sectional study with the purpose to analyse BHGAS

Liana Gavriliu

1 Dr. Calistrat Grozovici Str., Sector 2, București

e-mail: lianagavriliu@yahoo.com

susceptibility to antimicrobials, using real-life data provided by the microbiology laboratory. The BHGAS strains were isolated from patients hospitalized in National Institute of Infectious Diseases „Prof. Dr. Matei Balș“, during July 1st, 2009- June 30, 2010.

After the exclusion of the identical strains isolated from the same patient over a period less than 4 weeks or from more septic foci simultaneously (duplicated strains), the 172 remaining strains of BHGAS were investigated. The antimicrobial susceptibility tests were performed with disk diffusion method for 169 strains and with a semi-automated method (Vitek) for 3 strains.

In order to observe any significant changes in the antimicrobial susceptibility profile of BHGAS, two time periods were analyzed: T1 (July-December 2009), T2 (January-June 2010). For macrolides, an additional analysis has been conducted for narrower intervals of time, three months each (T1A: July-September 2009, T1B: October-December 2009, T2A: January to March 2010, T2B: April-June 2010) in order to evaluate any seasonal variations of BHGAS macrolide resistance.

Statistical analysis of the collected data was performed with EpiInfo software 3.4.3. Differences in resistance rates were evaluated using relative risk and 95% confidence interval. P value <0.05 was considered significant.

Results

The distribution and proportion of BHGAS isolates

172 BHGAS non-duplicate strains were analysed, divided between the two studied intervals, as follows: T1- 76 strains, T2- 96 strains.

BHGAS strains represented 76.44% of all the beta-hemolytic streptococci strains isolated. The other isolates belonged to the beta-hemolytic group B streptococci: 45 strains (20%), group D: 4 strains (1.77%), group F: 1 strain (0.44%), group G: 3 strains (1.33%) (Figure 1).

Septic foci that provided BHGAS strains

In most cases, the isolation of BHGAS strains was achieved from pharyngeal swabs obtained from patients with acute pharyngitis: 152 strains (88.37%) for the entire period. Other septic foci were represented by infected wound secretions: 13 strains (7.55%), deep collections: 2 strains (1.16%), blood cultures: 2 strains (1.16%) and other pathological products: 3 strains (1.74%) (Figure 2).

Antimicrobial susceptibility of BHGAS

The list of antimicrobials used for the susceptibility tests varied slightly during the 12 months study

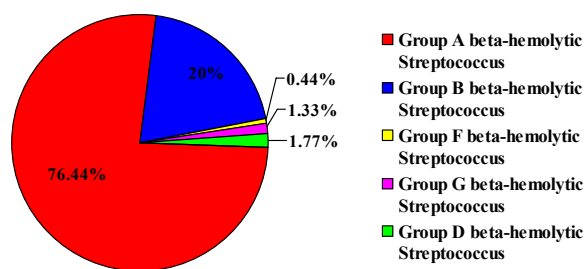


Figure 1. The proportion of BHGAS isolates compared to other beta-hemolytic streptococci

Legend: From all the isolated beta-hemolytic streptococci, BHGAS represented 76.44%

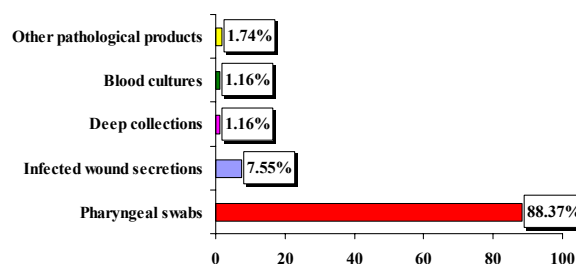


Figure 2. The clinical specimens that provided BHGAS strains

Legend: In most cases, the isolation of BHGAS strains was achieved from pharyngeal swabs: (88.37%). Other septic foci were represented by infected wound secretions: 7.55%, deep collections: 1.16%, blood cultures: 1.16%, other pathological products: 1.74%

period, due to the shortage of some antibiotic disks, but almost all the strains were tested to the antimicrobials with epidemiological and clinical relevance: penicillin, macrolides, clindamycin, levofloxacin, rifampin, glycopeptides, linezolid, cyclins (tetracycline, doxycycline), trimethoprim-sulfamethoxazole. We did not consider for analysis the antimicrobials with risk of severe adverse reactions (phenicols), or without clinical significance because of the level of susceptibility to penicillin (cephalosporins).

BHGAS antimicrobial susceptibility analysis throughout the entire period of the study revealed the following aspects (Figure 3):

- All the investigated strains were susceptible to penicillin
- We also did not record any strains resistant to trimethoprim-sulfamethoxazole, linezolid, glycopeptides and rifampin
- All, but one of the 74 strains tested, showed susceptibility to fluoroquinolones (98.65%)
- From the 170 isolates tested, 147 (86.45%) showed susceptibility to macrolides.
- From 68 of the 80 strains tested for clindamycin (85%) were susceptible.

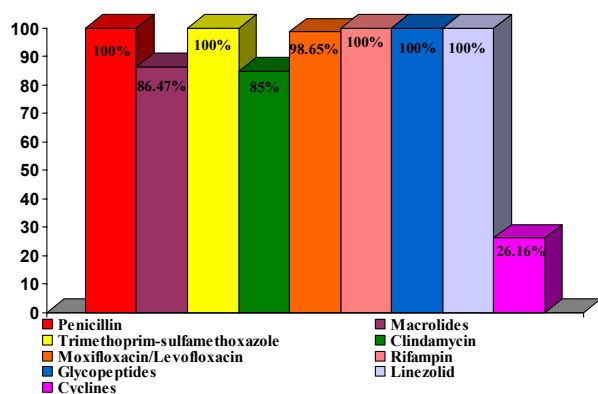


Figure 3. Antimicrobial susceptibility rates of BHGAS for the entire study period

Legend: The antimicrobial susceptibility rates for the entire study period were: 100% for penicillin, trimethoprim-sulfamethoxazole, linezolid, glycopeptides, rifampin; 98.65% for fluoroquinolones, 86.47% for macrolides, 85% for clindamycin and 26.16% for cyclines

- The susceptibility to the tested cyclins (tetracycline, doxycycline) was 26.16%

The analysis of the results for the strains which were tested simultaneously to macrolides and clindamycin indicated the presence of 11 strains resistant to both clindamycin and macrolides (phenotype MLS) and 2 strains resistant only to macrolides (phenotype M). Unfortunately, too few strains were tested for resistance to clindamycin, which makes impossible a meaningful assessment of the proportion of these phenotypes. Indeed, when we compared the confidence interval of susceptibility for both antimicrobials, we found an insignificant difference: clindamycin (75.59%; 91.21%), macrolides (80.52%; 90.81%).

In order to highlight the emergence of any significant changes in BHGAS antimicrobial susceptibility rates to the antibiotics with less than 100% susceptibility, we analyzed its temporal evolution between the two periods of study, pointing out the following facts:

- The proportion of fluoroquinolone-susceptible strains was 97.44% for the T1 period (1 resistant strain) and 100% for T2 ($p = 0.38$)
- The susceptibility to cyclins was low (26.67% for T1 and 27.59% for T2)
- We noted a decreasing susceptibility to clindamycin from 92.11% (T1) to 83.33% (T2), with no statistical significance ($p = 0.28$).
- There was a lower rate of BHGAS macrolide susceptibility (89.48% for the period T1, 84.05% for the period T2), with no statistical significance ($p=0.30$).

For macrolides, the second choice for the treatment of streptococcal tonsillitis and, especially for the patients with allergy to betalactams, we analyzed

the evolution of the antimicrobial susceptibility rates for four narrower intervals (three months each), in order to observe any significant changes or important seasonal variations of the susceptibility pattern (T1A: July- September 2009, T1B: October-December 2009, T2A: January-March 2010, T2B: April-June 2010).

Under the reservation of a very limited number of isolates tested for T1A and T2B, we found a decreasing susceptibility of BHGAS to macrolides from 100% (T1A), to 89.05% (T1B), 82.09% (T2A) and 88.89% (T2B). However there were no statistically significant differences for any of the analyzed pairs of intervals: T1A-T1B ($p=0.54$), T1B-T2A ($p=0.24$), T2A-T2B ($p=0.41$). Also, there were no significant differences between the rate of SBHA resistance strains isolated in the two cold seasons (17.14%) contained in the analyzed period (when an increase in macrolides consumption and consecutively in macrolide-resistance would be expected) compared to the two warm seasons (11%): T1A + T2B versus T1B + T2B, $p=0.53$.

Discussions

Antimicrobial resistance is an important problem for the therapeutic management of the patients with infectious diseases, regardless of their etiology. Therefore it is important to know the antimicrobial susceptibility patterns in order to be able to define useful alternative treatment options.

Therapeutic options for streptococcal infections include penicillin, cephalosporins (for patients with allergy to penicillin, except for those with immediate-type hypersensitivity to betalactam antibiotics) as well as macrolides, or clindamycin for the patients with allergy to betalactams [5,6].

BHGAS is a germ that preserved its susceptibility to penicillin and this was also the case in our study, therefore, penicillin remains the first line regimen for the treatment of the infections caused by BHGAS.

This fact does not apply for other antimicrobials. In our study we found susceptibility rates of less than 100% for several antibiotics.

The extremely low level of susceptibility to the tested cyclins (tetracycline, doxycycline) makes this class of antibiotics useless for treatment of infections caused by BHGAS.

We found only one strain of BHGAS resistant to fluoroquinolones. This situation is similar with the one noted several years ago (2005-2006) by Gracia et al in a study conducted in Europe, in which they found a 100% susceptibility rate of BHGAS to this class of antibiotics [7].

We also found susceptibility rates of 86.45% to macrolides and 85% to clindamycin, the two

alternative antimicrobials used for patients with allergy to penicillin who develop a streptococcal infection. The resistance of BHGAS to macrolides is a problem noticed all over the world. Recent data show higher resistance rates for some regions than the one found in our study (for example in France: 23%, Japan: 16.2%, China: 95%) [2, 3, 4], and lower in other regions (for example in Portugal: 11%) [2]. An analysis regarding the antimicrobial resistance of BHGAS conducted between 2005 and 2006 in several European countries showed a susceptibility rate of 91.7% to macrolides in Romania, this level being very close to the one found in our study. Higher levels of susceptibility were found only in Baltic countries (95.9%), and lower levels were noted in Poland (83%), Hungary (73.3%), Slovakia (66%), and Czech Republic (79.8%) [7]. The difference in macrolide susceptibility rates between various geographic regions could be correlated with differential antibiotic consumption; recent studies emphasize direct association between the resistance selection pressure exerted by the antibiotic consumption nationwide [8].

The limitations of the study were related to the small number of the tested strains and the lack of information that could provide data about the association between the previous antibiotic use and bacterial resistance.

The study highlights the necessity to keep on monitoring the antimicrobial susceptibility pattern of this bacteria, the temporal evolution of the resistance for wider periods of time, and the necessity to promote rational prescribing of the antimicrobials in order to prevent further increasing of the resistance rates.

Conclusions

1. Penicillin remains the treatment of choice for infections caused by BHGAS, all strains showing in vitro susceptibility to this antibiotic.

2. There were no resistant isolates to glycopeptides, linezolid, rifampin and trimethoprim-sulfamethoxazole identified.

3. Susceptibility rates below 100% were recorded for macrolides, clindamycin, fluoroquinolones and cyclins.

4. Although the resistance of BHGAS to macrolides and clindamycin may not be yet a clinically

significant issue in our country compared to other regions, the decreased susceptibility of BHGAS to these antibiotics highlights the need for an antimicrobial stewardship for community-acquired infections in order to preserve the usefulness of these therapeutic options for patients who are allergic to betalactams and who develop a streptococcal infection, and also highlights the need for a continuous monitoring of the susceptibility pattern of BHGAS.

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