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Beta hemolytic *Streptococci* strains isolated from clinical specimens, their characteristics and antibiotic susceptibility

Klinik örneklerden izole edilen beta-hemolitik *Streptokok* suşları, özellikleri ve antibiyotik duyarlılığı

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Abstract

Aim: Beta Hemolytic Streptococcus (BHS) species play a role in many infections, such as urinary tract infection, skin/soft tissue infections, neonatal meningitis, sepsis, pneumonia as well as upper respiratory tract infections like tonsillopharyngitis. The aim of this study was to determine the types of BHS species, their infectious characteristics and antibiotic susceptibility profiles in clinical specimens.

Methods: In this cross-sectional study, infectious features of 1276 streptococcus strains isolated from 1110 (87%) outpatients and 166 (13%) inpatients between January 2014 and June 2019 at our laboratory and antimicrobial susceptibility of the 320 strains were analyzed retrospectively.

Results: Retrospective analysis of 1276 BHS isolates revealed that 48.6% were group B, 33.9% were group A, 9.6% were group F, 5.7% were group C and 2.2% were group G BHS. Among isolated BHS infections, 42.9% caused urinary tract infection, 34.6% caused tonsillitis/tonsillopharyngitis, 15.7% were isolated from skin/soft tissue infections, 3% were found in the bloodstream, and 1% in meningitis, pneumonia, conjunctivitis, and peritonitis. About 2.8% Group B Streptococcus were considered vaginal colonization. Among all patients, 11.2% had more than one underlying disease. All isolates were susceptible to penicillin, vancomycin, linezolid and tigecycline. Erythromycin, clindamycin, and tetracycline resistance rates were determined as 5%, 2%, 40% respectively for Group A and 34%, 11%, 90%, respectively for Group B Streptococcus.

Conclusion: Early diagnosis and appropriate antibiotherapy are important parameters in the management of streptococcal infections. Although there is no penicillin resistance in beta-hemolytic *streptococci*, we think that antibiotic susceptibility should be closely monitored due to increasing clinical failures, penicillin Minimal inhibitory concentration (MIC) values, and macrolide and fluoroquinolone resistance, especially in Group B Streptococcus.

Keywords: Antibiotic susceptibility, Infection, Beta hemolytic Streptococcus spp

Öz

Amaç: Beta Hemolitik Streptococcus (BHS) türleri, idrar yolu enfeksiyonu, cilt/yumuşak doku enfeksiyonları, tonsillofarenjit gibi üst solunum yolu enfeksiyonları, yenidoğanda menenjit, sepsis ve pnömoni gibi birçok enfeksiyonda rol oynar. Bu çalışmanın amacı klinik örneklerden izole edilen BHS türlerini, enfeksiyon özelliklerini ve antibiyotik duyarlılık profillerini belirlemektir.

Yöntemler: Laboratuvarımızda Ocak 2014 - Haziran 2019 tarihleri arasında, 1110 (%87) ayaktan ve 166 (%13) yatarak tedavi gören hastadan izole edilen 1276 beta hemolitik streptokok (BHS) suşu, özellikleri ve 320 suşun antimikrobiyal duyarlılığı retrospektif olarak incelendi. Çalışmanın tipi kesitsel çalışmadır.

Bulgular: Toplam 1276 BHS izolatının; %48,6 grup B, %33,9 grup A, %9,6 grup F, %5,7 grup C ve %2,2 grup G BHS idi. İncelenen BHS enfeksiyonlarının; %42,9'u idrar yolu enfeksiyonu, %34,6'sı tonsillit/tonsillofarenjit, %15,7'si cilt/yumuşak doku enfeksiyonu, %3'ü kan dolaşımı enfeksiyonu ve %1'i menenjit, pnömoni, konjonktivit ve peritonit idi. %2,8 Grup B Streptokok izolatı vajinal kolonizasyon olarak kabul edildi. Hastaların %11,2'sinde birden fazla altta yatan hastalık vardı. Tüm izolatlar penisilin, vankomisin, linezolid ve tigesikline duyarlıydı. Eritromisin, klindamisin ve tetrasiklin dirençi Grup A Streptokok ve Grup B Streptokok için sırasıyla %5, %2, %40 ve %34, %11, %90 olarak belirlendi.

Sonuç: Erken tanı ve uygun antibiyoterapi streptokok enfeksiyonlarının tedavisinde önemli parametrelerdir. Beta-hemolitik streptokoklarda penisilin direnci olmasa da, klinik başarısızlıkların varlığı, özellikle Grup B Streptokok 'da penisilin Minimal İnhibitör Konsantrasyonu (MİK) değerlerinin artışı, makrolid ve florokinolon direncinin artması nedeniyle antibiyotik duyarlılığının yakından izlenmesi gerektiğini düşünüyoruz.

Anahtar kelimeler: Antibiyotik duyarlılığı, Enfeksiyon, Beta hemolitik Streptococcus spp

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Introduction

Streptococcus spp are common in nature. They can also be found in the normal flora of the human mouth, pharynx, lower gastrointestinal tract and vagina. *Streptococci* can cause serious life-threatening infections such as necrotizing fasciitis, endocarditis, newborn meningitis, sepsis and pneumonia, as well as upper respiratory infections such as tonsillopharyngitis. Among *streptococci*, beta hemolytic *streptococci* (BHS) constitute an important group causing invasive infections. They are divided into sera-groups (A through H and K through V) by antigenic differences in their cell wall carbohydrates by Lancefield, and the most common causative agents of infection in humans are the A, B, C and G groups [1]. The increase in invasive BHS infections worldwide has increased the importance of early diagnosis and treatment in life-threatening infections [2,3]. In this study, we aimed to evaluate the clinical characteristics and determine the antibiotic susceptibility patterns of patients with BHS isolated in their clinical specimens.

Materials and methods

In this study, infectious features of 1276 streptococcus strains isolated from 1110 (87%) outpatients and 166 (13%) inpatients between January 2014 and June 2019 at the medical microbiology laboratory of our hospital and antimicrobial susceptibility of the 320 strains were analyzed retrospectively.

Samples were fixed in 5% sheep blood agar medium and placed in a waxed jar, which would provide 5-10% CO2 medium, and incubated in 37 °C oven for 24 hours. At the end of incubation, colonies with β-hemolysis were evaluated. Of these colonies, gram positive cocci that formed chains and were negative for catalase were grouped with streptococcal slide agglutination kit (Streptococcal latex test, Plasmatec, UK). 5% sheep blood Müeller Hinton Agar was used for antibiotic susceptibility test. The prepared suspension from 24-hour pure cultures of strains at 0.5 McFarland tube turbidity was spread on the medium. For penicillin G sensitivity, the gradient test strip (ETEST, Biomerieux, France) and discs for other antibiotics (BD BBL Sensi-Disc, USA) were placed in the medium with the help of dispenser at enough distances from each other. The petri dishes were incubated in a 37 °C oven for 24 hours and the disc diffusion results were evaluated by measuring zone diameters. The points where the inhibition ellipse formed around the gradient test strip intersect with the E test strip were determined as the minimum inhibitory concentration (MIC) of the antibiotic. Evaluations were made according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria [4]. Penicillin G MIC values were recorded in all BHS isolates. The highest and lowest MIC values were defined as MIC range. MIC values that inhibited 50% and 90% of BHS growth were considered MIC_{50} and MIC_{90}, respectively. D test was used to determine erythromycin-inducible clindamycin resistance (MLS_B). %5 sheep blood Mueller-Hinton agar, erythromycin (15 µg) and clindamycin (2 µg) discs were placed at a distance of 12-15 mm between the outer edges of each other. Inducible MLS_B was defined as a bulging on the side facing erythromycin within the clindamycin zone and D test was considered positive. If the strains were resistant to both erythromycin and clindamycin, they were regarded as $CMLS_B$ phenotype. The M phenotype was considered erythromycin-resistant and clindamycin-susceptible if there was no bulging on the zone [5].

Statistical analysis

The total number of beta hemolytic streptococci, the biological samples they produced within the specified period and antibiotic susceptibility were calculated and percentages were found for each.

Results

Among 1276 strains in the study, 48.6% (n=620) were as Group B Streptococcus (GBS), 33.9% (n=432) were Group A Streptococcus (GAS), 9.6% (n=123) were Group F Streptococcus (GFS), 5.7% (n=73) were Group C Streptococcus (GCS) and 2.2% (n=28) were defined as Group G Streptococcus (GGS) (Figure 1). Among determined BHS infections, 42.9% (n=547) were urinary tract infections, 34.6% (n=441) were tonsillitis/tonsillopharyngitis, 15.7% (n=200) were skin/soft tissue infections, 3% (n=39) were bloodstream infections, and 1% (n=13) were meningitis, pneumonia, conjunctivitis and peritonitis (Table 1). Among GBS isolates, 2.8% (n=36) were considered vaginal colonization.

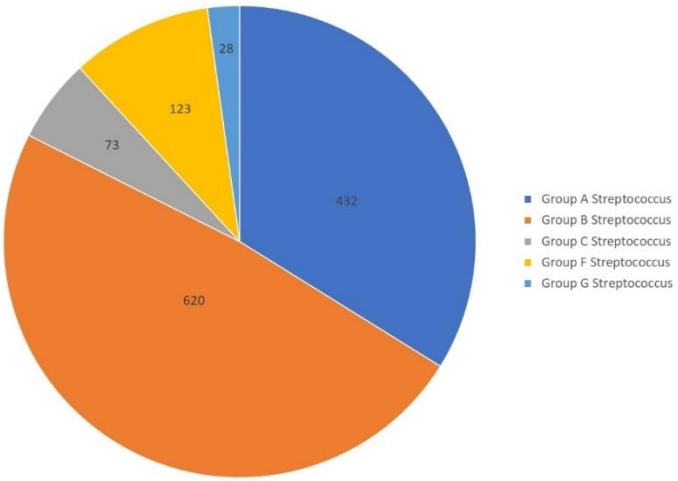

Figure 1: Distribution of *Streptococci* subgroups

Upon evaluation of the reproduction of BHS in blood and cerebrospinal fluid (CSF) samples, which were considered invasive infections, 42 (3.3%) patients had sepsis/bacteremia and meningitis. Seven of these patients had neonatal sepsis and 3 had neonatal meningitis. Diagnoses of inpatients were skin and soft tissue infection in 45.7%, sepsis/bacteremia in 23.4%, genitourinary tract infection in 21.9%, respiratory tract infection in 6%, meningitis in 1.8%, conjunctivitis and peritonitis in 1.2%. Outpatients included in the study were diagnosed with genitourinary system infection (48.8%), tonsillitis/tonsillopharyngitis (37%) and skin and soft tissue infections (14.2%).

Table 1: Distribution of isolated BHS strains

Material	GAS (n=432)	GBS (n=620)	GCS (n=73)	GFS (n=123)	GGS (n=28)	Total (n=1276)
Throat	312	2	30	79	18	34.6% (n=441)
Urine	9	533	0	5	0	42.9% (n=547)
Tissue /Abscess	94	25	43	30	8	15.7% (n=200)
Blood	8	21	0	8	2	3.0% (n=39)
Vagina	0	36	0	0	0	2.8% (n=36)
Sputum	8	0	0	0	0	0.06% (n=8)
CSF	0	3	0	0	0	0.02% (n=3)
Sterile body fluid	1	0	0	1	0	0.02% (n=2)

CSF: Cerebrospinal fluid

The rate of patients with more than one underlying disease was 11.2% (n=143). It was diabetes in 32.2% (n=46), kidney and ureteral stones in 21% (n=30), trauma and surgery in 20.3% (n=29), malignancy in 16% (n=23), renal failure in 6.3% (n=9), autoimmune diseases in 3.5% (n=5) and HIV in 0.7% (n=1). Among 9992 throat cultures, 4.4% (n=437) had BHS growth. Among strains, 70.5% were GAS, 18.0% were GFS, 6.9% were GCS, 4.1% were GGS, and 0.5% was GBS.

Antibiotic susceptibility testing was performed for 200 GBS, 100 GAS and 20 GCS, GGS, and GFS BHS isolates over a five-year period. All isolates studied for antibiotic susceptibility were susceptible to penicillin, vancomycin, teicoplanin, linezolid and tigecycline. Penicillin G minimal inhibitory concentration (MIC) results of 320 BHS strains and their erythromycin, clindamycin, tetracycline, levofloxacin, and nitrofurantoin disc diffusion results are shown in Table 2. Since all BHS isolates were susceptible to vancomycin, teicoplanin, tigecycline and linezolid by disc diffusion method, they are not shown in table 2. In five erythromycin resistant GAS, two $CMLS_B$, two M phenotypes and one $IMLS_B$ were identified. Sixty-eight erythromycin resistant GBS isolates consisted of 38 $IMLS_B$, 21 $CMLS_B$ and 9 M phenotypes. One $CMLS_B$ was detected among GCS and two $CMLS_B$ and one M phenotype were identified among three erythromycin resistant GGS.

Table 2: Antimicrobial resistance pattern in Beta-hemolytic *Streptococci* (n=320)

	MIC value (µg/ml)			Disc diffusion		
	MIC range	MIC_{50}	MIC_{90}	Susceptible (%)	Intermediate (%)	Resistant (%)
GAS (n=100)						
Penicillin G	0.004-0.047	0.008	0.023	100	-	-
Erythromycin	-	-	-	95	0	5
Clindamycin	-	-	-	98	0	2
Tetracycline	-	-	-	54	6	40
Levofloxacin	-	-	-	97	2	1
Nitrofurantoin	-	-	-	100	0	0
GBS (n=200)						
Penicillin G	0.016-0.125	0.047	0.094	100	-	-
Erythromycin	-	-	-	64	2	34
Clindamycin	-	-	-	89	0	11
Tetracycline	-	-	-	9.5	0.5	90
Levofloxacin	-	-	-	74	1	25
Nitrofurantoin	-	-	-	99	0	1
GCS (n=4)	-					
Penicillin G	0.012-0.047	0.012	0.032	100	-	-
Erythromycin	-	-	-	75	0	25
Clindamycin	-	-	-	75	0	25
Tetracycline	-	-	-	50	0	50
Levofloxacin	-	-	-	100	0	0
Nitrofurantoin	-	-	-	100	0	0
GFS (n=8)	-					
Penicillin G	0.016-0.047	0.023	0.023	100	-	-
Erythromycin	-	-	-	100	0	0
Clindamycin	-	-	-	100	0	0
Tetracycline	-	-	-	50	0	50
Levofloxacin	-	-	-	100	0	0
Nitrofurantoin	-	-	-	100	0	0
GGS (n=8)	-					
Penicillin G	0.008-0.047	0.012	0.016	100	-	-
Erythromycin	-	-	-	62.5	0	37.5
Clindamycin	-	-	-	75	0	25
Tetracycline	-	-	-	50	0	50
Levofloxacin	-	-	-	100	0	0
Nitrofurantoin	-	-	-	100	0	0

GAS: Group A Streptococcus, GBS: Group B Streptococcus, GCS: Group C Streptococcus, GFS: Group F Streptococcus, GGS: Group G Streptococcus, MIC: Minimal inhibitory concentration

Discussion

In this study, we analyzed the general clinical features and antibiotic susceptibility pattern of BHS in a tertiary center and determined that the most common isolates were GBS and GAS; the most common infections were urinary tract infection and tonsillitis/tonsillopharyngitis, and among throat cultures the most common group was GAS. All BHS isolates were susceptible to vancomycin, teicoplanin, linezolid and tigecycline.

Invasive GAS infections continue to be associated with increased morbidity and mortality rates worldwide. There are an estimated 10649- 13434 cases in the United States that result in 1136-1607 deaths each year. It is similar to the incidence of invasive GAS in Canada (4.3/100000) and to many European countries (2–4/100000). In the same study, they found that in the presence of underlying comorbid diseases, mortality rates increased in elderly and long-term patients in nursing homes [6]. In another study, it was emphasized that bacteremia due to GAS most commonly developed secondary to soft tissue infections, and diabetes mellitus was the most common comorbidity [7]. Similarly, in our study, diabetes was the most common comorbidity for all infections. In another study examining GAS, GBS, GCS and GGS bacteremia, cardiovascular diseases, malignancy, and diabetes mellitus were the most common underlying diseases. They concluded that the most common infection was skin/soft tissue infections and moreover, urinary tract infections were more common in the GBS group (12.4%) than the other groups [8]. In a study of Topkaya et al. [9] including 46 microbiology laboratories from different regions, only 65 invasive GAS isolates were identified within a year, and they concluded that invasive GAS infection incidence was low in Turkey. We detected invasive BHS infections in 3.3% of 1276 streptococcus strains. In a recent meta-analysis, clarithromycin was reported as a valid, effective, and largely well-tolerated treatment option for GAS pharyngitis patient who cannot benefit from other agents [10]. In our study, in five erythromycin resistant GAS, two $CMLS_B$, two M phenotypes and one $IMLS_B$ were identified.

In the study conducted by Unlu et al. [11], 9 (5.6%) of the 161 *streptococci* strains isolated from the throat samples were GAS, 64 (39.7%) were GBS, two (1.2%) were GCS and three (1.8%) Type D, two (1.2%) GGS, 57 (35.4%) were viridians *streptococci* and 24 (14.9%) were pneumococci. Among isolated *streptococci*, the most common infections were urinary tract infections (n=52; 32.2%), skin/soft tissue infection (n=48; 29.8%) and pneumonia (n=25; 15.5%). They detected more than one underlying disease in 87 (54%) patients. Penicillin resistance was found to be 0% and 4.9% in GAS and GBS isolates, respectively. Similarly, in our study, the most frequently isolated group was GBS, and the most common infections were urinary tract infection and skin/soft tissue infection. In our study, an underlying disease was detected in 11.2% of the patients, while this rate was 54% in the above-mentioned study. In our study, the absence of *viridians streptococci* and *pneumococci*, and the inclusion of throat samples may cause this rate to be low. Almost all of our throat specimens were isolated from outpatients who had no underlying disease. In recent years, GBS has been identified as one of the most common pathogens responsible for maternal and neonatal infections.

Although there is not enough data about GBS colonization in developing countries, it is known that 20-30% of women are colonized by GBS in developed countries. Maternal intrapartum GBS colonization is the primary risk factor for early-onset GBS infection in infants. It is estimated that 1-2% of infants born from colonized mothers with GBS will develop early-onset GBS infection, including neonatal pneumonia, sepsis and meningitis, when untreated or inadequate measures are

taken. Severe GBS infections may result in neonatal mortality or permanent damage [12]. In a study of Karadag et al. [13] GBS colonization was detected in 3% of 300 pregnant women in labor in Turkey. Antibiotic susceptibilities of the strains isolated in the same study were studied. While resistance to penicillin G, ampicillin, meropenem and vancomycin was not detected, they found 89% resistance to tetracycline and 22% resistance to erythromycin and clindamycin. In the study of Karadeniz et al. [14], the prevalence of GBS was found to be 8% in pregnant women and 5% in newborn babies, and they reported that none of the newborns with GBS colonization developed infection in one month following birth. In our study, three neonatal meningitis and seven newborn sepsis cases due to GBS were detected. However, colonization in mothers is unknown. In our study, in almost all patients with streptococcal genitourinary tract infection, GBS were found responsible. The presence of an underlying urological pathology was found in many of the cases followed up for urinary tract infections. In a study of Shayanfar et al. [15], the prevalence of GBS in females with urinary tract infection was 8.92% and GBS was highly susceptible to cephalothin, norfloxacin, ampicillin, nitrofurantoin and vancomycin. In our study, GBS isolates were highly susceptible to Penicillin G, nitrofurantoin and clindamycin.

In recent years, the incidence of invasive infections involving GCS and GGS has increased. They lead to clinical infection presentations like GAS [16]. In our study, GCS and GGS were isolated from soft tissue infections, similar to GAS. Bacteremia due to GGS was secondary to the internal prosthesis device. In a recent study from India, Srilaka et al. [17] reported that the highest percentage of *streptococci* isolated was from throat swabs (35.5%), followed by sputum (15.9%), urine (14.1%), blood (10.5%), pus(8.6%), cerebrospinal fluid (6.4%), bronchoalveolar lavage (5.9%) and endotracheal tips (3.2%). The highest percentage of BHS belongs to GCS (74, 33.6%), followed by GGS (51, 23.2%), GBS (42, 19.1%), GFS (28, 12.7%), GAS (21, 9.5%) and GDS (4, 1.8%). Shahin et al. [18] reported that GCS, GFS, and GGS were common pathogens in patients with an underlying malignancy, and they are usually associated with other pathogens requiring combinatorial therapeutic strategies.

In our study, it was found that 31.6% (n=25) of GFS positive throat isolates were from Family Medicine clinics and isolated from routine samples taken during the recruitment examinations. This may suggest that GFS are colonized in the throat and not clinically important in this population. However, lung abscess associated with GFS has been reported in literature and for that reason, clinicians should be aware of more dangerous infections associated with GFS [19].

All BHS were susceptible to penicillin. In a recent review, after 70 years of use, penicillin was still defined as universally active against GAS, GCS and GGS. However, therapeutic failures were recorded in 2-28% of pharyngitis cases [20]. On the other hand, GBS with reduced susceptibility to penicillin were described in previous literature [21]. Levofloxacin resistance in GBS may also cause important clinical problems in future. In this study we defined a high levofloxacin resistance rate of 25% in GBS. Previously some genetic mutations were reported to be associated with fluoroquinolone resistance in GBS [22]. Lee et al. [23] reported the levofloxacin resistance as 4.8% in 188 GBS isolates. However, Wang et al. [24] reported that 40 GBS isolates recovered from infected neonates less than 3 months of age were susceptible to levofloxacin. Recently Seki et al. [21] reported an increased tendency to multidrug resistance (to both macrolides and fluoroquinolones) reaching approximately 10% in GBS.

Limitations

There are some limitations of this study. First this is a single center, retrospective study. Secondly, the number of isolates with antibiotic susceptibility results was low. Although penicillin resistance was not found in among BHS, we think that antibiotic susceptibility should be closely monitored due to the increased clinical failures, penicillin MIC values, macrolide, and fluoroquinolone resistance, especially in GBS.

Conclusions

As a result, infections due to *streptococci* may be seen in a wide variety ranging from tonsillitis, tonsillopharyngitis, necrotizing fasciitis, and sepsis to invasive infections such as meningitis. These invasive infections may result in serious mortality and morbidity, especially in the presence of underlying comorbid diseases. Early diagnosis and appropriate antibiotherapy are important parameters in the management of streptococcal infections. It should be noted that soft tissue infections such as surgical site infection and necrotizing fasciitis due to GAS may progress rapidly. Newborn infections are especially important for GBS. Therefore, vaginal and rectal colonization should be investigated during pregnancy and necessary precautions should be taken according to the result.

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