

ANTIBIOTIC SUSCEPTIBILITY PATTERNS AND PREVALENCE OF GROUP B *STREPTOCOCCUS* ISOLATED FROM PREGNANT WOMEN IN MISIONES, ARGENTINA

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Submitted: July 31, 2007; Returned to authors for corrections: November 22, 2007; Approved: May 05, 2008.

ABSTRACT

This study was performed to determine the susceptibility patterns and the colonization rate of Group B *Streptococcus* (GBS) in a population of pregnant women. From January 2004 to December 2006, vaginal-rectal swabs were obtained from 1105 women attending Dr. Ramón Madariaga Hospital, in Posadas, Misiones, Argentina. The carriage rate of GBS among pregnant women was 7.6%. A total of 62 GBS strains were randomly selected for *in vitro* susceptibility testing to penicillin G, ampicillin, tetracycline, levofloxacin, gatifloxacin, ciprofloxacin, quinupristin-dalfopristin, linezolid, vancomycin, rifampicin, trimethoprim-sulfamethoxazol, nitrofurantoin, gentamicin, clindamycin and erythromycin, and determination of resistance phenotypes. No resistance to penicillin, ampicillin, quinupristin-dalfopristin, linezolid, and vancomycin was found. Of the isolates examined 96.8%, 98.3%, 46.8%, and 29.0% were susceptible to rifampicin, nitrofurantoin, trimethoprim-sulfamethoxazol and tetracycline, respectively. Rank order of susceptibility for the quinolones was: gatifloxacin (98.4%) > levofloxacin (93.5%) > ciprofloxacin (64.5%). The rate of resistance to erythromycin (9.7%) was higher than that of other reports from Argentina. High-level resistance to gentamicin was not detected in any of the isolates. Based on our finding of 50% of GBS isolates with MIC to gentamicin equal or lower than 8 µg/ml, a concentration used in one of the selective media recommended for GBS isolation, we suggested, at least in our population, the use of nalidixic acid and colistin in selective media with the aim to improve the sensitivity of screening cultures for GBS carriage in women.

Key-words: Group B *Streptococcus*, antibiotic susceptibility, prevalence, pregnant women, Argentina.

INTRODUCTION

Group B *Streptococcus* (GBS) is the most common cause of early-onset neonatal sepsis in developed countries (3).

Newborn acquire the organisms intrapartum from their mothers, who are colonized with GBS in the genital tract (41).

Different studies (10) reported that risk-based or screening-based strategies recommended by the Centers for Disease Control and Prevention (CDC) had caused a significant decline in the prevalence of neonatal GBS infections (9,41).

When public health decisions for implementing prevention strategies are needed, a basic point is the knowledge of the prevalence of maternal GBS colonization.

In Argentina, this prevalence varies widely between geographic areas and even between different populations. For instead, it was reported a maternal colonization rate of 1.4% in Cordoba, Argentina (29), 3.2% in Rosario, Argentina (46), or 18.15% in Jose de San Martin Clinical Hospital (22) and 9.39% in Posadas Hospital (17), both of them situated in Buenos Aires, Argentina.

Dr. Ramón Madariaga Hospital is a public institution that serves primarily the uninsured residents of Posadas, the most important city of Misiones, a province situated in the northeast of Argentina with strong boundaries with Paraguay and Brazil. Although Dr. Ramón Madariaga Hospital accounts for approximately 65% of the city's births, no data are available about the prevalence of maternal GBS carriers.

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Penicillin and ampicillin are the drugs of choice for prevention or treatment of GBS infections, and clindamycin and erythromycin are the recommended alternatives for patients who are allergic to β -lactam agents (41).

Widespread use of these antibiotics in various clinical conditions as well as their accepted efficacy of intrapartum prophylaxis in decreasing early-onset neonatal GBS infections has potentiated the emergence of antibiotic resistance (27). Antibiotic resistance amongst GBS is considered an increasing problem so that it was recommended (31) to test the susceptibility of other antibiotics than those recommended as part to established control measures and that could be used as alternative choices for prophylaxis or treatment of GBS infection.

This study was performed to determine the colonization rate of GBS in a population of pregnant patients at Dr. Ramón Madariaga Hospital in Posadas, Misiones and the susceptibility patterns of the isolates to a variety of antibiotics.

MATERIALS AND METHODS

Bacterial isolates: From January 2004 to December 2006, vaginal-rectal swabs were obtained at 35 to 37 weeks of gestation from 1105 women attending at Dr. Ramón Madariaga Hospital in Posadas; Misiones who agreed to participate in this study.

During the study period, no protocol for prevention of GBS disease, such as routine testing of pregnant women, had been established in the maternity unit of the Hospital.

The samples were collected without speculum. The swabs were placed in Cary-Blair transport media (Difco, Argentina) and transported to the laboratory at room temperature for microbiology analysis. Swabs were inoculated in a selective broth medium, Todd-Hewitt broth supplemented with colistin (10 μ g/ml) and nalidixic acid (15 μ g/ml) (Laboratorios Britania, Argentina) and incubated at 37°C for 24 hours. The broths were then cultured on 5% sheep's blood agar plates (Columbia agar base, Laboratorios Britania, Argentina). Culture plates were incubated at 37°C with 5% CO₂ for 24 hours. All suspected GBS colonies were sub-cultured and isolated for confirmatory testing. Biochemical standard methods were used to identify GBS (22). GBS identification was completed by group B-specific latex agglutination (Slidex Strepto-Kit, bioMérieux, Marcy l'Etoile, France)

Susceptibility testes: A total of 62 GBS strains were randomly selected for *in vitro* susceptibility testing. Susceptibility to penicillin G, ampicillin, tetracycline, levofloxacin, gatifloxacin, ciprofloxacin, quinupristin-dalfopristin, linezolid, vancomycin, rifampicin, trimethoprim-sulfametoxazol and nitrofurantoin was tested using microdilution panels (MicroScan, Dade Behring Inc, USA). Susceptibility to clindamycin and erythromycin and determination of resistance phenotypes were performed by the double-disk test on Mueller-Hinton agar (Biokar, France)

supplemented with 5% sheep blood (12). Disks of erythromycin (15 μ g) and clindamycin (2 μ g) were from Laboratorios Britania, Argentina. The different phenotypes of macrolide-lincosamide-streptogramin B (MLS_B) resistance were recognized as previously described (43). After 24 h of incubation at 35°C, blunting of the clindamycin inhibition zone proximal to the erythromycin disk was taken to indicate inducible macrolide-lincosamide-streptogramin B (MLS_B) resistance. Resistance to clindamycin with no blunting of the clindamycin inhibition zone indicated constitutive resistance. The M phenotype was characterized by susceptibility to clindamycin with no blunting of the inhibition zone around the clindamycin disk. The isolates were considered susceptible or resistant according MIC breakpoints recommended by the Clinical and Laboratory Standards Institute (CLSI) (12). The MIC of gentamicin (Bagó, Argentina) was determined by the agar dilution method according to the guidelines of the CLSI. High-level resistance to gentamicin was defined as a MIC of \geq 500 μ g/ml.

RESULTS

84 of 1105 (7.6%) women tested positive for GBS.

The susceptibilities of the 62 selected isolates to all antibiotics tested except gentamicin are summarized in Table 1. All GBS were susceptible to penicillin G, ampicillin, quinupristin-dalfopristin, linezolid, and vancomycin; and 29.0% were susceptible to tetracycline. 98.3% of the isolates were considered susceptible to nitrofurantoin, 96.8% to rifampicin, and 46.8% to trimethoprim-sulfametoxazol. Rank order of susceptibility for GBS for the quinolones was: gatifloxacin (98.4%) > levofloxacin (93.5%) > ciprofloxacin (64.5%).

Of the 62 isolates, 2 (3.2%) were resistant to clindamycin and 6 (9.7%) were resistant to erythromycin. Among the erythromycin-resistant isolates, 2 expressed the inducible macrolide-lincosamide-streptogramin B (MLS_B) resistance phenotype, 2 the constitutive MLS_B resistance phenotype and 2 the M resistance phenotype.

The gentamicin MIC ranged from 2 to 256 μ g/ml, MIC₉₀ = 64 μ g/ml and MIC₅₀ = 8 μ g/ml. High-level resistance to gentamicin was not detected in any of the isolates.

DISCUSSION

GBS is an important cause of infection in pregnant women and their newborns in many countries, but there are still few data available from Latin America (13,15,45,48). Maternal GBS colonization continues to be the most important risk factor for developing disease in the newborn (6). Implementation of rational GBS disease prevention protocols must be preceded by collection of data at the community level, due to variations in maternal GBS colonization in different populations (50).

Table 1. Antibiotic susceptibility profiles of group B *Streptococcus* isolated from pregnant women in Misiones, Argentina.

Antibiotic	No. (%) of the isolates with indicated response ^a		
	Susceptible	Intermediate	Resistant
Penicillin G ^b	100	-	-
Ampicillin ^b	100	-	-
Clindamycin ^b	96.7	-	3.3
Erythromycin ^b	90.2	-	9.8
Vancomycin ^b	100	-	-
Tetracycline ^b	71.0	-	29.0
Rifampicin ^c	96.8	1.6	1.6
Trimethoprim-sulfametoxazol ^c	46.8	-	53.2
Nitrofurantoin ^d	98.3	1.6	-
Gatifloxacin ^b	98.4	-	1.6
Levofloxacin ^b	93.5	4.8	1.6
Ciprofloxacin ^d	64.5	32.3	3.2
Quinupristin-dalfopristin ^b	100	-	-
Linezolid ^b	100	-	-

^an= 62; ^bClinical and Laboratory Standards Institute (CLSI) breakpoint for *Streptococcus* spp. other than *Streptococcus pneumoniae* (12); ^cCLSI breakpoint for *S. pneumoniae* (12); ^dCLSI breakpoint for *Enterococcus* spp. (12).

The prevalence of maternal colonization by GBS depends on the culture methods, including the number and type of sites cultured and type of medium used, time of pregnancy, race, origin, age, parity and social-economic level (26). In Argentina the prevalence of GBS in pregnant women varies from 1 to 19% (2,8,14,17,22,29,34,36,46).

The carriage rate of GBS among pregnant women in the present study was 7.6%. Due to the differences of the population size and socio-economic status in each study, it is difficult to determine if the difference on GBS colonization rates between the Argentinean study groups are due to genetic differences between the populations or the uneven geographic distribution of GBS.

In this study neither penicillin-resistant nor intermediately penicillin-susceptible GBS strains were found as it was reported by different authors (1,27,44).

At least in our population, penicillin or ampicillin remain the drugs of choice for intrapartum antibiotic prophylaxis for GBS colonization in pregnant women.

Penicillin is also the preferred choice for the treatment of infections caused by GBS. However, *in vitro* studies indicate that the rate of killing of GBS by these antibiotics is relatively slow compared with other streptococcal pathogens and have

led some authors to recommend dual therapy using a penicillin plus gentamicin for severe GBS-associated infection (31). This approach requires the pathogen to be susceptible to both penicillin and aminoglycoside antibiotics. High-level resistance to aminoglycoside indicates that the isolate will not be affected synergistically by the combination of both antimicrobial agents. None of the strains tested in this study showed high-level resistance to gentamicin.

Erythromycin and clindamycin are the drugs of choice for women with serious penicillin allergy who are colonized with GBS (11). An increase in resistance of GBS to erythromycin has been reported (5,18,25,32).

In our strains we found that 3.2 and 9.7% of the isolates were resistant to clindamycin and erythromycin, respectively. This rate of resistance to erythromycin was higher than that of other reports from Argentina like those of Lopardo *et al.* (5.2%) (33), Pérez *et al.* (6.0%)(39), Di Bartolomeo *et al.* (1.74%) (17), García *et al.* (2.1%) (22), and Mollerach *et al.* (2.4%) (37), similar to that reported by Lermontov Borges *et al.* (9.4%) in Brazil (30), but lower than reports from other countries (16, 19, 27).

Resistance to erythromycin and clindamycin is caused by 2 main mechanisms in *Streptococcus* spp.: target site methylation of the 23S ribosomal component of the large (50S) ribosomal subunit and an active efflux pump. The methylases can be expressed constitutively or they can be inducible. This mechanism renders the bacteria resistant to most macrolide, lincosamide and streptogramin B compounds (MLS_B phenotype). When the resistance mechanism due to active efflux is present, streptococci are resistant to macrolides, but susceptible to lincosamides and streptogramin B (M phenotype) (18).

M and MLS_B resistance phenotypes were observed in two and four erythromycin -resistant isolates, respectively. Other authors have highlighted the prevalence of MLS_B resistance phenotype over M phenotype in GBS (1,16,38,40).

Our study suggests that erythromycin and clindamycin resistance varied among geographic regions of Argentina. So that, for women who are allergic to penicillin the selection of an alternative prophylactic antibiotic should be guided by the antibiotic resistance patterns in each region. The rate of erythromycin resistance in GBS strongly supports the current CDC recommendation that antibiotic susceptibility testing should be performed if erythromycin or clindamycin therapy is needed to prevent neonatal GBS infection (25).

In agreement with other published studies all isolates tested in this study were susceptible to vancomycin (4,38,44), quinupristin-dalfopristin and linezolid (19,49).

We detected high percentages of tetracycline-resistant GBS. Our results were similar to those reported in Argentina (33) and those recorded in several studies performed in other countries (20,35,47).

Resistance to quinolones has only recently been described for GBS (28). In our study we identified 1.6 and 6.5% of the

isolates resistant to gatifloxacin and levofloxacin, respectively. As it was reported (23), gatifloxacin appeared to be more active than levofloxacin against GBS. As observed with pneumococci (21), our results find ciprofloxacin to be less active than the newer quinolones.

No resistance to nitrofurantoin was found in the GBS isolates tested by Simoes *et al.* (44). In this study, the susceptibility rate of nitrofurantoin was 98.3%. We agree with these authors that nitrofurantoin could be a good option for the treatment of both asymptomatic and symptomatic bacteriuria caused by GBS.

Of interest is our finding of 50% of GBS isolates with MIC to gentamicin equal or lower than 8 µg/ml in light of a controversy which has existed concerning the use of gentamicin (8 µg/ml) in selective broth medium (7). At least in our population, our finding supports the position of García *et al.* (22) who recommended the use of nalidixic acid and colistin in selective media with the aim to improve the sensitivity of screening cultures for GBS carriage in women.

With more widespread use of antibiotics, selection of antibiotic-resistant GBS may occur. If resistance continues to be identified and increasing, surveillance of antibiotic resistance patterns among several antimicrobial classes will be important in determining optimal prophylaxis and treatment of GBS infections.

RESUMO

Sensibilidade a antibióticos e prevalência de *Streptococcus* do grupo B em mulheres grávidas em Missiones, Argentina

Esse estudo objetivou determinar os padrões de sensibilidade a antibióticos e as taxas de colonização de *Streptococcus* do grupo B (GBS) em uma população de mulheres grávidas. Entre janeiro de 2004 e dezembro de 2006, foram obtidos swabs vaginais-retais de 1105 mulheres no Hospital Dr. Ramon Madariaga, em Posadas, Missiones, Argentina. A positividade para GBS nas mulheres grávidas foi 7,6%. Um total de 62 cepas de GBS foi selecionado ao acaso para testes *in vitro* de sensibilidade a penicilina G, ampicilina, tetraciclina, levofloxacina, gatifloxacina, ciprofloxacina, quinupristina-dalfopristina, linezolida, vancomicina, rifampicina, trimetoprim-sulfametoxazol, nitrofurantoína, gentamicina, clindamicina e eritromicina, e determinação dos fenótipos de resistência. Não foi encontrada resistência à penicilina, ampicilina, quinupristina-dalfopristina, linezolida e vancomicina. Entre as cepas, 96,8%, 98,3%, 46,8% e 29,0% foram sensíveis à rifampicina, nitrofurantoína, trimetoprim-sulfametoxazol e tetraciclina, respectivamente. Para as quinolonas, a ordem de sensibilidade foi: gatifloxacina (98,4%) > levofloxacina (93,8%) > ciprofloxacina (64,5%). A taxa de resistência à eritromicina (9,7%) foi superior a de outros relatos na Argentina. Nenhuma das cepas apresentou

alto nível de resistência à gentamicina. Devido a 50% das cepas de GBS terem apresentado MIC para gentamicina igual ou inferior a 8 mg/ml, correspondente à concentração usada em um dos meios seletivos recomendados para GBS, sugeriu-se ao menos em nossa população, o emprego de ácido nalidixico e colistina em meios seletivos para melhorar a sensibilidade da triagem de culturas para GBS em mulheres grávidas.

Palavras-chave: *Streptococcus* do grupo B, sensibilidade a antibióticos, prevenção, mulheres grávidas, Argentina.

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