Frequency of Antibiotic Resistance among Group B *Streptococcus* Isolated from Healthy College Students

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We report resistant rates to erythromycin and clindamycin among *Streptococcus agalactiae* (group B *Streptococcus*) isolated from a random sample of healthy male and nonpregnant female college students. Observed resistance rates were twice as high as those reported among pregnant women from the same geographic area 2 years prior.

The incidence of *Streptococcus agalactiae,* or group B *Streptococcus* (GBS) infection, the leading cause of neonatal sepsis and meningitis [1], has decreased by 65% since the implementation of an intrapartum chemoprophylactic prevention program [2], from 1.7 to 0.6 cases per 1000 live births [3]. GBS remains universally susceptible to the first-line chemoprophylactic agents penicillin and ampicillin. However, resistance rates for clindamycin or erythromycin, which is recommended for women reporting a history of penicillin allergy who require GBS prophylaxis [2], range from 9% to 19% for erythromycin and 2% to 15% for clindamycin in the United States [4]. Other countries have reported even higher rates [5, 6].

To gain insight on antibiotic resistance rates in future pregnant populations, we describe resistance rates among GBS isolated from a random sample of healthy male and nonpregnant female college students not seeking medical care or treatment.

Materials and methods. A total of 300 University of Michigan students were randomly selected from registration lists in September 1998 and invited to participate. After informed consent was obtained, participants completed a questionnaire and self-collected a random initial void urine and anal orifice specimen. A vaginal specimen was obtained from women by use of a tampon. Participants received monetary compensation. All individuals who tested positive for GBS at the initial visit and an equal number of GBS-negative participants were invited to return for a follow-up visit 4–7 weeks later. The follow-up study protocol was identical to the enrollment protocol.

Urine specimens were inoculated onto trypticase soy agar with 5% sheep blood (Baltimore Biological Laboratories [BBL]) and incubated overnight at 37°C with 5% CO_2. Anal specimens were collected and stored with the Culture Swab Plus Collection System (BBL) with Amies transport media until inoculation. Anal swabs and tampons were placed in Todd-Hewitt broth that contained gentamicin and nalidixic acid (BBL), and incubated overnight at 37°C in 5% CO_2. After incubation, the swab and tampon were inoculated directly onto trypticase soy agar with 5% sheep blood, streaked for isolation, and incubated with use of the same conditions. Plates were inspected for colonies with morphology and hemolysis consistent with GBS, and identification was confirmed serologically by use of the Slidex Strepto B kit (BioMérieux Vitek).

PFGE was performed on all GBS isolates. GBS DNA was isolated as described elsewhere [7], digested with *Sma*I, and electrophoresed for 18 h (initial switch time, 4 s; final switch time, 16 s) by use of a CHEF III apparatus (BioRad). Gels were stained for 1 h with Vistra Green (Amersham Life Science Products) at 4°C and visualized with a Storm PhosphorImager (Molecular Dynamics). ImageQuant (Molecular Dynamics) was used for the gel analyses. PFGE banding patterns within a person were considered identical if the strains differed by ⩽1 band.

The antibiotic susceptibility profile of each unique GBS isolate, as determined by PFGE, was obtained. If an individual was colonized with >1 genetically distinct GBS strain, then susceptibility testing was performed on each strain. If a woman was colonized with GBS in 3 sites that were identical by PFGE, then susceptibility testing was performed on only 1 isolate, and we inferred that all isolates had identical susceptibility profiles. Susceptibility testing was performed on unique follow-up isolates, irrespective of the initial PFGE banding pattern.

The National Committee for Clinical Laboratory Standards (NCCLS) disk-diffusion method was used to determine inhibitory zone sizes for penicillin (10 IU), ampicillin (10 μg), levofloxacin (5 μg), quinupristin-dalfopristin (15 μg), imipenem

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Informed consent was obtained from all study participants. Approval to conduct research on human subjects was obtained from the Institutional Review Board at the University of Michigan.

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Table 1. Characteristics of healthy male and female college students colonized with group B *Streptococcus*.

Characteristic	Women (n = 82)	Men (n = 68)
Age in years		
19–22	47 (58)	30 (44)
23–27	24 (30)	22 (32)
⩾28	10 (12)	16 (24)
Race		
White	53 (65)	41 (60)
Black	8 (10)	3 (4)
Hispanic or Latino	4 (5)	2 (3)
Asian	13 (16)	19 (28)
Native American	1 (1)	0 (0)
Other	2 (4)	3 (4)
Prescription use during past 2 weeks	42 (51)	16 (24)
Antibiotics during past 2 weeks	6 (7)	5 (7)

NOTE. Data are no. (%) of subjects.

(10 μg), cefazolin (30 μg), vancomycin (30 μg), clindamycin (2 μg), and erythromycin (15 μg) (BBL) [8]. GBS was inoculated in 5 mL of Todd-Hewitt broth, grown to a 0.5 McFarland turbidity, inoculated onto Mueller-Hinton agar with 5% sheep blood (BBL), and incubated overnight at 37°C without CO_2. *Streptococcus pneumoniae* ATCC 49619 was used as the control. NCCLS interpretations were not provided for cefazolin and imipenem; therefore, we used break points for cefazolin (S, ⩾28 mm; I, 26-27 mm, and R, ⩽25 mm) [9] and imipenem (S, ⩾30 mm). Strains that demonstrated resistance or marginal susceptibility to penicillin, ampicillin, or imipenem by disk diffusion were retested by use of E-test strips (AB Biodisk, North America) to determine the MIC. Similarly, the NCCLS microdilution method was used to test strains with intermediate resistance to cefazolin [10]. NCCLS standards M100-S10 were used to interpret the MIC results.

We described the frequency of and risk factors for colonization with a GBS strain resistant to either erythromycin or clindamycin, using descriptive statistics. We tested the association of sociodemographic and behavioral factors with resistance using χ^2 tests.

Results. Among the 147 female and 142 male students contacted for participation, 82 women (56%) and 68 men (48%) enrolled. Ninety-eight participants with (n = 49) and without (n = 49) GBS at the initial visit were invited to return for a follow-up visit. Forty-five women and 38 men returned; colonized and uncolonized participants were equally likely to return.

The average age of women and men was 22 and 24 years, respectively (table 1), and 81% (121 of 150) of all participants were sexually active at the initial visit. At enrollment, 28 (34%) of 82 women and 21 (31%) of 68 men were colonized with GBS in at least 1 site, whereas 2 participants acquired (7-week incidence, 6%) and 4 participants (8%) lost GBS between the enrollment and follow-up period. Seventy-one isolates were obtained at enrollment: 16 vaginal, 13 urine, and 43 anal. Seventeen colonized participants (35%) carried GBS in multiple sites at enrollment.

Overall, 14 (29%) of 49 individuals carried GBS resistant to erythromycin, whereas 9 (18%) of 49 carried GBS resistant to clindamycin (figure 1). All clindamycin-resistant isolates were also resistant to erythromycin. Each individual who carried resistant GBS at enrollment continued to carry the genetically identical (by PFGE) resistant strain 4–7 weeks later, whereas 2 men who carried a sensitive GBS strain at enrollment acquired a unique erythromycin-resistant GBS strain by follow-up. One woman without GBS at enrollment acquired a resistant strain by follow-up.

The MIC range for erythromycin was 1 to >156 and 4 to >256 μg/mL for clindamycin. Although GBS from men had lower resistance levels than those from women, the difference was not statistically significant. All GBS isolates were sensitive to penicillin, ampicillin, levofloxacin, quinupristin-dalfopristin, imipenem, cefazolin, and vancomycin. Twenty-three isolates had intermediate resistance to cefazolin, penicillin, ampicillin, and imipenem by disk diffusion but were determined to be susceptible when E-test strips and microdilution were used. Age, race, frequency of handwashing, various sexual behaviors such as vaginal-penile sex and oral sex, and antibiotic use within the preceding 2 weeks were not significantly associated with carriage of a resistant strain.

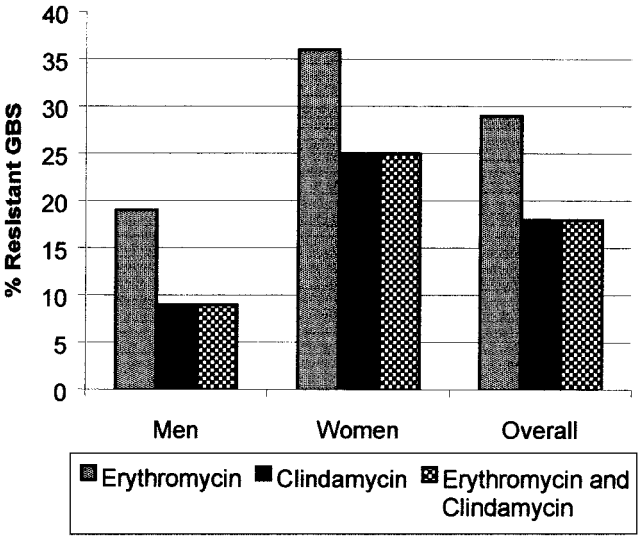


Figure 1. Frequency of erythromycin and clindamycin resistance among group B *Streptococcus* (GBS) isolated from healthy male (n = 21) and female (n = 28) college students.

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Discussion. Clindamycin and erythromycin are used to treat a broad range of infections and have been used routinely for GBS chemoprophylaxis among pregnant women during labor and delivery since 1996 [2] . The high rate of resistance observed among GBS isolates from healthy college students (29%) underscores how the frequent administration of antibiotics selects for resistant bacteria.

Because GBS remains sensitive to β-lactamase, we recommend that empiric treatment should be with a β-lactam antibiotic (penicillin or ampicillin). In the penicillin-allergic patient, the use of a first-generation cephalosporin such as cefazolin is appropriate if the patient has had no previous significant allergic reactions to cephalosporin. Otherwise, the use of clindamycin is acceptable, but if it is being used for intrapartum prophylaxis, the pediatrician should be notified. If the antepartum-screening GBS culture is positive in a penicillin-allergic patient, susceptibility testing should be done at that time, to determine whether that isolate is sensitive to clindamycin or not.

We found resistance levels twice as high as those reported in pregnant women from the same geographic area 2 years earlier [9]. The present study was not designed to assess whether this represents a true increase in resistance. Nine (75%) of 12 of our participants with GBS resistant to erythromycin or clindamycin at enrollment, however, continued to carry the identical resistant strain 4–7 weeks later, whereas only 3 of 49 participants lost the organism. This suggests that resistant GBS isolates may be carried longer.

Our small sample size and the low prevalence of recent antibiotic use (7%) limited our power to detect an association with antibiotic resistance and antibiotic use. Furthermore, it is possible that we may have overlooked resistant strains within a person by using PFGE to select strains for susceptibility testing. An individual may be colonized with 2 GBS strains in different sites that are identical by PFGE but have different susceptibility profiles. Thus, we may have underestimated the overall number of resistant strains.

This study population broadly represents the next generation of pregnant women and provides some insight into the expected antibiotic resistance rates of GBS in the near future. It is likely, however, that there are local variations in resistance, which limits the validity of broader generalizations. Larger studies in diverse populations are required to assess the impact of antibiotic use on resistance rates; to describe GBS acquisition, loss, and carriage rates; and to determine whether resistance is associated with duration of GBS carriage.

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