High Rates of Perinatal Group B *Streptococcus* Clindamycin and Erythromycin Resistance in an Upstate New York Hospital

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The objective of this study was to evaluate the rates of clindamycin and erythromycin resistance among group B *Streptococcus* (GBS)-positive isolates cultured from pregnant women in an upstate New York community hospital. All GBS-positive perinatal rectovaginal cultures obtained from January 2010 through October 2011 were tested for resistance to erythromycin and clindamycin. Among the 688 GBS-positive cultures, clindamycin resistance was found in 38.4% and erythromycin resistance was found in 50.7%. Rates of GBS resistance to clindamycin and erythromycin are much higher than reported in earlier U.S. studies, suggesting both increasing resistance and regional variation in resistance. These findings lend strong support to the CDC and American College of Obstetricians and Gynecologists (ACOG) recommendations that clindamycin use for intrapartum antibiotic prophylaxis be restricted to penicillin-allergic women at high risk of anaphylaxis and that GBS isolates be tested for antibiotic resistance prior to the use of clindamycin in these women.

Routine screening for maternal colonization by group B *Streptococcus* (GBS) and intrapartum treatment of infected mothers have been a significant public health success. According to the Centers for Disease Control and Prevention (CDC), the incidence of neonatal GBS infection, a major cause of morbidity and mortality, has declined dramatically over the past 15 years, from 1.7 cases per 1,000 live births in the early 1990s to 0.34 to 0.37 cases per 1,000 live births in recent years. The most recent perinatal GBS guidelines issued by the CDC in November 2010 uphold previous antibiotic recommendations for the prophylactic treatment of GBS-colonized women during labor, except for the withdrawal of erythromycin as a second-line prophylactic antibiotic for women with penicillin allergy (6). These recommendations have also been endorsed by the American Congress of Obstetricians and Gynecologists (ACOG) in their recent committee opinion issued in April 2011 (1). According to the CDC and ACOG recommendations, clindamycin is still an acceptable alternative for women with penicillin allergy, provided that the GBS isolates have been tested for clindamycin susceptibility (1, 6). Although intrapartum antibiotic prophylactic (IAP) treatment with penicillin and ampicillin has been shown to prevent early-onset GBS disease in clinical trials, concerns have been raised regarding the ability of clindamycin, erythromycin, and vancomycin to reliably reach bactericidal levels in the amniotic fluid, fetal circulation, and fetal tissues. Additionally, according to the CDC guideline report, *in vitro* resistance to both clindamycin and erythromycin has been increasing, with reports published from 2006 to 2009 finding GBS resistance ranging from 25% to 32% for erythromycin and from 13% to 20% for clindamycin (6).

In May 2009, Ellis Hospital, the only hospital with maternity services in Schenectady, NY, initiated testing of all GBS isolates for resistance to both erythromycin and clindamycin. This initiative was started due to the inherent difficulties in determining which submitted isolates were obtained from pregnant women with known penicillin allergy. Initial observations following the adoption of this routine sensitivity testing revealed higher rates of both clindamycin and erythromycin resistance than had been reported elsewhere in the literature. As a result, we began to collect GBS

resistance data for all perinatal GBS isolates. This paper summarizes our findings.

MATERIALS AND METHODS

All rectovaginal cultures obtained from pregnant women for GBS screening that were submitted to the Ellis Hospital laboratory from January 2010 through October 2011 were included in this study. GBS culture results and results of GBS isolate antimicrobial susceptibility testing were reviewed retrospectively. Ages and races of patients were ascertained from hospital computerized registration records. Data were compiled onto a Microsoft Excel spreadsheet and analyzed using EpiInfo 3.5.3 (CDC) epidemiologic software. Analysis of variance (ANOVA) was used to test for significant difference in ages between women with antibiotic-resistant and antibiotic-susceptible isolates. The chi-square test was used to test for differences in racial composition between the groups. The study was approved by the hospital's institutional review board.

The Ellis Hospital laboratory followed accepted GBS culture techniques, as summarized in the CDC recommendations (6). All rectovaginal swabs were tested by both direct plating and enriched broth culture techniques. A sheep blood agar plate (BAP) was inoculated, followed by a Lim broth. The BAP was incubated in 5% CO₂; the Lim broth was incubated in ambient air. Both were incubated at 35 to 37°C for 18 to 24 h. The BAP was then examined for colonies morphologically consistent with GBS. A streptococcal grouping latex agglutination test was performed to definitively identify GBS. Negative cultures from the BAP direct plating were incubated for another 18 to 24 h in 5% CO₂ at 35 to 37°. In addition, the corresponding Lim broth was then subcultured to a BAP and incubated in 5% CO₂ at 35 to 37° for 18 to 24 h. If both the 48-h direct-culture BAP and the 24-h broth enrichment BAP were negative for GBS, the culture was recorded as GBS negative. If GBS was isolated by either the direct-plating or enriched-broth culture techniques, the culture was recorded as GBS positive.

Antibiotic susceptibility testing and inducible clindamycin testing

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FIG 1 Total numbers of rectovaginal cultures and GBS-positive cultures and percentages of GBS-positive isolates resistant to erythromycin or clindamycin.

were performed concurrently on all GBS-positive cultures. The disk diffusion methodology followed the recommendations of the Clinical and Laboratory Standards Institute (CLSI) (8).

A 0.5 McFarland turbidity standard suspension of GBS was prepared from isolated GBS colonies and used to inoculate a plate of Mueller-Hinton agar (with 5% sheep blood). After the entire surface of the plate was swabbed three times, clindamycin (2 μ g) and erythromycin (15 μ g) disks were placed on the plate 15 mm apart, and the plates were then incubated at 35 to 37°C in 5% CO₂ for 20 to 24 h. Presence of a “D zone” on the plate (flattening of the zone of inhibition adjacent to the erythromycin disk) was interpreted as evidence of inducible clindamycin resistance. If there was no “D zone” present, the zone size for each drug was measured and recorded. Interpretation of GBS resistance followed CLSI recommendations. For clindamycin, a zone size of ≥ 19 mm indicates susceptible, 16 to 18 mm indicates intermediate, and ≤ 15 mm indicates resistant. For erythromycin, a zone size of ≥ 21 mm indicates susceptible, 16 to 20 mm indicates intermediate, and ≤ 15 mm indicates resistant.

RESULTS

The results of GBS and susceptibility testing are summarized in Fig. 1. Physicians who deliver babies at Ellis Hospital use either the Ellis Hospital laboratory or outside reference laboratories to process rectovaginal GBS samples, which are routinely obtained during the third trimester of prenatal care. From January 2010 through October 2011, a total of 3,055 rectovaginal cultures were processed by the Ellis Hospital laboratory, representing 75.1% of all women who delivered babies at the hospital during that time frame. Of the 679 (22.2%) GBS-positive isolates, 344 (50.7%; range, 39.3% to 72.7%/month) were resistant to erythromycin and 261 (38.4%; range, 25.0% to 54.5%/month) were resistant to clindamycin. Two GBS-positive isolates exhibited intermediate resistance to clindamycin, and nine isolates had intermediate resistance to erythromycin. Dual resistance of isolates to both drugs was high, with 94.3% of clindamycin-resistant isolates also exhibiting resistance to erythromycin and 71.5% of erythromycin-resistant isolates exhibiting resistance to clindamycin.

From April through October 2011, data were recorded separately for constitutive versus inducible resistance. During this period, 94/105 (89.5%) of the clindamycin-resistant isolates exhibited constitutive resistance and 11/105 (10.5%) of the isolates exhibited inducible resistance.

The median age of women with GBS-positive cultures was 28 years (range, 15 to 48 years), with no significant difference in age between women with clindamycin- and/or erythromycin-resistant isolates and those with susceptible isolates. Sixty-six percent of the women with GBS-positive cultures were white, 17% were African-American, 6% were Hispanic, and 11% were “other” or unknown. There was no significant difference in race between the women with resistant isolates and those with susceptible ones.

DISCUSSION

While the rate of colonizing GBS among pregnant women in this study falls within the range reported in the literature, the rates of resistance to both erythromycin and clindamycin (50.7% and 38.4%, respectively) are much higher than those reported in the studies published from 2006 to 2009, which are cited in the 2010 CDC guidelines (25% to 32% and 13% to 20%, respectively) (3, 4, 6, 17). Since the CDC first issued guidelines for universal perinatal GBS screening in 2002 (5), studies from Texas, Michigan, Rhode Island, Connecticut, and Utah reported rates of GBS resistance to erythromycin ranging from 10% to 44% and resistance to clindamycin ranging from 11% to 26% (2, 7, 10, 12, 13, 16). We identified only one published study which reported a rate of clindamycin resistance almost as high as the rate that we report. This study, from Ohio, reported that of the 200 GBS isolates obtained between 2001 and 2004, 54% were resistant to erythromycin and 33% were resistant to clindamycin (9).

It is likely that resistance rates for GBS, like those for other bacteria, vary regionally and are influenced by antibiotic usage. The increase in clindamycin resistance parallels the marked in-

crease in methicillin-resistant *Staphylococcus aureus* (MRSA) and may be driven at least partly by the reported 300% increase in clindamycin use for the treatment of MRSA infections over the past decade (11). There is considerable evidence of increasing resistance of GBS to clindamycin and erythromycin in both the general population (4, 6) and among pregnant women (15, 16). For example, investigators from Connecticut reported a 400% increase in GBS clindamycin resistance (from 5.3% to 21%) over a 7-year period from 2000 to 2007 (16, 18). A 2010 study from Utah which reports relatively high rates of GBS resistance to erythromycin (44%) and clindamycin (24%) for isolates collected between 2007 and 2008 is the most recent study in the literature prior to our report (2). Our data were collected in 2010 and 2011 and may reflect the increasing rate of GBS resistance, not yet reported from other areas of the United States.

Although not explicitly discussed, the current CDC recommendation that erythromycin should no longer be used for IAP is likely due to the high observed rate of erythromycin resistance, a rate which is actually lower than the 38% clindamycin resistance rate that we found among our GBS-positive isolates. Even if the rates reported in the present study are not yet being observed in other regions, the trend of increasing clindamycin resistance widely reported in the last decade should prompt discussion regarding the elimination of clindamycin, like erythromycin, as an option for IAP.

The high rates of antibiotic resistance that we found, along with the widely observed trend of increasing antibiotic resistance, underscore the need for universal implementation of the CDC guidelines recommending that GBS isolates be tested for antibiotic resistance prior to initiating prophylaxis with clindamycin. Several studies have shown that, although antenatal screening and the use of IAP for GBS have increased, health care providers are not adequately testing GBS isolates for resistance prior to administering erythromycin or clindamycin and are not following the recommendations to use cefazolin in penicillin-allergic women at low risk for anaphylaxis. A 10-state study evaluating the implementation of the 2002 CDC guidelines among women who delivered in 2003 and 2004 found that less than 1% of isolates from GBS-colonized women with reported penicillin allergy were tested for GBS susceptibility prior to IAP (19). In this study, clindamycin was overwhelmingly used even in women who were at low risk for anaphylaxis, while vancomycin was used in only 0.3% of all women receiving IAP. Similar findings were reported from a hospital system in Utah, where only 4% of 3,698 GBS-positive isolates obtained during 2007 and 2008 were tested for antimicrobial susceptibility (2). Although the authors of this study did not state what percentage of women reported a history of penicillin allergy, they analyzed a subset of hospitals with pharmacy information and found that GBS susceptibility was known for only 38% of the women in these hospitals who received clindamycin.

Although 10 to 30% of pregnant women are colonized with GBS, the attack rate of early-onset disease among infants was only 1.7 cases per 1,000 births even in the pre-IAP era (6). Thus, even when using clindamycin prophylaxis in a woman colonized with clindamycin-resistant GBS, the vast majority of babies will not develop GBS infection. Yet, the consequences will be dire for the rare infant who becomes infected, as illustrated by a case report from Utah which described an infant who developed early-onset clindamycin-resistant GBS disease after his mother had received prophylactic clindamycin (2). Both the failure to test the suscep-

tibility of GBS isolates from penicillin-allergic women and the underuse of cefazolin to treat women at low risk for anaphylaxis have led to the overuse of clindamycin, thereby both increasing the number of infants inadequately protected from GBS infection and likely contributing to the increased rates of antibiotic-resistant GBS which have been reported over the past decade.

Both the 2002 and 2010 CDC guidelines recommend susceptibility testing only for GBS-positive isolates from penicillin-allergic women who are at high risk for anaphylaxis (5, 6). Real world compliance with guidelines, though, is often suboptimal, especially without significant institutional intervention. Following release of the 2002 CDC guidelines, our institution developed a GBS laboratory requisition form that requested ordering physicians to identify whether the patient had a penicillin allergy, but this information was not consistently provided, and isolates from penicillin-allergic women were not routinely tested for antibiotic susceptibility. We were successful in determining susceptibility for all GBS-positive cultures from penicillin-allergic women only by initiating universal susceptibility testing for all GBS isolates. This approach, while slightly more expensive (estimated \$3.38 to \$5.88 per isolate at our institution, accounting for both labor and supplies), may be a cost-effective alternative to be considered by other institutions which are also grappling with attaining 100% compliance with CDC recommendations. Although there is little recent data regarding the cost of caring for a child with GBS disease, a California study published in 1999 estimated an economic cost (medical and long-term sequelae) of \$70,000 per case of early-onset GBS disease in a term infant, not accounting for life years lost (14). In addition to preventing the inappropriate use of clindamycin, universal susceptibility testing has alerted us to the high rates of clindamycin resistance at our institution, a benefit that we believe will be important in monitoring local GBS resistance patterns in other institutions as well.

A strength of this study is that it is the largest published study in the past decade to report GBS resistance data for rectovaginal cultures obtained from pregnant women. In addition, the data for rates of antibiotic resistance were consistent during the 22-month data collection period. The study is limited, however, by the fact that the sample was completely derived from a single hospital in upstate New York. As a result, it is not known how our results compare with those from other geographic locations. We do believe, though, that it is likely that some geographic regions have very high rates of GBS clindamycin resistance, similar to those that we found. Further research is needed to determine if other local and regional rates of GBS antibiotic resistance are indeed higher than those used by the CDC to formulate its IAP guidelines. If research confirms higher and increasing rates of clindamycin resistance, the CDC and ACOG may need to consider revising the guidelines to limit the use of clindamycin as an acceptable antibiotic option for intrapartum antibiotic prophylactic treatment.

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