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### Abstract

STUDY/PRINCIPLES: Antibiotic prophylaxis of Group B Streptococcus (GBS) positive women during labour reduces the risk of early-onset neonatal sepsis. Penicillin is the first choice, and clindamycin and erythromycin are second choices for penicillin-allergic women. Resistance to these antibiotics is rising. The aims of this study were to evaluate the rates of clindamycin and erythromycin resistance among GBS-positive isolates cultures from pregnant women in the University Hospital of Geneva and to evaluate the legitimacy of new Centres for Disease Control and Prevention (CDC) recommendations for our context.

### Reference

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# Antibiotic resistance patterns among group B *Streptococcus* isolates: implications for antibiotic prophylaxis for early-onset neonatal sepsis

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## Summary

**STUDY/PRINCIPLES:** Antibiotic prophylaxis of Group B *Streptococcus* (GBS) positive women during labour reduces the risk of early-onset neonatal sepsis. Penicillin is the first choice, and clindamycin and erythromycin are second choices for penicillin-allergic women. Resistance to these antibiotics is rising. The aims of this study were to evaluate the rates of clindamycin and erythromycin resistance among GBS-positive isolates cultures from pregnant women in the University Hospital of Geneva and to evaluate the legitimacy of new Centres for Disease Control and Prevention (CDC) recommendations for our context.

**METHODS:** We collected a vagino-rectal swab from pregnant women at 35–37 weeks gestation. We recovered 124 GBS positive isolates. Identification was based on the characteristic of the colony on the chromogenic agar, the streptococcal agglutination test and confirmation by mass spectrometry. Antimicrobial susceptibility was determined by disk diffusion, according to CLSI guidelines 2010.

**RESULTS:** The rate of resistance to clindamycin was 28% and to erythromycin was 30%. Only 3 of the 38 erythromycin resistant strains (7.9%) were susceptible to clindamycin, and only 3 out of the 35 clindamycin resistant GBS (8.6%) were identified as “inducible resistance”. The rate of co-resistance to clindamycin of erythromycin-resistant strains was 92%. Penicillin remained efficacious in all cases.

**CONCLUSION:** Rates of clindamycin and erythromycin resistance are also increasing in our context. These antibiotics should not be used for GBS neonatal sepsis prevention, without adequate antimicrobial susceptibility testing. In case of penicillin allergy and lack of antibiogram, cephalosporins or vancomycin should be used as recommended in CDC guidelines.

**Key words:** Group B *Streptococcus*; antibiotic resistance; antibiotic prophylaxis; early-onset neonatal sepsis

## Introduction

Group B *Streptococcus* (GBS), or *Streptococcus agalactiae*, is a Gram positive bacterium that causes invasive disease primarily in infants, and pregnant or postpartum women [1–3]. GBS is a leading infectious cause of morbidity and mortality among infants all over the world [4]. Infections in newborns occurring within the first week of life are designated early-onset disease. Late-onset infections occur in infant aged >1 week, with most infections evident during the first 3 months of life [4].

The use of intravenous intrapartum antibiotic prophylaxis (IAP) to prevent early-onset GBS disease in the infant was first studied in the 1980s. Clinical trials and well-designed observational studies found that intrapartum antibiotic prophylaxis reduced vertical transmission of GBS, as measured by infant colonisation [5–8] or by protection against early-onset disease [5, 7, 9–12]. The Centres for Disease Control and Prevention (CDC) and the Swiss Society of Obstetrics and Gynaecology recommend antenatal screening with vagino-rectal cultures and selective IAP administration to GBS-positive women for a minimum of four hours [13, 14]. As a result of prevention efforts, the incidence of GBS in the USA has declined dramatically over the past 15 years, from 1.7 cases per 1,000 live births in the early 1990s to 0.34–0.37 cases per 1,000 live births in recent years [4].

Penicillin G is the antibiotic of choice for prophylaxis [13, 14]. Other options include ampicillin, and for penicillin-allergic patients, cefazolin, clindamycin, erythromycin or vancomycin. Although GBS remains sensitive to penicillin, the preferred agent for GBS infections and IAP, an estimated 12% of pregnant women report having a penicillin allergy requiring the use of an alternative agent. Resistance to the second-line antibiotics, clindamycin and erythromycin, has been identified [15, 16] and it has increased since 1996 [5, 17–20]. The prevalence of resistance among invasive GBS isolates in the United States ranged from 25% to 32% for erythromycin and from 13% to 20% for clindamycin in reports published during 2006–2009 [5]. Current CDC recommendations still consider clindamycin as

an acceptable alternative for women with penicillin allergy, provided that the GBS isolates have been tested for clindamycin susceptibility. Erythromycin has been withdrawn as a second-line prophylactic antibiotic for women with penicillin allergy [5].

In our hospital, antimicrobial susceptibility testing (AST) is not routinely performed for isolates retrieved from antenatal screening, contrarily to “invasive specimen”, such as cerebrospinal fluid or blood cultures. The rates of GBS resistance to erythromycin and clindamycin were determined as 15 and 6% respectively in invasive samples in 2008. (laboratory local data). Due to concerns regarding the increase of antibiotic resistance, we decided to evaluate the antibiotic resistance patterns of GBS-positive isolates cultured from pregnant women who had vagino-rectal samples for GBS antenatal screening. We also wanted to evaluate the legitimacy of new CDC recommendations for our local context.

## Material and methods

We conducted a prospective study from February to April 2011 in the Maternity Unit and the microbiology laboratory of the University Hospitals of Geneva, Switzerland. Antenatal GBS screening is part of the standard follow-up of pregnant women as recommended in the Swiss guidelines for GBS early-onset disease prevention (no extra-sampling was done for the study) [14]. The ethical committee was informed about the study, which was done as part of the continuous quality assessment of the microbiology laboratory and women were not required to sign an informed consent. We collected a vagino-rectal swab from pregnant women at 35–37 weeks' gestation. Samples were taken using a COPAN 7LMR (COPAN Diagnostic SpA, Brescia, Italy) and sent to the microbiology laboratory for culture within 24 hours. Sampling was done on the lower third of the vagina followed by the rectum. Culture samples were collected in a uniform manner following CDC recommendations and sent to the laboratory [5]. GBS detection was performed as follows: inoculation of the sample in Todd-Hewitt broth supplemented with antibiotics (TODD H-T, BioMerieux) and then subculture on selective chromogenic agar (ChromID Strepto B Agar, BioMerieux) at 35 °C for 24 h. Identification of suspect colonies was further confirmed by mass spectrometry (MALDI-TOF MS) and a streptococcal agglutination test (Slidex strepto Plus, BioMerieux) to ensure specific identification of GBS [21]. AST was performed according to CLSI guidelines 2010 for disk diffusion (CLSI document M100-S20, Wayne, PA: Clinical and Laboratory Standards Institute; 2010). Direct colony suspension, equivalent to a 0.5 McFarland standard, was plated on Muller-Hinton agar with 5% sheep's blood. An antibiotic disk (Becton Dickinson, Allschwil, CH) was deposited on the agar with clindamycin and erythromycin disks placed 16 mm from each other in order to detect inducible resistance to clindamycin (D-zone). After 20 hours of incubation at 35 °C with 5% CO<sub>2</sub>, susceptibility to penicillin, clindamycin, erythromycin, vancomycin, and other antibiotics was determined by measuring the diameter of inhibition on a Sirscan (i2a, Montpellier, FR).

## Results

We evaluated samples from 760 pregnant women during the study period. A total of 124 samples were GBS positive, resulting in a prevalence rate of 16.3%. The resistance rates to the different antibiotics tested with the AST test are shown in table 1. Penicillin remained efficacious in all cases, as did vancomycin. The rate of resistance to clindamycin was 28% and to erythromycin it was 30%. Strains resistant to erythromycin were usually (92% of them) also resistant to clindamycin. Inducible resistance was rather seldom, representing only 8.6% of the clindamycin resistant strains.

## Discussion

Revised guidelines from the CDC recommend screening for GBS to pregnant women at 35–37 weeks' gestation using vagino-rectal culture and performing AST on antenatal GBS isolates from penicillin-allergic women at high risk for anaphylaxis. AST is considered crucial for appropriate antibiotic prophylaxis in this situation since the resistance to erythromycin and clindamycin is increasing among GBS isolates [5].

In a recent study performed in the USA, the rates of resistance to erythromycin and clindamycin were 50.7% and 38.4%, respectively [20]. Dual resistance of isolates to both drugs was also very high, with 94.3% of clindamycin-resistant isolates being also resistant to erythromycin and 71.5% of erythromycin-resistant isolates exhibiting co-resistance to clindamycin. High antibiotic co-resistance of GBS is well known and it is due to the share mechanism of resistance of GBS to Macrolides (such as erythromycin), Lincosamides (such as clindamycin) and Streptogramin (MLS). Resistance of GBS to erythromycin can be due to an efflux pump or to the methylation of 23S rRNA by erm (erythromycin ribosomal methylase) enzymes. The latter blocks the binding of MLS to the 50S ribosomal subunit, conferring resistance to other antibiotics [17]. This enzyme can be expressed inducibly by antibiotic “pressure” (for example by erythromycin, explaining the D-zone test). If a D-zone test is positive, treatment with clindamycin will induce the expression of this enzyme and resistance will appear. Taking into account the high resistance and co-resistance rates found in the former study. Back questioned the option of clindamycin as an acceptable option of intrapartum antibiotic prophylaxis [20].

Our study also shows higher rates of resistance to erythromycin (30%) and clindamycin (28%) than in the previous

**Table 1:** Resistance (%) of 124 strains of *Streptococcus agalactiae* (GBS) isolated from antenatal screening samples.

Penicillin	0%	0/124
Gentamicin	<1%	1/124
Levofloxacin	1.6%	2/124
Moxifloxacin	1.6%	2/124
Erythromycin	30%	38/124
Clindamycin	28%	35/124
Rifampicin	0%	0/124
Vancomycin	0%	0/124
Tetracyclin	89%	110/124
Linezolid	0%	0/124

Swiss recommendations (17% for clindamycin), which are similar to the resistance rates described in the USA [5]. The co-resistance rates were also high and comparable to those found in the study by Back et al. [20].

The new CDC guidelines recommend that penicillin-allergic women at high risk for anaphylaxis should receive clindamycin if their GBS isolate is susceptible to clindamycin and erythromycin. Due to the MLS shared mechanism of resistance, if the isolate is sensitive to clindamycin but resistant to erythromycin, clindamycin may be used only if testing for inducible clindamycin resistance is negative [5]. Vancomycin is reserved to allergic women if their isolate is intrinsically or inducibly resistant to clindamycin, as well as if the susceptibility to both agents is unknown [5]. Nevertheless, we could argue about the importance of inducible resistance while using clindamycin for GBS IAP. Inducible resistance is especially important when planning a long treatment. The clinical importance of an “*in vitro*” induced resistance while using an antibiotic for a very short time (such as IAP) is not known.

Before the knowledge of these results, in our maternity hospital, we performed GBS antenatal culture at 35–37 weeks of gestation and GBS-rapid PCR to women in labour without culture, such as those delivering preterm, not followed or not tested during pregnancy. In penicillin-allergic women, erythromycin or clindamycin were given without AST. Based on the results of our study, these antibiotics cannot be used with this indication any longer without performing AST. Now, in penicillin-allergic women tested by culture, we perform AST and we adapt in-labour antibiotic prophylaxis upon its results (clindamycin if sensitive, vancomycin if resistant to the former). In penicillin-allergic women tested by rapid PCR, AST is not available and vancomycin is recommended. Other antibiotics (GBS was 100% sensitive to linezolid in our study) are not recommended for this indication as their placental transfer is not known.

Nevertheless, the use of vancomycin is not without risk and it is associated with the development of resistance [22]. In order to limit the use of vancomycin, we recommend the use of cefazolin when penicillin allergy is considered low grade (stage I and II), as cross-allergies in-between penicillins and cephalosporins are expected in less than 4–6% of cases [23]. This is in agreement with the updated Swiss guidelines [24].

Finally, GBS susceptibility should be monitored locally periodically, and identification of factors associated with colonisation (especially colonisation with resistant organisms) is important in maintaining the success of current programmes to reduce perinatal morbidity and mortality from invasive GBS disease [25, 26].

In conclusion, the antenatal GBS resistance to erythromycin and clindamycin is increasing in Geneva, Switzerland. In our setting, these antibiotics can no longer be used for intrapartum prophylaxis of early-onset GBS neonatal sepsis if their susceptibility is not assessed according to CLSI or EUCAST guidelines, including the evaluation of clindamycin's inducible resistance.

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