

Appropriate Antibiotic Use for Group B *Streptococcus* Prophylaxis Among Penicillin-Allergic Patients in Academic and Nonacademic Hospitals

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This study estimated prophylactic antibiotic usage rates for the prevention of early-onset invasive neonatal group B *Streptococcus* infection among patients with penicillin allergy. Undertreatment (no antibiotics, underuse of cefazolin, overuse of clindamycin inconsistent with resistance patterns) and overtreatment (vancomycin use) were common. Academic hospitals were marginally more adherent to guidelines than nonacademic hospitals.

Keywords. antibiotic; GBS; group B *Streptococcus*; penicillin allergy; pregnancy.

Group B *Streptococcus* (GBS) is a leading cause of neonatal infection, affecting 0.23 infants per 1000 live births in 2015 [1]. In 1 study, the case-fatality rate was 22.4% [2]. During pregnancy, vaginal-rectal GBS surveillance is conducted in late pregnancy so that intrapartum antibiotic prophylaxis can be administered to GBS-positive patients to prevent early-onset invasive neonatal GBS infection [1, 3]. Universal screening and prophylaxis have reduced rates of early-onset invasive neonatal GBS infection, but it remains an important cause of neonatal mortality [2].

Guidelines from the American Society for Microbiology (ASM) endorsed by the United States (US) Centers for Disease Control and Prevention and from the American College of Obstetricians and Gynecologists (ACOG) recommend penicillin for intrapartum antibiotic prophylaxis in

patients without penicillin allergies [1, 3]. In patients with penicillin allergies, if there is no history of severe IgE-mediated hypersensitivity reactions, patients should receive cefazolin [1, 3]. If such severe allergic history is present, GBS isolates should be tested for clindamycin susceptibility [1, 3]. If the isolate is found to be susceptible, clindamycin should be given; otherwise, vancomycin should be given [1, 3]. Previous single-center studies found that half of GBS-positive, penicillin-allergic patients received inappropriate antibiotics at delivery [4, 5]. The objectives of this study were (1) to determine national patterns of antibiotic use for GBS prophylaxis in patients with penicillin allergy; and (2) to compare appropriateness of antibiotic use for GBS prophylaxis in patients with penicillin allergy between academic and nonacademic centers.

METHODS

We conducted a retrospective observational cohort study of patients who delivered in hospitals that submit data to the Premier Healthcare Database, an all-payer repository of claims and clinical data from approximately 20% of US hospital discharges [6]. The study population included all 2019 encounters for women aged 15–45 years, with a diagnosis of GBS infection/colonization (*International Classification of Diseases, 10th Revision, Clinical Modification* [ICD-10-CM] code O99.82x) and an allergy to penicillin (ICD-10-CM code Z88.0), who delivered a live infant vaginally between 24 and 42 weeks of gestation (ICD-10, *Procedure Coding System* procedure codes 10E0XZZ, 10D07Z3, 10D07Z4, 10D07Z5, 10D07Z6, 10D07Z7, and 10D07Z8). Patients with therapeutic indications for antibiotic use were excluded: infections (intra-amniotic, gastrointestinal, urinary tract, other puerperal), sepsis, bacterial pneumonia, and third- or fourth-degree perineal laceration (n = 199 [3.9%]).

For each encounter, using patient charge data, we extracted all antibiotics administered between admission and delivery day, inclusive. Antibiotics were categorized as penicillins (penicillin or ampicillin), cefazolin, clindamycin, vancomycin, or other. In cases where multiple antibiotics were given, patients were assigned to the highest antibiotic in the guideline-driven hierarchy (vancomycin > clindamycin > cefazolin > penicillins). The primary study exposure was a hospital's academic status. Premier defined an academic hospital by a medical school affiliation [6]. The primary outcome was each hospital type's proportion of deliveries that received each antibiotic category.

Antibiotic Prophylaxis Appropriateness

To evaluate rates of antibiotic prophylaxis appropriateness (ie, compliance with ASM guidelines), the expected proportions of deliveries in which each antibiotic should be given were

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Table 1. Antibiotic Use by Academic Affiliation of Hospital and Ideal/Expected Antibiotic Use Among Patients With Group B *Streptococcus* and Penicillin Allergy

Antibiotic ^a	Academic Hospitals (n = 2518)	Nonacademic Hospitals (n = 2361)	Expected (Ideal)
No antibiotic	15.2% (13.8%–16.6%)	12.2% (10.9%–13.5%)	0%
Penicillin ^b or ampicillin	5.4% (4.6%–6.3%)	3.3% (2.6%–4.0%)	0%
Cefazolin ^c	25.1% (23.4%–26.7%)	21.1% (19.5%–22.7%)	69.3%–75.0%
Clindamycin ^d	17.7% (16.3%–19.2%)	28.8% (27.0%–30.6%)	15.0%–26.1%
Vancomycin ^e	36.5% (34.6%–38.3%)	33.8% (32.0%–35.7%)	3.8%–12.3%
Other antibiotic	0.2% (.0%–.3%)	0.8% (.5%–1.2%)	...

Observed proportions in academic and nonacademic hospitals are presented as percentage (95% confidence interval); Expected proportions are presented as ranges based on the guidelines and estimates of penicillin reactions and GBS sensitivities from the literature [1, 3]. Bold indicates a statistically significant difference between academic and non-academic hospitals (non-overlapping 95% confidence intervals).

^aNo vaginal deliveries with GBS colonization should fail to receive an antibiotic (expected percentage without an antibiotic received = 0%).

^bNo penicillin-allergic patients should receive penicillins (expected percentage receiving penicillins = 0%).

^cCefazolin should be used in all penicillin-allergic patients without a self-reported severe immunoglobulin E (IgE)-mediated hypersensitivity reaction, which, based on literature estimates, is 69.3%–75.0% (expected percentage receiving cefazolin = 69.3%–75.0%) [4, 7].

^dPatients with self-reported severe IgE-mediated hypersensitivity reactions to penicillins (25.0%–30.7% based on literature estimates) [4, 7] should receive clindamycin or vancomycin. Clindamycin should be used in patients whose GBS isolate demonstrates sensitivity to clindamycin. Because the American Society for Microbiology guidelines report 15.0%–40.0% clindamycin resistance, the remainder are susceptible (60.0%–85.0%) [1, 8–11]. Thus, between 15.0% (25% × 60%) and 26.1% (30.7% × 85%) of patients with penicillin allergy should receive clindamycin (expected percentage receiving clindamycin = 15.0%–26.1%).

^eVancomycin should be used in those patients whose GBS isolate demonstrates resistance to clindamycin. Thus, between 3.8% (25.0% × 15.0%) and 12.3% (30.7% × 40.0%) of patients with penicillin allergy should receive vancomycin (expected percentage receiving vancomycin = 3.8%–12.3%).

calculated. The calculations used assumptions based on the ACOG and ASM recommendations and literature estimates of allergy and clindamycin susceptibility prevalences [1, 3]. Assumptions were the following: (1) No vaginal deliveries with GBS colonization should fail to receive an antibiotic (expected percentage without an antibiotic received = 0%). (2) No penicillin-allergic patients should receive penicillins (expected percentage receiving penicillins = 0%). (3) Cefazolin should be used in all penicillin-allergic patients without self-reported severe IgE-mediated hypersensitivity reactions, which based on literature estimates is 69.3%–75.0% (expected percentage receiving cefazolin = 69.3%–75.0%) [4, 7]. (4) Patients with self-reported severe IgE-mediated hypersensitivity reactions to penicillins (25.0%–30.7% based on literature estimates) [4, 7] should receive clindamycin or vancomycin. Clindamycin should be used in patients whose GBS isolate demonstrates sensitivity to clindamycin. Because the ASM guidelines report 15.0%–40.0% clindamycin resistance, the remainder are susceptible (60.0%–85.0%) [1, 8–11]. Thus, between 15.0% (25% × 60%) and 26.1% (30.7% × 85%) of patients with penicillin allergy should receive clindamycin (expected percentage receiving clindamycin = 15.0%–26.1%). (5) Vancomycin should be used in those patients whose GBS isolate demonstrates resistance to clindamycin. Thus, between 3.8% (25.0% × 15.0%) and 12.3% (30.7% × 40.0%) of patients with penicillin allergy should receive vancomycin (expected percentage receiving vancomycin = 3.8%–12.3%). Analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

Across 524 hospitals, 4879 deliveries to patients with GBS colonization and penicillin allergy were included. No antibiotic

was administered in 15.2% (95% confidence interval [CI], 13.8%–16.6%) and 12.2% (95% CI, 10.9%–13.5%) of deliveries at academic and nonacademic hospitals, respectively (Table 1). Penicillin was administered in 5.4% (95% CI, 4.6%–6.3%) and 3.3% (95% CI, 2.6%–4.0%) of deliveries at academic and non-academic hospitals, respectively.

The proportion of patients expected to receive cefazolin was 69.3%–75.0%, higher than the observed proportions at both academic (25.1% [95% CI, 23.4%–26.7%]) and nonacademic hospitals (21.1% [95% CI, 19.5%–22.7%]; Table 1). The proportion of patients expected to receive clindamycin was 15.0%–26.1%, similar to the observed proportion at academic hospitals (17.7% [95% CI, 16.3%–19.2%]) and lower than that observed at nonacademic hospitals (28.8% [95% CI, 27.0%–30.6%]). The proportion of patients expected to receive vancomycin was 3.8%–12.3%, lower than the observed proportions at both academic (36.5% [95% CI, 34.6%–38.3%]) and nonacademic hospitals (33.8% [95% CI, 32.0%–35.7%]). The proportion of any other antibiotic used was 0.2% (95% CI, .0%–.3%) at academic and 0.8% (95% CI, .5%–1.2%) at nonacademic hospitals.

DISCUSSION

This is the only national study to examine appropriate use of antibiotics for GBS prophylaxis and the first to compare academic and nonacademic hospitals. Despite clear guidelines for GBS prophylaxis in patients with penicillin allergies, both undertreatment (no antibiotics, underuse of cefazolin, overuse of clindamycin inconsistent with resistance patterns) and over-treatment (vancomycin use) were common. Nearly 1 in 6 GBS-positive, penicillin-allergic patients failed to receive any

intrapartum antibiotic. This has direct consequences for neonatal disease. In 1 study, only 63.3% of infants with early-onset invasive neonatal GBS disease who had an indication for intrapartum prophylaxis received it [2].

Academic hospitals have more robust antibiotic stewardship policies [12], which affects antibiotic prescribing. We found that at academic hospitals, use patterns for cefazolin and clindamycin were closer to guideline expectations. However, academic hospitals more frequently did not administer any antibiotic and administered penicillins. Both academic and nonacademic hospitals had similarly high usage rates of vancomycin, at more than double the guideline-expected rates under even the most conservative assumptions. GBS resistance to vancomycin has been reported [13]. Both academic and nonacademic hospitals need improvement in guideline-compliant GBS prophylaxis.

This study had several limitations. First, among patients coded as penicillin-allergic in this study, information about their specific reaction to penicillin (eg, anaphylaxis, rash) was unavailable. However, the frequency of severe IgE-mediated hypersensitivity reactions, both documented and reported, is well-established in the literature [4, 7, 14, 15]. Because in the clinical setting, patient report is the only immediately available information regarding penicillin allergy, we used the expected proportion of penicillin-allergic patients with self-reported severe IgE-mediated hypersensitivity reactions (25%–31%) [4, 7]. With penicillin challenges, these reactions occur in only 5% of patients with self-reported penicillin allergies [15]. Thus, estimates of the expected rate of cefazolin use is lower, and the expected rates of clindamycin and vancomycin use are higher, than if the proportion with actual reactions was used. Second, timing of delivery after admission was unavailable; thus, whether there was adequate time for antibiotic administration was unknown. Third, these results for patients with GBS colonization cannot be extrapolated to patients with unknown GBS colonization status and penicillin allergy. Finally, during their hospitalization, some patients may have received a new diagnosis of penicillin allergy or had a preexisting allergy diagnosis removed. In a validation analysis (data not shown), we found that among GBS-positive patients, 82% of those without a penicillin allergy received penicillin, compared to 5% among those with a penicillin allergy, suggesting that allergy status was available at the time of treatment. Nevertheless, either of these possibilities may have contributed to the 3%–5% of patients who received penicillin despite a documented penicillin allergy diagnosis.

Factors that may contribute to inappropriate antibiotic use include the lack of detailed allergy history and lack of GBS susceptibility testing. In a survey of obstetric providers at an academic medical center, though 70% always asked about symptoms of the index penicillin allergy reaction, 25%–34% asked detailed questions about allergy history [16]. Among patients with severe IgE-mediated hypersensitivity reactions,

guidelines recommend GBS susceptibility testing for clindamycin, with vancomycin administration if the isolate is not susceptible or results are unavailable [1]. One study found that GBS susceptibility testing was performed in only 65% of patients in whom it was indicated [5], which may help explain the high rate of vancomycin use seen in our study.

Outpatient penicillin allergy testing during pregnancy has shown promise in reducing the use of broad-spectrum antibiotics [7, 17]. In addition, cross-reactivity of cephalosporins to penicillins is overestimated [16], and quality improvement studies to encourage cefazolin use for surgical prophylaxis in penicillin-allergic patients found no cases of anaphylaxis [18, 19], including in 1 study that used cefazolin even for patients with histories of severe IgE-mediated hypersensitivity reactions to penicillin [20]. For GBS prophylaxis in patients with penicillin or cephalosporin allergies, a standardized allergy-guided order set increased appropriate antibiotic use from 47% to 85% [21]. These innovative approaches may improve antibiotic stewardship in GBS prophylaxis. Guideline adherence needs improvement both in administering any GBS prophylaxis and increasing fidelity to the penicillin-allergy algorithm.

Notes

Patient consent. This study does not include factors necessitating patient consent and was deemed exempt human subjects research by the University of Maryland School of Medicine Institutional Review Board.

Potential conflicts of interest. The authors: No reported conflicts of interest. No financial support was received for this study.

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