



Intrapartum antibiotic exposure for group B *Streptococcus* treatment did not increase penicillin allergy in children

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ABSTRACT

Background: Group B *Streptococcus* (GBS) is the leading infectious cause of neonatal morbidity and mortality in the United States. Intrapartum administration of antibiotics to mothers with positivity to GBS is performed for prevention, with penicillin being the drug of choice. Previous studies have noted an increase in atopic diseases other than drug allergy associated with intrapartum antibiotic exposure.

Objective: To determine whether intrapartum exposure to penicillin for GBS increases the likelihood of penicillin allergy in children.

Methods: Retrospective chart review was performed for patients from a birth cohort. The birth cohort included children born in 2007 at a tertiary care hospital and had local addresses. Information on GBS status of the mother, intrapartum antibiotic exposure, delivery mode, and birth order was collected and analyzed.

Results: Of 927 children identified, 804 were included in the cohort. Eighty children (10%) had a reported penicillin allergy; most were white (79%) and boys (61%). Intrapartum exposure to penicillin (odds ratio 0.84, 95% confidence interval 0.45–1.57, $P = .59$) or to amoxicillin or ampicillin (odds ratio 0.22, 95% confidence interval 0.01–3.71, $P = .29$) did not increase the risk of penicillin allergy in children. In addition, all other factors evaluated did not affect the risk of penicillin allergy in children.

Conclusion: To the authors' knowledge, this is the first study to evaluate intrapartum exposure to penicillin for GBS treatment and subsequent development of penicillin allergy in the child. In contrast to other atopic diseases, intrapartum antibiotic exposure does not alter the risk of penicillin allergy. Parents and obstetricians should be reassured when using penicillin for prevention of neonatal GBS.

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Introduction

Group B *Streptococcus* (GBS) commonly colonizes the genital and gastrointestinal tracts of pregnant women without producing symptoms. During onset of labor when membranes rupture, the fetus becomes exposed to GBS and transmission can occur with no warning signs.¹ GBS is the leading infectious cause of neonatal morbidity and mortality in the United States.^{2,3} Prevention of GBS neonatal infections is imperative and is achieved with intrapartum administration of intravenous (IV) antibiotics to mothers whose GBS status is positive or unknown.^{3–5} Penicillin is the drug of choice; alternatively, ampicillin also is effective in mothers not allergic to penicillin.^{3,5–7} In mothers allergic to penicillin, alternatives include cefazolin, clindamycin, or vancomycin, depending on allergy history.³

With implementation of recommendations for IV antibiotic administration for GBS prophylaxis, antibiotic exposure to the fetus

has increased in the recent past. Previous studies have demonstrated that in utero⁸ and intrapartum⁹ exposures to antibiotics increase the risk of asthma, atopic dermatitis, and/or hay fever in children. Longer exposure to antibiotics appears to increase this risk even more, with exposure for more than 24 hours conveying the greatest risk of atopy.⁹ GBS prophylaxis recommendations call for IV antibiotic administration for at least 4 hours before delivery,^{3,5–7} but timing can be extended significantly by the length of labor. In addition to antibiotic exposure, delivery mode can increase the risk of atopic diseases. Wegienka et al¹⁰ showed that vaginal delivery was protective against atopic dermatitis in children compared with cesarean delivery. However, this protection was decreased if IV antibiotics were administered. All these studies looked at various atopic diseases, but none evaluated drug allergy or specifically penicillin allergy.

The development of drug allergy requires prior exposure to the same or similar drug that leads to sensitization with formation of antibodies. Therefore, multiple and frequent treatments with penicillin increase the likelihood of penicillin allergy.¹⁰ Interestingly, the route of penicillin delivery also affects the risk of sensitization, with IV administration being more likely than oral

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Table 1
Reported reactions to penicillin antibiotics in study population of 80 children

Drug	Reported reaction, n (%)					
	Rash	Hives	Hives + GI symptoms	GI symptoms	Other	Unknown
Amoxicillin	40 (50)	15 (18.75)	1 (1.25)	2 (2.5)	1 (1.25)	4 (5)
Amoxicillin and clavulanate	5 (6.25)	6 (7.5)	0 (0)	2 (2.5)	0 (0)	0 (0)
Penicillin	1 (1.25)	1 (1.25)	0 (0)	1 (1.25)	1 (1.25)	0 (0)
Total	46 (57.5)	22 (27.5)	1 (1.25)	5 (6.25)	2 (2.5)	4 (5)

Abbreviation: GI, gastrointestinal.

administration to cause penicillin allergy.¹¹ Because intrapartum antibiotic exposure has been linked with increased atopy and sensitization to a drug is more likely to occur with IV administration, the authors sought to determine whether intrapartum exposure to IV penicillin for GBS treatment could increase the likelihood of penicillin allergy in children.

Methods

Study Design

This retrospective cohort study was performed using the Mayo Clinic (Rochester, Minnesota) electronic research database tool and the local electronic medical record. The Mayo Clinic institutional review board approved this study without formal consent from the children or their parents, because the study was of low risk. Consent for chart review is often obtained from the parents at the time of entry into the medical system at Mayo Clinic. All patients included in the cohort had consented to clinical chart review.

Patient Population

The birth cohort was developed using the Mayo Clinic electronic database search engine. The cohort included children born at Mayo Clinic in Rochester in 2007 who had a local address documented in the electronic medical record. Children were excluded if they were deceased or had no encounters documented within the past 5 years. The study population from this cohort was identified using the same electronic database search tool. To ensure that all reported penicillin allergies were captured, all medical notes were searched for documented reaction terms in the allergy section. Searchable terms included *unknown, anaphylaxis, angioedema, anxiety, blisters, contact dermatitis, cough, diarrhea, dizziness, edema, fever, gastrointestinal upset, hives, hypertension, hypotension, tachycardia, itching, nasal congestion, nasal discharge, nausea, vomiting, rash, red man syndrome, redness, respiratory distress, shortness of breath, Stevens-Johnson, swelling, wheezing, and other*. All identified notes were reviewed individually for reported penicillin allergy, including the specific penicillin and type of reaction. This information was entered and recorded into the developed birth cohort database. The control population included the remainder of the children in this birth cohort who did not have a reported penicillin allergy in the electronic medical record.

Demographic data were collected for all patients included in the cohort. Data obtained included birth date, sex, race, and ethnicity. Demographic information is entered into the electronic medical record as reported by the child's primary caregiver minus the birth date. The electronic search tool was used to extract this information. In addition, personal review of clinical notes was performed to obtain information regarding birth order of the child. This information was documented in the child's hospital admission note or the mother's obstetric record.

Intrapartum Antibiotics

Data on intrapartum antibiotic use were acquired and recorded in the birth cohort database. Information was extracted by personal review of clinical notes and the electronic medication administration record. Data that were gathered included type of antibiotic given, reason for treatment, and timing of antibiotic exposure in relation to delivery time. Specifically, penicillin use, type of penicillin, and vancomycin use in regard to treatment of GBS in mothers were recorded. GBS status of mothers also was obtained by review of clinical notes. Other antibiotic use and indications for treatment were extracted and recorded in similar fashion.

Statistical Analysis

Demographic data, including sex, race, ethnicity, and birth order, are presented as absolute numbers and percentages of the population. Age was not included in the statistical analysis, because all children were born in the same year as defined in the birth cohort. The χ^2 test was used to compare any differences in demographics between the control group and the study population. The absolute number of births per month for each group was documented.

In addition, indications for intrapartum antibiotic use in the 2 groups are presented as percentages. GBS treatment in the control group was divided further into treatment of GBS alone or in addition to other indications. The type of antibiotic used for the treatment of GBS is documented as a percentage for the 2 groups, and the control group was divided further by the specific penicillin used.

Table 2
Demographics of control group and penicillin-allergic group

	Control group (n = 724)		Study group (n = 80)		P value
	n	%	n	%	
Boys	363	50.3	49	61.3	.06
Race					
American Indian or Alaskan Native	2	0.3	0	0	.64
Black or African American	61	8.4	4	5	.30
White	494	68.4	63	79	.29
Other	101	14.0	8	10	.36
Asian	45	6.2	3	4	.39
Unknown	14	1.9	1	1	.67
Chose not to disclose	5	0.7	1	1	.59
Ethnicity					
Hispanic or Latino	47	6.5	4	5	.61
Not Hispanic or Latino	642	88.9	74	93	.75
Unknown	25	3.5	1	1	.30
Chose not to disclose	8	1.1	1	1	.91
Birth order					
First born	272	37.5	28	35	.73
Second born	245	33.8	28	35	.86
Third born or later	208	28.7	24	30	.84

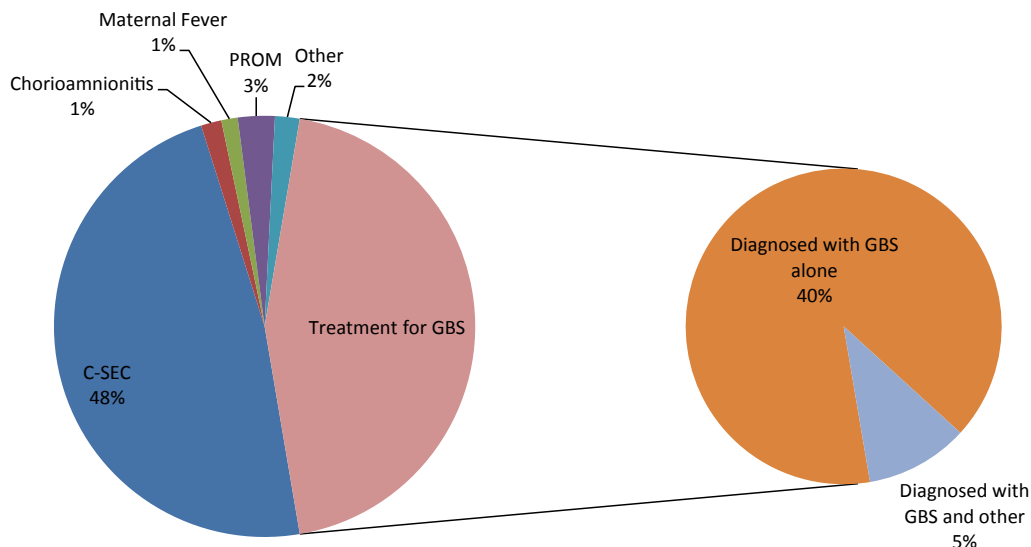


Figure 1. Indications for intrapartum antibiotic treatment in mothers of control group. In total 320 mothers received antibiotics for various reasons, most commonly for preoperative prophylaxis before cesarean section (C-SEC) and for group B *Streptococcus* (GBS) treatment. PROM, premature rupture of membranes.

Various factors were analyzed to determine whether an association between certain intrapartum exposures or clinical variations increased the risk of penicillin allergy in children and specifically whether intrapartum penicillin exposure for the treatment of GBS increased this risk. Odds ratios were calculated to determine the effect of these factors on the risk of penicillin allergy. Factors included in this analysis were penicillin, aminopenicillin, and vancomycin exposure; timing of antibiotic delivery; GBS status of the mother; and mode of delivery. A *P* value less than .05 was considered statistically significant.

Results

Demographics

In total 927 children were born at Mayo Clinic in Rochester in 2007 and had current local addresses. The cohort included a total of 804 children because 115 had been lost to follow-up and 8 were no longer living. Of the remaining children, 724 were included in the control group, and 80 had a reported penicillin allergy and were included in the study population. Amoxicillin was the most common penicillin reported and typically led to a rash (Table 1). None of these children were lost to follow-up. The control group was composed equally of boys (50.3%) and girls and was primarily white (Table 2). More than 70% were first or second born (Table 2). The number of births per month ranged from 50 to 70. The study population included more boys (61%) than girls and was primarily white (Table 2). However, there was no statistical difference between groups in regard to sex (Table 2). The number of births per month in the study group ranged from 3 to 12, with most births occurring in September. As in the control group, most were first or second born (Table 2).

Intrapartum Antibiotic Use

Mothers in the control group received antibiotics frequently (44%) for various reasons. The most common reason was preoperative prophylaxis before cesarean delivery (48%), with treatment of GBS being a close second (45%; Fig 1). Antibiotic administration to mothers in the study group was similar, with 41% receiving antibiotics; however, the majority of antibiotic use was for GBS treatment (55%) and a smaller percentage was for preoperative prophylaxis (42%; Fig 2). Other indications for antibiotic

administration were not documented in the study group, and 1 mother received antibiotics for unknown reasons (Fig 2). Intrapartum antibiotic treatment for GBS was indicated in approximately one third (29.2%) of deliveries in the control group, and these mothers received antibiotics most of the time (70%). Penicillins were the most frequently used drug, and vancomycin was given in only 3% of cases (Fig 3). Similarly, 30% of mothers in the study group had an indication for GBS treatment, and most (75%) received intrapartum antibiotics. Interestingly, unlike the control group, no mother in the study group received amoxicillin or ampicillin and non-penicillins were used at a greater frequency (Fig 4). Penicillin was still the most commonly used drug (76%) in this group.

Risk of Penicillin Allergy

Evaluation of multiple factors and their effect on the risk of children having a penicillin allergy was performed. Intrapartum penicillin use did not increase the risk of penicillin allergy in children (odds ratio 0.84, 95% confidence interval 0.45–1.57, *P* = .59). This also was the case for other penicillins, such as amoxicillin and ampicillin (odds ratio 0.22, 95% confidence interval

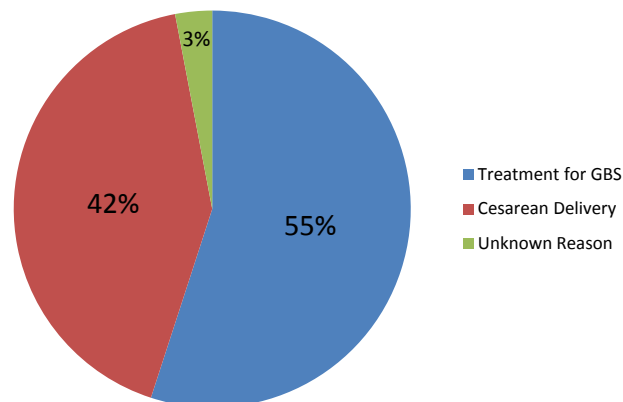


Figure 2. Indications for intrapartum antibiotic treatment in mothers of study group. Thirty-three mothers received antibiotics for limited reasons. GBS, group B *Streptococcus*.

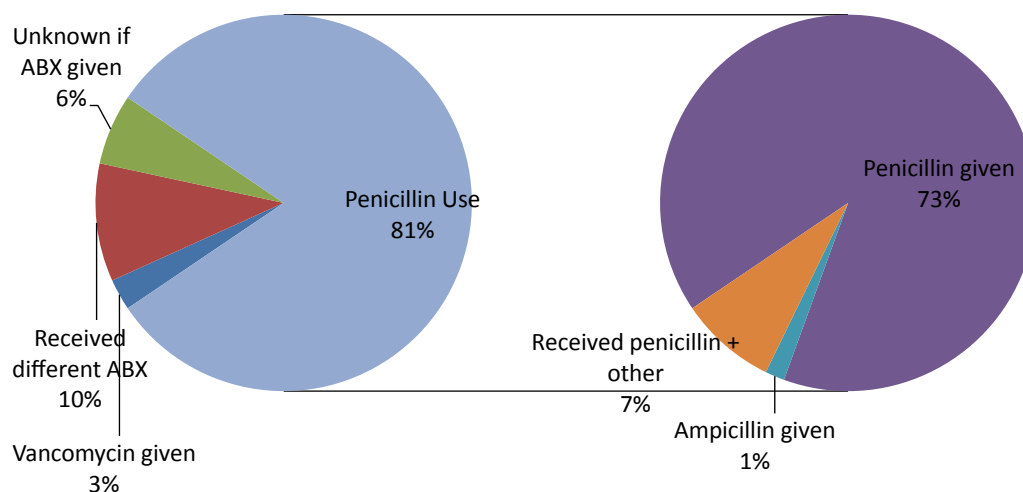


Figure 3. Antibiotics (ABX) used for group B *Streptococcus* treatment in control group. In total 142 mothers received antibiotics for group B *Streptococcus* treatment.

0.0133–3.713, $P = .30$) or vancomycin (Table 3). In addition, timing of antibiotic administration, diagnosis of GBS in the mother, and mode of delivery did not alter the risk (Table 3).

Discussion

Previous studies have shown an association between intrapartum antibiotic use and cesarean delivery and an increased risk of atopic diseases in children. However, these studies did not evaluate drug allergy in children. To the authors' knowledge, this is the first study to evaluate the risk of penicillin allergy in children associated with intrapartum antibiotic use and delivery mode. Treatment of GBS is imperative in this population, because GBS is the most common cause of infectious morbidity and mortality in the neonatal population, and therefore intrapartum antibiotic use is required. This need for treatment increases intrapartum antibiotic use. In this study, more than 40% of mothers received intrapartum antibiotics primarily for GBS treatment or preoperative prophylaxis before cesarean delivery and even more so in the control group. This percentage is smaller than data extrapolated from the Centers of Disease Control and Prevention census data that would estimate approximately 65% of expecting mothers are eligible to receive antibiotics for GBS prophylaxis (25%) or preoperative prophylaxis (32.7%).^{12,13} Preoperative prophylaxis has been shown to decrease

postoperative infections in mothers.¹⁴ In this study, it appears that most mothers requiring GBS treatment received intrapartum antibiotics according to guidelines, including the drug of choice, with penicillin being the antibiotic most commonly used. Incidence of atopy is increasing in children, and development of atopic diseases is a concern for parents and for health care providers. Parents and obstetric providers should be reassured that neither treatment of GBS nor cesarean delivery appears to increase the risk of penicillin allergy in children.

In theory, intrapartum penicillin exposure could increase the risk of penicillin allergy. Immunoglobulin E–mediated drug reactions require sensitization from previous use of the drug. When penicillin is used for GBS treatment, recommendations call for dosing at least 4 hours before delivery to ensure that penicillin concentrations in the placenta are adequate to inhibit transmission. With this dosing, it is assumed that the fetus is exposed and therefore a sensitizing exposure could have occurred. Therefore, infants exposed to penicillin in the womb could have increased risk of penicillin allergy. However, this study refutes this theory by showing no increased risk of penicillin allergy in children who were exposed to intrapartum penicillin. Unfortunately, only 10 of the children with reported penicillin allergy were evaluated with skin prick testing and none underwent oral challenge. Of the 10 tested, only 1 had a positive reaction. This suggests that penicillin allergy in this cohort might have been even lower than 10% if evaluation for immunoglobulin E–mediated penicillin allergy had been performed on all 80 children. In addition to total penicillin allergy risk, type of penicillin did not alter the risk, even when amoxicillin was used for GBS treatment (amoxicillin was the most common cause of penicillin allergy in this cohort).

This study was limited in that it was a retrospective cohort study that relied on documentation of penicillin allergy in the local electronic medical record system. Mayo Clinic, a tertiary care facility,

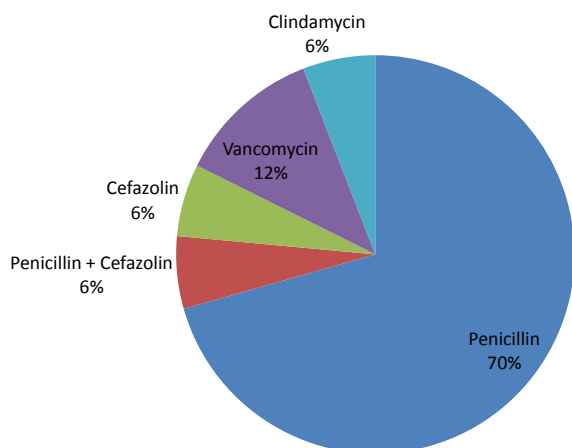


Figure 4. Antibiotics used for group B *Streptococcus* treatment in study group. Eighteen of 24 women with an indication for group B *Streptococcus* treatment received antibiotics.

Table 3

Data showing risk of penicillin allergy in children not affected by intrapartum antibiotic use, GBS status, or mode of delivery

Factor	OR (95% CI)	P value
Penicillin use	0.84 (0.45–1.57)	.59
Amoxicillin or ampicillin use	0.22 (0.01–3.71)	.30
Vancomycin use	1.51 (0.18–12.74)	.70
Antibiotic delivery ≥ 4 h	1.00 (0.53–1.88)	.99
Positive for GBS or unknown	1.04 (0.63–1.71)	.89
Cesarean delivery	0.74 (0.43–1.26)	.27

Abbreviations: CI, confidence interval; GBS, group B *Streptococcus*; OR, odds ratio.

provides care to many trainees who leave after training is done. Therefore, many children (12%) born at the local hospital in 2007 were lost to follow-up. In addition, because this is a tertiary care facility, this cohort could represent a high-risk or unique patient population; however, 40% of total births in the local county occurred at Mayo Clinic in 2007. Therefore, the birth cohort might adequately represent the local population. It is important to note that this cohort is primarily white, because risk of other atopic diseases varies among races.

Intrapartum antibiotic exposure for treatment of GBS, GBS status, and cesarean delivery did not increase the risk of penicillin allergy in children. Parents and obstetric providers should be reassured when this vital treatment is needed to protect neonates from GBS infections.

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