



Skin testing and oral amoxicillin challenge in the outpatient allergy and clinical immunology clinic in pregnant women with penicillin allergy

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ABSTRACT

Background: Penicillin allergy is frequently reported. In pregnant women, reported penicillin allergy is associated with negative health outcomes and suboptimal group B streptococcal prophylaxis. For individuals having penicillin allergy, skin testing followed by an observed oral challenge is recommended. Previous data indicate a low risk of adverse reaction with skin testing in pregnant women, but the subsequent oral challenge was not routinely pursued.

Objective: To determine whether skin testing followed by the outpatient oral challenge is tolerated by pregnant women.

Methods: We conducted a retrospective review of all pregnant women who underwent penicillin allergy evaluation at an outpatient allergy and clinical immunology clinic. The patients underwent oral amoxicillin challenges based on the discretion of the allergy provider. We evaluated the index reaction history, skin test results, oral challenge results, and subsequent antibiotic exposure.

Results: A total of 46 pregnant women underwent skin testing without adverse reactions, of whom 44 patients (95.6%) received negative results. A total of 18 women (39%) completed an oral challenge without adverse reactions. Patients challenged vs not challenged did not differ in patient age, gestational age, latency since index reaction, or reaction history risk level. Notably, 28 women received intrapartum antibiotics. There was no difference in intrapartum antibiotic administration between those who did or who did not complete an in-office oral challenge ($P = .90$).

Conclusion: Penicillin skin testing and oral challenge in pregnant women can safely be performed in the outpatient setting. There was no difference in the intrapartum antibiotic use between women who were and those who were not challenged. Further research is needed to determine the utility of oral challenge in pregnant patients.

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Introduction

Penicillin allergy is the most frequently reported drug allergy, affecting an estimated 10% of the US population and 8% of pregnant women.^{1,2} A number of untoward health care outcomes have been associated with penicillin allergy, including longer hospital stays, more frequent drug-resistant infections, and increased health care costs.³ In pregnant women, there are also adverse health outcomes

associated with self-reported penicillin allergy, including increased risk of cesarean delivery and increased length of hospital stay.² Beta-lactam antibiotics, particularly cefazolin, are the preferred treatment for surgical site infection (SSI) prophylaxis in women undergoing cesarean delivery. Women who do not receive beta-lactam antibiotic prophylaxis are at higher risk of SSI.⁴ Pregnant women with premature rupture of membranes are at increased risk of endometritis when a nonpenicillin antibiotic regimen is used.⁵

In addition to risks in pregnant women, there are risks for adverse health outcomes to the newborn child.^{6,7} Group B *Streptococcus* (GBS) is a common cause of sepsis in newborns and is often transmitted by means of maternal vaginal colonization.^{6,7} Screening for GBS vaginal colonization is the standard of care in

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pregnant women. Those who received positive test results are given intrapartum antibiotic prophylaxis, typically with beta-lactam antibiotics, to prevent neonatal GBS infection. This practice has drastically decreased the incidence of GBS infection in newborns.⁸ In GBS-positive women, the preferred treatment is a beta-lactam antibiotic, particularly penicillin or ampicillin.⁷ However, most women with a listed penicillin allergy do not receive first-line therapy.^{9,10} For women with listed penicillin allergy, susceptibility testing is recommended on all GBS samples given the increasing resistance patterns; however, this is not reliably performed.¹¹ Because of increased risk of resistance, treatment with non-beta-lactam antibiotics can result in early-onset GBS disease in the neonate.¹²

Further increasing the urgency to clarify penicillin allergy in pregnant patients is the fact that more than 90% of patients who report penicillin allergy in the general population are able to tolerate penicillin.¹³ Similarly, 89% of pregnant women with reported penicillin allergy had negative penicillin testing.¹⁴ Skin testing, followed by an observed oral challenge, is a safe and effective means to evaluate for the presence of an immunoglobulin E (IgE)-mediated penicillin allergy.¹³ Penicillin skin testing has been reported to be safe in pregnant women.^{14,15} However, in these previous studies, patients with negative skin test results did not undergo an outpatient in-office oral challenge. In this population, general recommendations have either advised intrapartum penicillin administration or inpatient challenge.^{14–19} Limited data are available on the safety of penicillin skin testing and oral challenge in pregnant patients. Given the increased risks surrounding penicillin avoidance in pregnant women, the evaluation of penicillin allergy is paramount.

Our study aimed to evaluate the use of outpatient in-office oral challenge after negative skin testing in pregnant women with penicillin allergy. Oral challenges have not typically been conducted in pregnant women. Previous studies of penicillin allergy in pregnant women consist of small cohorts and performed the drug challenges inpatient.^{14,15,20} We conducted a retrospective chart review to report on the results of outpatient penicillin skin testing and in-office oral challenges in pregnant women and to determine whether completing an outpatient oral challenge affected intrapartum outcomes. To the best of our knowledge, this is the first cohort reported of outpatient penicillin oral challenges in pregnant patients.

Methods

We conducted an observational, descriptive, retrospective chart review of pregnant women who underwent outpatient evaluation for penicillin allergy at our tertiary academic health care institution between June 1, 2013 and June 1, 2019. The study was reviewed and approved by the institutional review board.

The inclusion criteria for the study included current pregnant status during penicillin allergy evaluation. All women aged 18 to 55 years who underwent penicillin allergy skin testing at the outpatient allergy and immunology clinic were initially identified in the electronic medical record (EMR), and their pregnancy status was manually reviewed for inclusion by the authors. Pregnancy status was confirmed by either patient report documented during the allergy visit or active obstetrical care documented in the EMR. We used the following penicillin reagents for testing: 0.2 mL of penicillin G potassium 2000 units in 0.9% sodium chloride (compounded in the hospital pharmacy) and single-dose vial manufactured by Pre-Pen (AllerQuest LLC, Plainville, Connecticut). Skin responses were measured 15 minutes after reagent placement. We interpreted a wheal of 3 mm and a flare of 6 mm greater than the negative control (0.2 mL of 0.9% sodium chloride) as a positive result. We placed a histamine-positive control (6 mg/mL histamine

base manufactured by Jubilant HollisterStier LLC, Spokane, Washington).

Data were obtained from patients' medical records from July to November 2019. The following variables were collected: (1) penicillin allergy history; (2) penicillin skin testing results; (3) oral challenge results (if applicable); (4) GBS status; (5) intrapartum use of antibiotics; (6) adverse reaction to intrapartum antibiotic exposure; (7) mode of delivery; (8) hospital length of stay; and (9) postpartum beta-lactam exposure. Penicillin allergy history variables included latency of reaction, symptoms reported, and treatment required. Based on this history, a risk score was assigned according to Shenoy et al.¹ This was determined by 2 independent reviewers. Any discrepancies in risk scores were evaluated by a third reviewer. Whether or not to pursue oral challenge after negative penicillin skin testing results were determined by the evaluating physician and patient preference after discussion of potential harms and benefits. Patients who underwent an oral challenge received single dose of 250 mg amoxicillin in the outpatient allergy and immunology clinic.

Our primary outcome of interest was whether pregnant patients tolerated outpatient penicillin oral challenge. The secondary outcome was whether pregnant women who underwent in-office oral challenge were more likely to receive intrapartum beta-lactam antibiotic therapy. In addition, we described the results of penicillin skin testing, whether patients underwent an intrapartum test dose challenge, postpartum beta-lactam exposure, and subsequent adverse reaction with antibiotic exposure. Finally, we evaluated whether or not conducting oral challenge at penicillin allergy evaluation affected mode of delivery or hospital length of stay.

The patients' collected information was summarized as median and interquartile range for continuous variables, and as counts and percentage for all categorical variables. Kruskal-Wallis test was used to compare non-normally distributed continuous variables between challenge groups, χ^2 test was used to compare the categorical variables, and Fisher's exact test was used for categorical variables when 1 or more of the cells have an expected frequency of 5 or less. All statistical analyses were conducted using Statistical Analysis System 9.4 for Linux (SAS Institute, Inc, Cary, North Carolina). The level of statistical significance was set at $P < .05$ (2-tailed).

Results

A total of 46 pregnant women underwent penicillin allergy evaluation during our study period. The mean age was 31.9 years ($SD \pm 5.8$). Most women were in their second trimester, with a mean gestational age of 25.8 weeks ($SD \pm 9.1$ weeks). Most women ($n = 29$, 63%) reported a reaction occurring greater than 20 years ago. The most common symptom reported was rash ($n = 36$, 82%), and most reaction histories were determined to be of moderate risk ($n = 40$, 87%). Only 2 participants had positive test results (4.3%). One individual received a positive test result on intradermal testing to penicillin G, and the other received a positive test result on intradermal testing to penicillin G and benzylpenicilloyl polylysine. All patients tolerated the penicillin skin testing without adverse reactions.

Of the 44 patients who had negative skin test results (Table 1), 18 patients underwent oral challenge (41%) (Fig 1). There was no difference among patients who underwent oral challenge from those who did not in terms of age, gestational age, latency since reaction occurred, and symptoms reported during an allergic reaction (rash, respiratory symptoms, gastrointestinal symptoms, and angioedema) (Table 1).¹ All 18 patients who underwent oral challenge tolerated the procedure without adverse reaction.

Of the 44 patients who had negative skin testing, 3 did not have intrapartum information available in the EMR. Of these 3 patients, 2 patients transferred care before completion of their pregnancy,

Table 1
Summary Statistics of Pregnant Patients With Negative Penicillin Skin Testing

Factor	Overall (N = 44)		No oral challenge (n = 26)		Oral challenge (n = 18)		P value
	N	Statistics	n ^a	Statistics	n ^a	Statistics	
Patient age, y	44	33.5 (29.0–35.0) 31.9 ± 5.9	26	34.0 (32.0–35.0) 32.4 ± 5.1	18	32.0 (26.0–35.0) 31.1 ± 7.0	.30 ^b
Gestational age at visit (wk)	44	26.0 (17.0–34.5)	26	25.0 (16.0–35.0)	18	30.0 (18.0–33.0)	.64 ^b
Latency since reaction occurred, y	44		26		18		.33 ^c
1–5		2 (4.5)		1 (3.8)		1 (5.6)	
5–10		6 (13.6)		3 (11.5)		3 (16.7)	
10–20		1 (2.3)		1 (3.8)		0 (0.0)	
Greater than 20 y		28 (63.6)		18 (69.2)		10 (55.6)	
Never had a reaction to penicillin		2 (4.5)		2 (7.7)		0 (0.0)	
Unable to determine		5 (11.4)		1 (3.8)		4 (22.2)	
Rash	42		24		18		.61 ^c
No		4 (9.5)		3 (12.5)		1 (5.6)	
Yes		34 (81.0)		18 (75.0)		16 (88.9)	
Unable to determine		4 (9.5)		3 (12.5)		1 (5.6)	
Respiratory symptoms	42		24		18		.22 ^d
No		22 (52.4)		14 (58.3)		8 (44.4)	
Yes		2 (4.8)		2 (8.3)		0 (0.0)	
Unable to determine		18 (42.9)		8 (33.3)		10 (55.6)	
Angioedema	42		24		18		.10 ^d
No		20 (47.6)		13 (54.2)		7 (38.9)	
Yes		3 (7.1)		3 (12.5)		0 (0.0)	
Unable to determine		19 (45.2)		8 (33.3)		11 (61.1)	
Gastrointestinal symptoms	42		24		18		.86 ^c
No		10 (23.8)		5 (20.8)		5 (27.8)	
Yes		2 (4.8)		1 (4.2)		1 (5.6)	
Unable to determine		30 (71.4)		18 (75.0)		12 (66.7)	
Allergy history level of risk ¹	44		26		18		.69 ^c
High-risk		1 (2.3)		1 (3.8)		0 (0.0)	
Low risk		2 (4.5)		2 (7.7)		0 (0.0)	
Moderate risk		38 (86.4)		21 (80.8)		17 (94.4)	
Unable to determine		3 (6.8)		2 (7.7)		1 (5.6)	
Intrapartum use of antibiotics	41		24		17		0.90 ^d
No		14 (34.1)		8 (33.3)		6 (35.3)	
Yes		27 (65.9)		16 (66.7)		11 (64.7)	

Abbreviations: P25, 25th percentile; P75, 75th percentile.

^aStatistics presented as mean ± SD, median (P25–P75), or n (column percentage).

^bP values were calculated by Kruskal-Wallis test.

^cP values were calculated by Fisher's exact test.

^dP values were calculated by Pearson's χ^2 test.

1 owing to change of insurance, and 1 because they moved out of state. In addition, 1 patient experienced intrauterine fetal demise unrelated to penicillin allergy evaluation. Of the remaining 41

patients, 27 patients (66%) received intrapartum antibiotics. Most (96%) received a beta-lactam antibiotic. A total of 15 patients received penicillin or ampicillin, and 11 patients received

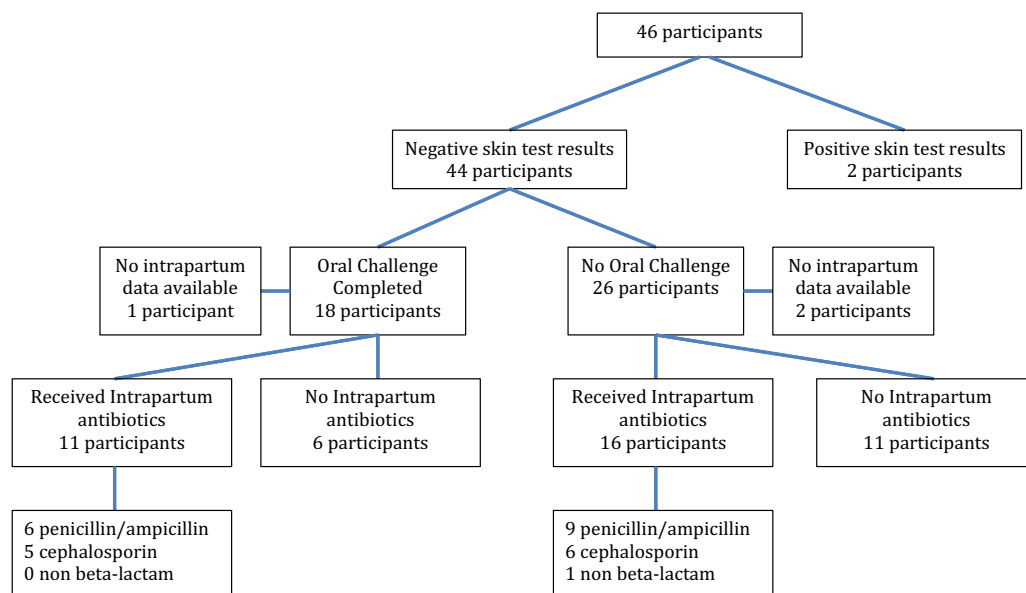


Figure 1. Descriptive data for pregnant women with self-reported penicillin allergy undergoing skin testing, oral challenge, and antibiotic administration.

cephalosporin. No adverse reactions to intrapartum antibiotics were recorded in the EMR.

Patients who underwent an oral challenge were not more likely to receive intrapartum beta-lactam antibiotics (Table 1). There was no difference in the mode of delivery ($P = .91$) nor hospital length of stay ($P = .58$) between individuals challenged vs not challenged. Of the 11 patients who underwent oral challenge and received an intrapartum antibiotic, 6 (55%) received either penicillin or ampicillin, all of which were for GBS prophylaxis. A total of 5 (45%) received cephalosporins; most (4 of 5) was for SSI prophylaxis (Fig 1). Of the 16 patients who did not undergo an oral challenge and received an intrapartum antibiotic, 9 (56%) received either penicillin or ampicillin, most (7 of 9) for GBS prophylaxis. A total of 6 (38%) received cephalosporins. Only 3 of the 6 received a cephalosporin for SSI, whereas the other 3 received this for GBS prophylaxis. Notably, 1 patient (6%) received a non-beta-lactam antibiotic (Fig 1). She had received positive results for GBS and underwent a cesarean section for malpresentation. She received intraoperative gentamicin and clindamycin. It was not clearly documented in the EMR why this antibiotic regimen was used. The sample size was inadequate to evaluate statistical significance in these findings.

Of the 16 patients who did not undergo an in-office challenge, only 2 patients (12.5%) received an intrapartum test dose challenge. One of these 2 patients received a test dose of 500,000 units of parenteral penicillin G (10% of goal dose) and was monitored for 30 minutes for any evidence of adverse reaction before administration of the remainder of the dose. The other patient received a single dose of 25 mg oral amoxicillin 10 hours before initiating parenteral penicillin G. In the EMR of both patients, the allergy provider note recommends a 10% test dose of the desired beta-lactam antibiotic with a 30-minute observation period.

A total of 22 individuals (54% of the 41 individuals for which postpartum information was available) received a subsequent postpartum course of beta-lactam antibiotics. Although 3 patients reported an adverse reaction with postpartum beta-lactam exposure, 1 patient had successfully undergone an oral challenge and tolerated intrapartum ampicillin without an untoward reaction. She received a course of amoxicillin for sinusitis 28 months postpartum, and 4 hours after the first dose reported nausea and slight dizziness. Her health care provider advised that this was likely an adverse effect, but the patient opted to transition to an alternative antibiotic. Notably, 1 patient tolerated oral amoxicillin challenge without an adverse reaction but did not receive intrapartum antibiotic therapy. At 4 months postpartum, she experienced biopsy-proven erythema multiforme 7 days into a course of Augmentin (amoxicillin-clavulanate). In addition, 1 patient did not undergo oral challenge but tolerated intrapartum cefazolin without a problem. She was given cephalexin 2 weeks postpartum for mastitis. After 5 doses, she reported a rash on hands and feet and lip swelling; both symptoms resolved with at-home diphenhydramine and discontinuation of the antibiotic.

Discussion

Our findings provide further support for the safety of penicillin skin testing in pregnant women and further confirmation that most pregnant women with a history of penicillin allergy have negative penicillin testing (44 of 46, 96%). Our study also suggests that many pregnant women with negative penicillin skin testing are able to tolerate beta-lactam antibiotics. All 18 women who underwent oral challenge had no adverse reactions. Among those who did not undergo oral challenge, 15 received intrapartum beta-lactam antibiotics. All patients who received intrapartum beta-lactam antibiotics tolerated them. Performing an oral challenge did not increase the likelihood of receiving intrapartum beta-lactam antibiotics.

In the general population, the incidence of adverse reactions to beta-lactam exposure after negative skin testing to penicillin is very low. One study revealed that only 0.8% of patients had an objective oral amoxicillin reaction after negative skin testing, and all were adequately treated with an oral antihistamine such that the symptoms resolved within 1 hour.²¹ Adverse reactions to oral amoxicillin challenge requiring epinephrine administration have been described, but are rare, and respond appropriately to epinephrine.^{22,23} A United Kingdom study reported only 1 fatal case of oral amoxicillin ingestion in over 35 years and approximately 100 million treatment courses of oral amoxicillin in their general population.²⁴ Despite the low risk of adverse reaction with oral amoxicillin challenge after negative skin testing, limited data are available evaluating this in pregnant patients.

A recent systematic review investigated penicillin allergy evaluation in pregnant women, most of which involved desensitization.²⁰ Most peripartum indications for penicillin require timely antibiotic administration. For example, GBS prophylaxis requires administration 4 hours or more before delivery.⁷ Desensitization is a prolonged process and requires management by an experienced provider; these 2 factors can prevent the use of beta-lactam therapy. Oral amoxicillin challenge before delivery rules out an IgE-mediated hypersensitivity and eliminates the need for desensitization. The review by Furness et al²⁰ described only 16 pregnant women who underwent oral challenge, all of whom tolerated penicillin without adverse reaction. These data are derived from 2 case reports and 2 abstracts. In addition, all challenges from these publications were conducted on inpatients.^{16–20} Our study expands these data and is unique in that it evaluates outpatient oral challenge immediately after negative skin testing results. All 18 patients who underwent oral challenge to amoxicillin tolerated the procedure without adverse reaction. This finding is promising and supports the safety of outpatient oral challenge being performed in pregnant women after negative skin testing to definitively evaluate IgE-mediated penicillin allergy.

Previous studies have reported that penicillin skin testing is safe in pregnant women, but these studies did not pursue an oral challenge before the intrapartum period. After negative penicillin skin testing, Macy¹⁵ gave patients written instructions to continue penicillin avoidance until they required intrapartum treatment. No acute adverse reactions were noted with intrapartum beta-lactam administration, although 2 women reported delayed rashes.¹⁵ Philipson et al¹⁴ recommended intrapartum oral challenge with a dose of 250 mg penicillin VK after negative skin testing; however, data on patient tolerance were not reported. In our patient population, all patients tolerated intrapartum beta-lactam antibiotic therapy regardless of whether they underwent a previous oral challenge to amoxicillin.

Mounting data support the contention that penicillin skin testing is safe in pregnant patients. The optimal time for the introduction of a beta-lactam antibiotic after negative skin testing is less clear. Although penicillin skin testing has an excellent negative predictive value, oral challenge after negative results is recommended to ensure tolerance.¹ In pregnant patients, ensuring tolerance is particularly crucial given that adverse reactions with antibiotic exposure could pose a risk to not only the patient but also the fetus. Allergy-immunology providers may favor deferring initial administration of beta-lactam antibiotics until the intrapartum period to facilitate possible delivery in the case of severe adverse reaction. However, allergists have unique training to quickly and appropriately treat adverse reactions that may occur during initial beta-lactam oral challenge, suggesting, perhaps, that an allergist-supervised oral challenge may be preferable. In addition, outpatient in-office oral challenge provides an opportunity for allergy-immunology providers to definitively determine the safety of intrapartum beta-lactam administration. Despite detailed instructions documented

in the EMR, most patients in our study did not receive the recommended oral challenge before the administration of treatment dose penicillin. Of the patients who were recommended inpatient test dosing in the intrapartum period, only 2 patients received any form of test dose challenge, and 1 arguably received an inadequate test dose (25 mg oral amoxicillin) before administration of full-dose parenteral penicillin G. Patients often receive parenteral forms of penicillin during the intrapartum period, which carries a higher risk for adverse reaction than an initial oral challenge.²⁵ Notably, most patients in our study had a moderate risk history ($n = 38, 86\%$). High-risk individuals, such as those with a recent history of a severe reaction, may benefit from further consideration of inpatient challenge or the use of an alternative agent during pregnancy. Additional studies with larger patient populations are needed to definitively determine the optimal time for the introduction of beta-lactam antibiotics after negative skin testing.

Another consideration in the timing of oral challenge is the possibility of penicillin resensitization. If patients are evaluated early in their pregnancy course, the oral challenge after negative skin testing could potentially induce resensitization. This would put the patient at risk of having an adverse reaction when she receives intrapartum penicillin therapy. Studies performed in nonpregnant patients have revealed that resensitization is unlikely with oral penicillin exposure.^{26–28} One study reported that after day 3 of a 10-day course of oral penicillin V potassium, no participants converted from negative to positive skin testing.²⁸ These data suggest that testing earlier in pregnancy did not put patients at increased risk of resensitization; however, future non-IgE-mediated reactions would still be possible.

Although all patients tolerated oral challenge and intrapartum beta-lactam exposure, 3 patients reported adverse reactions with subsequent postpartum beta-lactam exposure. In 1 patient, her symptoms are suggestive of an adverse effect or intolerance to the drug. In 2 patients, a delayed rash of varying severity occurred. Skin prick testing does not adequately evaluate for delayed hypersensitivity reactions.²⁹ Pregnant women who undergo negative skin testing and tolerate the oral challenge may still be at risk for delayed hypersensitivity and other non-IgE-mediated immunologic reactions with subsequent beta-lactam exposure, but there is no evidence that this would be greater than the risk of the general population. Given that these reactions are generally mild and delayed in nature, it seems they would not affect immediate birth outcomes.²⁹

Interestingly, whether or not patients underwent outpatient in-office oral challenge did not affect their likelihood of receiving an intrapartum beta-lactam antibiotic. This finding could be because of patient preference. Previous literature reveals that many patients are hesitant to receive beta-lactam antibiotics even after a negative penicillin allergy evaluation.^{30,31} In addition, the persistent documentation of antibiotic allergy in the EMR may have contributed to whether or not a beta-lactam antibiotic was used. Often, despite negative skin testing and successful oral challenge, the penicillin allergy remains in the chart or is erroneously reentered.^{30,31} Data regarding this factor were beyond the scope of this study but could be evaluated in future research.

Although our study suggests outpatient in-office oral challenge is safe in pregnant women who complete negative penicillin skin testing, we are limited by the study's retrospective nature and its relatively small sample size. Whether or not patients received oral challenge depended entirely on the provider and patient preference. Our statistical analysis suggests these patients did not differ by important factors such as age, gestational age, or index reaction risk level; however, further studies are required to substantiate this finding. In addition, given the low incidence of adverse reaction to penicillin skin testing and oral challenge in the general population,

a much larger sample size would be needed to adequately evaluate the safety of these procedures in pregnant women.

Penicillin allergy evaluation in pregnant women allows for increased use of first-line therapy for GBS and SSI prophylaxis, and also other infections. The most recent American College of Obstetrics and Gynecology Committee Opinion on GBS prophylaxis recognizes that penicillin allergy testing is safe in pregnancy and acknowledges the benefit of testing in all women with penicillin allergy.⁷ Although there is a clear need for penicillin skin testing in pregnant patients, practices among allergists for performing this testing varies considerably. A recent American College of Allergy, Asthma, and Immunology DocMatter forum discussed penicillin testing in pregnant women. Practices varied from complete avoidance of all allergy evaluation to standard skin testing with immediate in-office oral challenge.³² The American Academy of Allergy, Asthma, and Immunology recommends routine penicillin allergy evaluation and states that this can be done safely in pregnant patients.³³ Our study suggests that outpatient skin testing, followed by an outpatient in-office oral amoxicillin challenge, is an acceptable strategy to evaluate penicillin allergy in pregnant women. Continued investigation in this area is needed to establish a standard of practice that facilitated improved health care outcomes and better antibiotic stewardship in pregnant women with self-reported penicillin allergy.

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