

The Importance of Penicillin Allergy Evaluation in Pregnant Women



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Penicillin allergy is self-reported by 8% of pregnant women; however, approximately 90% of these patients are not truly allergic and can tolerate penicillins.¹⁻⁴ These data are comparable to the rate of self-reported and confirmed penicillin allergy in the general population.⁵ The unnecessary withholding of penicillin and beta-lactam treatment in pregnant women mislabeled as penicillin-allergic leads to deleterious clinical outcomes. For example, beta-lactams are preferred treatments for surgical site infection prophylaxis in women undergoing cesarean delivery and for pregnant women with premature rupture of membranes (PROM). When non-beta-lactams are used, surgical site infections and PROM-related infectious endometritis occur at higher rates.^{6,7} In addition, treatment of Group B *Streptococcus* (GBS) infections may be compromised in women with a history of penicillin allergy. Up to a third of women have GBS vaginal colonization during pregnancy, placing neonates at risk of vertical transmission of the bacterial infection. Penicillin (or ampicillin) is the treatment of choice for intrapartum antibiotic prophylaxis because GBS is universally sensitive to these penicillins. Because GBS resistance to alternate non-beta-lactam treatments has risen, guidelines recommend penicillin allergy testing in all pregnant women who report a history of penicillin allergy.⁸ However, testing is rarely performed, resulting in suboptimal antibiotic prophylaxis.

Previous studies have demonstrated the safety and efficacy of penicillin skin testing in pregnant women. Macy et al² evaluated 56 pregnant women with GBS colonization and history of penicillin allergy, 95% of whom were skin test-negative. Although elective oral challenges were not performed to confirm tolerance, 47 patients (89%) subsequently received at least 1 course of intrapartum parenteral penicillin for GBS prophylaxis; 2 developed delayed-onset rashes. In a similar study by Philipson et al³ of 28 GBS-colonized pregnant patients with a history of penicillin allergy, 25 (89%) had negative penicillin skin testing. Although these patients did not undergo elective amoxicillin challenges, all 25 subsequently tolerated intrapartum penicillin for GBS

prophylaxis. Recently, Kuder et al⁴ confirmed the safety of penicillin skin testing followed by an elective outpatient oral amoxicillin challenge in pregnant women with a history of penicillin allergy. Forty-four of 46 (96%) pregnant women (irrespective of GBS status) with a history of penicillin allergy were skin-test negative. All 18 who proceeded with an amoxicillin challenge tolerated the antibiotic, as well as 27 patients who subsequently received intrapartum beta-lactam antibiotics.

In this issue of the *Journal of Allergy and Clinical Immunology: In Practice*, Wolfson et al⁹ report the results of a retrospective study on the evaluation of penicillin allergy in pregnant women receiving obstetric care at Massachusetts General Hospital between September 2017 and December 2019. All referrals to board-certified allergists were initiated by the treating obstetrician via an e-consult. Recommendations to the referring provider followed a structured approach based on the available allergy history in the patient's electronic health record: (1) for an intolerance (such as headache or gastrointestinal symptoms), penicillins may be used; (2) for a severe reaction (such as Stevens-Johnson syndrome) or for recurrent reactions to penicillins/beta-lactams, all beta-lactams should be avoided; (3) for a potentially IgE-mediated reaction (including all rashes) within the last 5 years, penicillins should be avoided; and (4) for a potentially IgE-mediated reaction or an unknown reaction more than 5 years ago, proceed with in-person evaluation with penicillin skin testing followed by single-dose amoxicillin 500 mg drug challenge in the third trimester; cefazolin use was encouraged, if needed, by a direct challenge/test dose procedure.

An in-person evaluation was recommended for 363 of 389 (93%) obstetric patients with a history of penicillin allergy. Of the 222 patients (62%) who received the recommended in-person evaluation, 220 (99%) underwent penicillin skin testing. Only 1 patient described subjective throat and tongue swelling during skin testing. Two hundred seventeen patients (99%) had negative skin tests, of whom 213 underwent an amoxicillin challenge and 210 (97%) passed. One patient experienced an immediate rash after the challenge, and 2 patients experienced delayed rashes, which resolved with antihistamines. Ultimately, 209 skin-tested patients (94%) had their penicillin allergy label removed. Compared with the 141 patients who did not follow through with an in-person evaluation, patients who completed an evaluation had decreased use of peripartum vancomycin (adjusted odds ratio [aOR]: 0.07 [95% confidence interval (CI): 0.01, 0.33]), clindamycin (aOR: 0.17 [95% CI: 0.08, 0.34]), and gentamicin (aOR: 0.39 [95% CI: 0.19, 0.78]), and increased penicillin use (aOR: 17.95 [95% CI: 6.30, 51.16]). Patients who completed evaluations also had increased first-line antibiotic prophylaxis for GBS (aOR: 26.87 [95% CI: 6.32, 114.33]) and Cesarean section (aOR: 1.94 [95% CI: 1.06, 3.52]).

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To date, the Wolfson et al study is the largest published cohort of pregnant women who underwent evaluation of penicillin allergy.⁸⁻⁴ By demonstrating the safety and efficacy of penicillin skin testing followed by a single-dose amoxicillin challenge, the study provides reassurance to allergists tasked with evaluating pregnant women reporting penicillin allergy. The addition of a confirmatory amoxicillin challenge after negative skin testing also aligns with the gold standard for assessing drug tolerance.¹⁰

Although the vast majority of penicillin-allergic pregnant women were delabeled, there are a few limitations to this study. Given that the setting of the study was a large, urban academic medical center with a predominantly white patient cohort (75%), the results may not be generalizable to other settings with more diversified demographics. The use of an e-consult program for referrals may also not be feasible for practices operating outside of academic settings. The authors also deemed all rashes to be potentially IgE-mediated. Although it is understandable that the intention was to maximize the safety of the protocol, positive penicillin skin tests do not reliably predict non-IgE-mediated challenge reactions, such as maculopapular exanthems.¹¹ However, because only 3 patients had a positive skin test, the study was minimally impacted. If patients report a remote history of a mild, delayed rash associated with positive skin tests, they could potentially be counseled to return for an amoxicillin challenge in the future after delivery.

Although the majority of in-person evaluations led to a significant reduction in the use of broad-spectrum antibiotics in favor of first-line beta-lactam antibiotics, 15% of patients with negative evaluations still received a beta-lactam alternative, whereas 54% did not receive a first-line antibiotic for GBS or Cesarean-section prophylaxis. Further research would be necessary to determine the barriers involved leading to suboptimal antibiotic choices despite negative penicillin allergy evaluations. It is possible that patients had concurrent infections that led to the decision to use a different antibiotic. However, it is also possible that some providers or patients remain leery of penicillin allergy testing and require additional education.

Notably, 141 of 363 patients (39%) did not complete the recommended in-person evaluation, most commonly (52%) for unknown reasons. An additional 15% canceled their appointments. For a delabeling program to have a greater impact, reasons why patients forwent evaluations should be investigated. As the authors noted, the use of an asynchronous e-consult rather than a

synchronous telemedicine consult may have played a role. Some pregnant patients may be anxious about the evaluation and may require further education. Ideally, penicillin allergy should be evaluated before pregnancy as a component of preconception counseling.

In summary, Wolfson et al's study demonstrated that a single-dose oral amoxicillin challenge in penicillin skin test-negative pregnant patients with low-risk histories is safe and can result in significant reductions in the use of broad-spectrum antibiotics and increased use of first-line beta-lactams in the peripartum period. This study positively impacts our current approach to the evaluation of penicillin allergy in pregnant patients by providing allergists with a safe and effective structured protocol.

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