

Safety of direct oral challenge to amoxicillin in pregnant patients at a Canadian tertiary hospital

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Clinical Implications

Low-risk pregnant patients can safely receive direct oral challenge without preceding skin testing to rule out a penicillin allergy.

Penicillin allergy assessment during pregnancy relies heavily on penicillin skin testing (PST).¹ Recently, Trubiano et al² have published a validated, point-of-care penicillin allergy clinical decision tool called PEN-FAST, which predicts the chance of a positive skin test with a negative predictive value of 96.3%. However, even after negative skin testing, very few pregnant patients receive oral challenge to penicillin because of unfounded risks.³ A 2019 systematic review evaluating PST and desensitization in 231 pregnant women reported that of 203 who underwent PST, 170 tested negative.⁴ Yet, only 16 participants completed the oral challenge despite a 100% success rate.⁴

In nonpregnant patients, direct oral challenge (DOC) in low-risk patients without preceding PST has good safety data.⁵ Several studies have shown that DOC is safe in ruling out allergy in patients with non-life-threatening historical penicillin reactions.⁶ Macy et al⁷ compiled results from 6 large studies showing a cumulative 1.3% (immediate) and 3.9% (delayed) reaction rate to DOC. Still, there remains limited data for the utilization of DOC among pregnant patients. Our group previously published data from our dedicated penicillin allergy clinic at BC Women's Hospital and Health Centre (BCWH).⁸ Here, we report the outcomes of the first 207 pregnant patients receiving DOC.

This study received an ethics and consent waiver from University of British Columbia Research Ethics Board as it was deemed a quality improvement and clinical care optimization project. Our clinic included pregnant women in their third trimester (28–36 weeks' gestation) with a history of penicillin allergy who planned to deliver at BCWH. Enrolled patients had their data prospectively collected into our clinic's REDCAP database. Parameters included baseline demographics, the timing and nature of their initial penicillin reaction, acute and delayed reactions after oral challenge, and subsequent treatments required for reactions.

Based on history, patients were stratified into low-, medium-, or high-risk groups using our validated algorithm.⁸ After the publication by PEN-FAST² in May 2020, we adopted it as our risk assessment tool. The PEN-FAST clinical decision tool categorized patients based on a score of 0 to 5.² Patients with a PEN-FAST score of 0 were classified as very low-risk and were offered DOC. Scores of 1 to 3 were grouped as medium-risk and

TABLE I. Baseline demographics for all enrolled participants

Baseline demographics	
Total number of patients	245
Maternal age	34.15 ± 3.99 y
BMI	26.51 ± 5.19
Gestational age	33.63 ± 2.93 wk
First pregnancy	68/269 (25.3%)
Maternal comorbidities	
Group B strep	30/151 (19.9%)
Gestational diabetes	26/151 (17.2%)
Preeclampsia	7/151 (4.6%)

Values for maternal age, body mass index (BMI), and gestational age are listed by mean ± standard deviation values. Values for first pregnancy, group B strep status, gestational diabetes, and preeclampsia are listed by number of patients (percentages).

scores of 4 to 5 were deemed high-risk. All patients who received DOC were included in the analysis. Of note, some individuals were delabeled of their allergy status through history alone because of recent documented tolerance to penicillins or avoidance due to family history. These were not included. Patients from the medium- and high-risk groups were also excluded from the final analysis.

Patients received 500 mg of amoxicillin orally and were monitored for 1 hour. Vital signs were done at baseline, 15 minutes, and 1 hour after ingestion. If there was no evidence of an IgE-mediated reaction, patients were discharged with written instructions to call the clinic if they had concerns of a delayed reaction.

Between July 2019 and September 2021, 245 pregnant patients were enrolled and assessed in our clinic, and their baseline demographics are displayed in Table I. Their penicillin allergy delabeling results are summarized in Figure 1. A total of 216 (88.2%) women were deemed low-risk: 207 (95.8%) underwent DOC and 9 (4.2%) were delabeled based on history alone. Twenty-eight medium-risk patients underwent PST before oral challenge. Of the 28 patients, 2 had equivocal tests to the PST and received no further testing. The rest received oral challenge without any reaction. One patient was excluded from testing because of being categorized as high-risk.

Most patients reported reactions over 10 years ago (77.0%), involving a maculopapular rash (49.0%) lasting <24 hours (20.3%) (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). After delabeling, 90% of patients were not worried about penicillin allergy reactions and 84% expressed comfort in taking penicillins in the future (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). Of the 207 women with DOC, 203 reported no immediate or delayed hypersensitivity. Only 4 (1.93%) women noted delayed-onset cutaneous reactions, all benign maculopapular rashes, and were subsequently treated with betamethasone valerate 0.1% ointment and oral antihistamines. One patient had delayed vomiting, which was deemed to be a side effect of pregnancy rather than the oral challenge. There were no cases of anaphylaxis and no admissions to hospital with complications of testing.

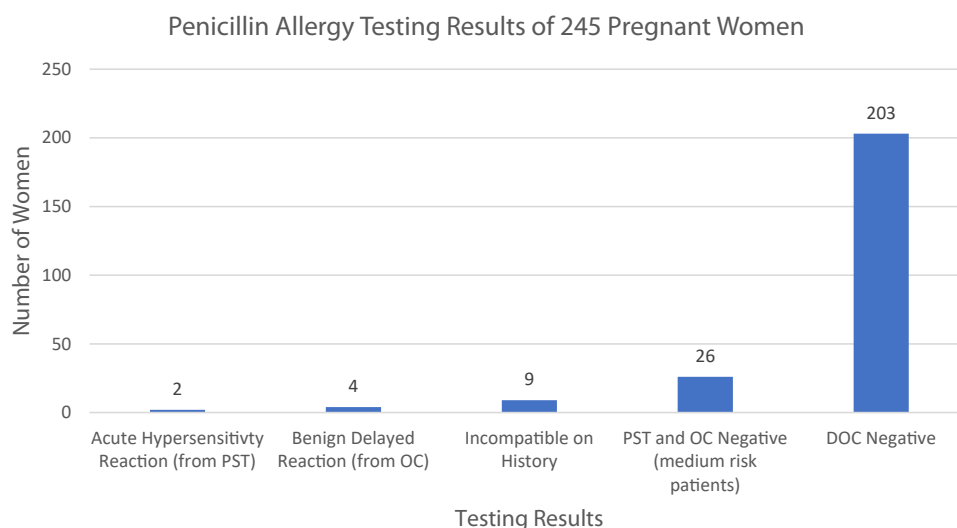


FIGURE 1. Testing of 245 pregnant women assessed at our penicillin allergy delabeling clinic. *DOC*, Direct oral challenge; *OC*, oral challenge; *PST*, penicillin skin testing.

We report the largest number of pregnant women to undergo DOC. Like nonpregnant populations, DOC in pregnant patients with low-risk allergy histories is safe in confirming current tolerance. Our observed rate of delayed cutaneous reactions (1.93%) was similar to the 1.99% reported among the nonpregnant adult population⁵ and 2.5% among pregnant populations.⁹ No patients were observed to have an objective immediate reaction and no patients required epinephrine in our study.

Over 85% of patients referred to our clinic were considered low-risk and candidates for DOC using a widely accessible risk stratification tool. With 1 study showing 86% of high-risk pregnant patients testing negative on intradermal testing to penicillin,⁹ there is the potential for oral challenge testing to be extended to these groups as well. Ultimately, DOCs can be performed safely in pregnant women by nonallergists, increasing access to penicillin allergy assessment in areas where allergists are not readily available. Reducing the need of PST will reduce costs associated with reagents, clinic time, and the need to see a subspecialist. Given the possible impact on prescribing during labor and delivery, this has the potential to significantly improve patient care.

Our study had a few limitations. First, all patients were recruited from a single tertiary care centre in Vancouver, BC. However, our population represents most obstetrical centers and pregnant persons, thus increasing generalizability. In addition, we changed our clinical risk stratification algorithm mid-way through the study in line with the best evidence in the field. Compared with PEN-FAST,² our original algorithm was more conservative. Thus, some earlier patients may have been candidates for oral challenge but received skin testing instead. Lastly, the true rate of delayed reactions may be higher than reported as patients with mild reactions may not feel the need to call our clinic to make a report.

The use of a risk stratification tool allows for point-of-care assessment of testing eligibility in pregnancy. Because DOC is safe and effective in delabeling penicillin allergies in the obstetric

population, pregnancy itself does not modify one's allergy risk score nor should it present as a barrier to DOC in the setting of allergy assessment.

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TABLE E1. Allergy history and patient satisfaction questions after assessment

Allergy History Questionnaire	
Nature of reaction	
Maculopapular rash	74/151 (49.0%)
Hives	52/151 (34.4%)
Angioedema	14/151 (9.3%)
Respiratory distress	8/151 (5.3%)
Gastrointestinal symptoms	11/151 (7.3%)
Unknown	23/151 (15.2%)
Length of reaction	
Reaction lasting <24 h	30/148 (20.3%)
Reaction lasting >48 h	23/148 (15.5%)
Unknown	95/148 (64.2%)
Last reaction to penicillin?	
>10 y ago	114/148 (77.0%)
>5 y ago	15/148 (10.1%)
1-5 y ago	8/148 (5.4%)
<1 y ago	2/148 (1.4%)
Patient Satisfaction Questions After Assessment	
How worried about a potential reaction are you if you were exposed to a penicillin?	
Very worried	0/140 (0.0%)
Somewhat worried	14/140 (10.0%)
Not worried	126/140 (90.0%)
Would you feel comfortable taking penicillin for an infection in the future?	
Not comfortable	2/142 (1.4%)
Somewhat comfortable	21/142 (14.8%)
Very comfortable	119/142 (83.8%)

Values are listed by number of patients (percentages).