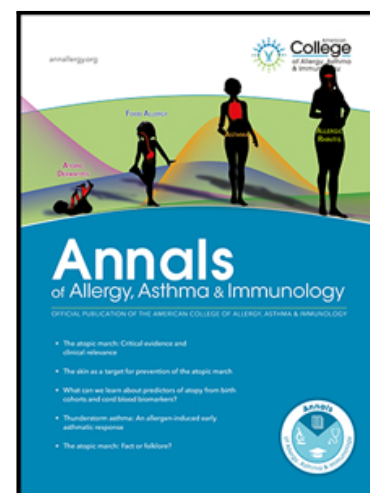


Accepted Manuscript

Direct oral amoxicillin challenge without antecedent penicillin skin testing in low-risk patients

Merin Kuruvilla MD Assistant Professor , Jamie Thomas PharmD

PII: S1081-1206(18)30608-2
DOI: [10.1016/j.anai.2018.07.024](https://doi.org/10.1016/j.anai.2018.07.024)
Reference: ANAI 2637



To appear in: *Annals of Allergy, Asthma Immunology*

Received date: 16 June 2018
Revised date: 7 July 2018
Accepted date: 17 July 2018

Please cite this article as: Merin Kuruvilla MD Assistant Professor , Jamie Thomas PharmD , Direct oral amoxicillin challenge without antecedent penicillin skin testing in low-risk patients, *Annals of Allergy, Asthma Immunology* (2018), doi: [10.1016/j.anai.2018.07.024](https://doi.org/10.1016/j.anai.2018.07.024)

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Direct oral amoxicillin challenge without antecedent penicillin skin testing in low-risk patients**Authors:**

- **Merin Kuruvilla, MD**

Assistant Professor – Allergy/Immunology

Emory University

- **Jamie Thomas, PharmD**

University of Illinois at Chicago

Corresponding Author Contact Information:

Merin Elizabeth Kuruvilla, MD

Address: 1365 Clifton Rd NE, Bldg A, 3rd Flr

Atlanta, GA-30322

Email: merin.ek1@gmail.com

Phone: 972-890-3847 (Home)

404-778-3261 (Business)

Fax: 404-778-4431

Financial support: None

Trial registration: Not applicable

Conflict(s) of Interest: None

Keywords: penicillin; drug allergy; skin test; drug provocation test

Direct oral amoxicillin challenge without antecedent penicillin skin testing in low risk patients

Temino et al recently described outcomes of an outpatient penicillin skin testing initiative in an allergy clinic (1). Consistent with other studies, >90% of patients labeled as penicillin (PCN) allergic were found to be tolerant of PCN. This is in accordance with current guidelines encouraging routine PCN allergy

verification in all comers with this diagnosis, in view of the substantial clinical and economic consequences of a PCN allergy label.

However, the standard performance of PST in all comers with PCN allergy may be prohibited by time, personnel, and/or other resource constraints. We currently recommend direct oral amoxicillin challenge in subjects who report a low-risk history of penicillin allergy, which accounts for a sizeable proportion of this population. Specifically, direct drug provocation testing (DPT) is advocated in patients with a remote history (>1 year) of benign rash, other benign somatic symptoms, or unknown reaction.

Our protocol (Figure 1) is based upon the accumulating body of evidence exploring the safety of direct oral challenges without antecedent skin tests in populations with histories of low-risk penicillin allergy (2-5). With careful selection the vast majority of direct PCN challenges in the literature have been negative. In a cohort of Marine recruits, only 5 (1.5%) recruits had immediate reactions during direct amoxicillin challenges (2). Five-day oral challenges without preliminary skin testing have also been found to safely exclude clinically significant delayed-onset reactions in children with previous nonimmediate reactions to penicillin (5). In another pediatric study of patients with amoxicillin-induced rashes – 94% of children tolerated DPT while the remainder developed mild reactions (4). Most recently, Iammatteo et al. reviewed the outcomes of 155 direct amoxicillin challenges and found a reaction rate of 2.6% (3).

We currently recommend obtaining a penicillin allergy history in all patients with this label and performing a single full dose challenge with oral amoxicillin 250 mg in eligible patients. Our current success rate is greater than 99% (manuscript in preparation).

Another important caveat is that a positive PST does not necessarily predict challenge reactions. A recent study demonstrated that 60% of patients with a positive skin test were challenge-negative to the culprit penicillin (6). Several other studies have also reported negative challenges in patients with a positive skin test and vice-versa (7-9). Positive PSTs also tend to decline over time, and even within the space of a few months (10).

Other studies have described the safety of direct oral challenges in low-risk adult patients and poor correlation between positive oral challenge and positive skin and/or in vitro test results. Caubet et al. provided additional data supporting direct oral challenge to evaluate penicillin allergy in all patients with benign rashes as the index event (7). They noted that both PST and in-vitro testing add little to safety and are associated with a high rate of false positive reactions. Another recent study showed a reaction rate of 6.1% with drug challenge regardless of PST results (8) – and all reactions were uniformly mild and benign. Most recently, Ibanez et al highlight the superfluity of PST in a large pediatric cohort (9). PCN allergy was diagnosed based on positive DPT in 35 (4.8%) out of 732 patients and this was unrelated to PST results.

Further, the results of PST are only predictive of IgE-mediated reactions and PST is thus only useful for patients with a history of penicillin allergy that is consistent with IgE-mediated allergy. PST offers no predictive value for non-IgE-mediated events which accounts for the bulk of penicillin allergy. Concern has also been raised regarding the need for using both minor determinant mixture and amoxicillin as PST reagents, neither of which are currently included for PST in the United States.

However, most of the data supporting DPT has originated from single center studies. Pending further multi-institutional studies with larger cohorts, this approach of DPT without antecedent skin testing

should be considered only in subjects with a history of mild cutaneous reactions or similarly benign symptoms.

References:

1. Temino VM, Gauthier TP, Lichtenberger P. Outpatient penicillin skin testing has greater value in targeted patient populations. *Ann Allergy Asthma Immunol.* 2018;120(4):441-2.
2. Tucker MH, Lomas CM, Ramchandrar N, Waldram JD. Amoxicillin challenge without penicillin skin testing in evaluation of penicillin allergy in a cohort of Marine recruits. *J Allergy Clin Immunol Pract.* 2017;5(3):813-5.
3. Iammatteo M, Alvarez Arango S, Ferastraoraru D, et al. Safety and Outcomes of Oral Graded Challenges to Amoxicillin without Prior Skin Testing. *J Allergy Clin Immunol Pract.* 2018.
4. Mill C, Primeau MN, Medoff E, et al. Assessing the Diagnostic Properties of a Graded Oral Provocation Challenge for the Diagnosis of Immediate and Nonimmediate Reactions to Amoxicillin in Children. *JAMA Pediatr.* 2016;170(6):e160033.
5. Labrosse R, Paradis L, Lacombe J, et al. Efficacy and Safety of 5-Day Challenge for the Evaluation of Nonsevere Amoxicillin Allergy in Children. *J Allergy Clin Immunol Pract.* 2018.
6. Tannert LK, Mortz CG, Skov PS, Bindselev-Jensen C. Positive Skin Test or Specific IgE to Penicillin Does Not Reliably Predict Penicillin Allergy. *J Allergy Clin Immunol Pract.* 2017;5(3):676-83.
7. Caubet JC, Kaiser L, Lemaitre B, Fellay B, Gervais A, Eigenmann PA. The role of penicillin in benign skin rashes in childhood: a prospective study based on drug rechallenge. *J Allergy Clin Immunol.* 2011;127(1):218-22.
8. Confino-Cohen R, Rosman Y, Meir-Shafir K, et al. Oral Challenge without Skin Testing Safely Excludes Clinically Significant Delayed-Onset Penicillin Hypersensitivity. *J Allergy Clin Immunol Pract.* 2017;5(3):669-75.
9. Ibanez MD, Del Rio PR, Lasa EM, et al. Prospective assessment of diagnostic tests for pediatric penicillin allergy, from clinical history to challenge tests(,,). *Ann Allergy Asthma Immunol.* 2018.
10. Tannert LK, Falkenroth S, Mortz CG, Bindselev-Jensen C, Skov PS. Is a positive intracutaneous test induced by penicillin mediated by histamine? A cutaneous microdialysis study in penicillin-allergic patients. *Clin Transl Allergy.* 2017;7:40.

111
112

4

ACCEPTED MANUSCRIPT