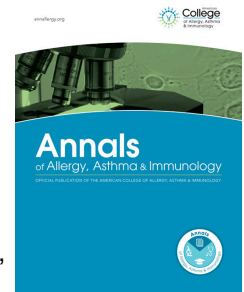


Accepted Manuscript

Evaluating Penicillin Allergies in Children Using a Standard EMR-based Questionnaire

Cathleen A. Collins, M.D., Ph.D., David Choe, Pharm.D., Dylan Mochizuki, Pharm.D., Christopher R. Cannavino, M.D.



PII: S1081-1206(19)30181-4

DOI: <https://doi.org/10.1016/j.anai.2019.03.002>

Reference: ANAI 2840

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

Received Date: 30 January 2019

Revised Date: 25 February 2019

Accepted Date: 4 March 2019

Please cite this article as: Collins CA, Choe D, Mochizuki D, Cannavino CR, Evaluating Penicillin Allergies in Children Using a Standard EMR-based Questionnaire, *Annals of Allergy, Asthma and Immunology* (2019), doi: <https://doi.org/10.1016/j.anai.2019.03.002>.

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.

Evaluating Penicillin Allergies in Children Using a Standard EMR-based Questionnaire

Cathleen A. Collins* M.D., Ph.D.¹, David Choe, Pharm.D.³, Dylan Mochizuki Pharm.D.³, Christopher R. Cannavino, M.D.²

¹Division of Allergy, Immunology, ²Infectious Disease, University of California San Diego and Rady Children's Hospital, San Diego, La Jolla, California and Rady Children's Hospital San Diego Pharmacy³

Correspondence:

*Cathleen Collins, MD, PhD
Assistant Professor of Pediatrics
7960 Birmingham Drive
San Diego, CA 92123
C4collins@ucsd.edu
Phone: 858-966-5961
Fax: 858-966-6791

Conflicts of interest: None.

Funding source: none

Clinical trial registration: N/A

Key words: Beta-lactam allergy, Penicillin allergy, Drug allergy

Abbreviations: None

Word-count: 1000

Figures: 1

Tables: None

A 2016 AAAAI position statement recommended routine evaluation of penicillin allergies due to the burden of pervasive mislabeled or outgrown allergies.¹ Overdiagnosis of penicillin allergies is an increasingly recognized public health problem, resulting in longer hospitalizations, use of costly antibiotics with potential harmful side effects and infection with resistant organisms.² The scale of the problem is daunting; for example, at Rady Children's Hospital San Diego (RCHSD), with 1.4 million children in its EMR, there are more than 40,000 (2.8%) children labeled with penicillin allergies. Significant resources will be needed to clear these.

Recent consensus reports agree that skin testing can be bypassed in patients with low-risk histories and it is safe to proceed directly to an oral challenge amoxicillin to confirm current tolerance.^{3,4,5,6} In children, this practice would be safest in patients with histories of mild delayed reactions but there are no standardized tools supported by evidence to confirm the history; studies have excluded those "life-threatening reactions" but drug allergies are often unpredictable.⁷ In one study, there was a 2% immediate reaction rate among those tested without skin testing⁴; though there were no severe reactions, this level of risk may not be acceptable to parents and pediatricians, especially if the challenges are to be conducted outside an allergist's office, which may be necessary to deal with the scope of the problem. Here we describe a tool allowing for safe administration of direct oral amoxicillin challenge without skin testing.

We used a survey tool built as an EPIC Smartform to evaluate children presenting to allergy clinic with penicillin allergies (Figure 1). The survey focused on four variables: the day the reaction occurred and 3 features of the associated rashes (mobility, elevation, and duration). Children received skin testing if they had a reaction on the first day, if the rash was mobile and elevated (suggestive of hives) or if the rash

lasted less than one day. Skin testing was also offered if the parent was uncomfortable proceeding directly to challenge. Contraindications to testing were also included in the survey, i.e. features of dangerous delayed hypersensitivity reactions. The oral amoxicillin dose was weight-based at 45 mg/kg (maximum 875 mg) and divided in two doses (10% then 90%) with 15 minutes of observation after the first dose and an hour observation after the final dose.

Based on these criteria, 17 out of 64 (26.6%) children qualified for penicillin skin testing using a standard protocol of prick and intradermal testing. Two children had positive intradermal tests, one with 10 mm wheal/15 mm flare to penicillin, and the other with 4 mm wheal/8 mm flare to penicillin. One had a history of a reaction involving only lip swelling on the first day of penicillin, and the other had an unclear reaction on the first day of amoxicillin. Nine had prick and intradermal skin testing and 6 had incomplete skin testing due to discomfort; all 15 tolerated oral challenges. The remaining 48 had direct oral challenges. Two had reactions; both were 2-year-old boys with history of raised, nonmobile rashes on the 2nd to 3rd day of amoxicillin. During the challenge, one had a single hive that developed on his lip and resolved without treatment, and the other had worsening of an eczematous rash that was already present. Both had history of rashes unrelated to penicillins, and will follow-up for skin testing and rechallenge. 60 out of 64 children received oral challenges without reactions (93.8%).

As expected from clinical experience, many patients gave histories that mixed elements of immediate and delayed reactions. To quantify this phenomenon, we assigned one point for every aspect of a delayed reaction (occurring after the first 24

hours; a rash that was fixed or started in one spot and spread; a flat rash; or a rash lasting longer than 24 hours). Points were given for any features that were remembered. Ten children had a score of 0, consistent with immediate reactions, and 11 had a score of 4 out of a total of 4 points possible. Reaction on the first day of the medication was the most consistent predictor of a positive skin test; however, there were 12 children with reactions on the first day that passed oral challenges after skin testing was negative. Seven children qualified for skin testing based on having both a raised and a mobile rash; all of these children had negative oral challenges.

In addition to using the tool to direct skin testing in clinic, we administered it to study the features of reactions among hospitalized children at RCHSD over a 6 month period. The survey was given by pharmacy residents and students, based on a real-time EPIC list identifying all admitted children labeled with penicillin allergies. A Best Practice Advisory and automatic referral to allergy clinic was created.

Of the 104 admitted children interviewed, 31 had reactions that would qualify them for skin testing based on a reaction on the first day (29.5%), or a rash that moved around and was raised (4%). Eight had reactions where all 4 elements of delayed hypersensitivity were endorsed (7.6%).

Caveats to this study include potential bias of children self-selected into the study; not all families agreed to be interviewed, and there may be a natural selection of families who are interested to have their allergies cleared. In addition, as RCHSD is a tertiary care center; we might expect different features among a broader patient population.

70 However, the strength of this study is that it provided a practical assessment tool
71 that may be used to triage children into allergy clinics in the future. Safely expanding the
72 capacity to do challenges will require careful risk assessment, especially as
73 documented many patients have histories with mixed features. Here we provide
74 evidence that patients with history of reactions on the first day of medication and
75 younger patients that are prone to other rashes are the most suitable for triage into full
76 evaluation by an allergist, as this is often the rate-limiting step in expanding penicillin
77 allergy delabeling as part of antibiotic stewardship.

78

References:

1. Lang, DM, Castells MC, Khan DA, Macy EM, Murphy AW. Penicillin Allergy Testing Should Be Performed Routinely in Patients with Self-Reported Penicillin Allergy. *J Allergy Clin Immunol Pract.* 2016;5: 333–4.
2. Macy E, Contreras R. Healthcare utilization and serious infection prevalence associated with penicillin “allergy” in hospitalized patients: a cohort study. *J Allergy Clin Immunol.*2014;133:790-6.
3. 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; 5:813-5.
4. 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; 7:236-43.
5. Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and Management of Penicillin Allergy. *JAMA.*2019; 321:188-99.
6. Torres MJ, MD, Adkinson Jr NF, Caubet JC, et al. Controversies in drug allergy: beta-lactam hypersensitivity testing. *J Allergy Clin Immunol Pract.*2019;7:40-5.
7. 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. doi: 10.1001/jamapediatrics.2016.0033.

An EPIC Smart-Form with clickable tabs for documentation of allergies, with the questions listed here. Free text boxes were included for parent response to open ended questions.

Beta-Lactam Allergy Questionnaire Epic Smart-form

Approximately how old were they when the reaction occurred?

What was the indication for amoxicillin?

Had they had amoxicillin before without problems? Yes/ No / Unsure

On what day of taking the medication did the reaction occur? 1st Day / Day 2-3 / Day 3-10 / After Day 10 / Unsure

Did they have a rash? Yes / No / Unsure

Was it raised, flat or both? Raised / Flat / Both / Unsure

Was it itchy? Yes / No / Unsure

Different kinds of rashes can behave differently. Some stay in the same place. Some come and go or move around and will change location within a few hours of starting. Other rashes start in one spot and spread out from there. If you had to pick one description, which would fit:

Stayed in the same location / Move around & come and go / Started in one spot and spread / Unsure

How many days did it last? Less than a day / 2-4 days / More than 4 days / More than a week / Unsure

Did your child receive antihistamines such as Benadryl? Yes / No / Unsure

Did the antihistamines help? Yes / No / Unsure

Do you have any pictures of the rash? Yes / No / Unsure

Did they have a fever at the time? Yes / No / Unsure

Did you take your child to the doctor during the reaction? Yes / No / Unsure

Please note any associated symptoms that occurred during the reaction?

Vomiting / Diarrhea / Trouble breathing / Facial swelling / Lip swelling / Lip peeling / Skin peeling / Tongue itching / Throat itching / Throat closing / Enlarged lymph nodes / Joint swelling / Joint pain / Trouble walking / Dizziness / Low blood pressure / None / Unsure

Please describe the reaction in your own words.

What other antibiotics has your child had since the reaction? None / Amoxicillin /

Penicillin Augmentin / Azithromycin / Bactrim / Ciprofloxacin / Clindamycin / Other / Unsure

What other antibiotics have had they had reactions to? None / Amoxicillin / Penicillin / Augmentin / Azithromycin / Bactrim / Ciprofloxacin / Clindamycin / Other / Unsure

Do you have a family history of drug allergy? If so, please describe.