Amoxicillin challenge without penicillin skin testing in evaluation of penicillin allergy in a cohort of Marine recruits

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Clinical implications

- Most patients reporting penicillin allergy are not truly penicillin allergic. Excluding penicillin allergy in these individuals has significant benefits. Oral amoxicillin challenge is a safe way to evaluate low-risk individuals with a history of penicillin allergy.

TO THE EDITOR:

Penicillin (PCN) allergy is reported by approximately 7% to 10% of patients, which makes it one of the most common medication allergies.[1,2] Having the diagnosis of PCN allergy on one's record has a significant impact on health-related outcomes. It increases cost, antibiotic-related complications, and hospital length of stay.[3,4] In addition, more than 90% of individuals reporting PCN allergy are not found to be allergic after appropriate evaluation.[5] These findings highlight the importance of evaluating patients reporting PCN allergy to determine whether the diagnosis is appropriate.

Marine recruits commonly report PCN allergy upon arrival to basic training. More than 16,000 Marine recruits are trained annually at the Marine Corps Recruit Depot (MCRD) in San Diego, California. Only male recruits typically between the ages of 18 and 25 years are trained at MCRD San Diego. The diagnosis of PCN allergy has significant implications during and after recruit training. Recruits typically receive injections of PCN G benzathine as part of a standard prophylaxis strategy against streptococcal infections. However, if they report PCN or cephalosporin allergy, they will receive prophylactic azithromycin instead. Time constraints during recruit training often prevent a thorough evaluation of reported PCN allergy and many recruits will be assigned to locations that do not have access to an allergist, thus allowing this diagnosis to remain with them throughout their time in the service.

Skin testing with commercially available PCN determinants, followed by oral amoxicillin challenge, if skin test result is negative, has been shown to be a safe and effective method to determine acute PCN tolerance.[6] However, there are certainly individuals, such as military recruits, who may not get such an in-depth evaluation due to their unique circumstances. This study is a retrospective chart review intended to determine the safety of oral amoxicillin challenge without preceding PCN skin testing in Marine recruits at MCRD. This streamlined method of testing may allow more individuals to receive appropriate evaluation and avoid the negative consequences of carrying the diagnosis unnecessarily. Previous studies have suggested that PCN skin testing has a relatively high rate of false-positive results,[7,8] and that oral challenge alone may be a suitable method of evaluation, particularly in patients who had nonimmediate cutaneous reactions.[9]

Many of the Marine recruits arriving at MCRD between July 2014 and March 2016 were evaluated by an allergist stationed at MCRD if they reported PCN or cephalosporin allergy. PCN allergy evaluation took place only if the recruit training schedule permitted and the allergist on site was available. Of the recruit companies screened, there was approximately a 5% self-reporting PCN allergy rate. Reaction history, exposure since reaction, and additional pertinent medical history were obtained before evaluation. Initially, under the supervision of the allergist, the recruits were evaluated via PCN skin testing with penicilloylpolylysine (PRE-PEN) and PCN G, and if negative, they were challenged with amoxicillin 250 mg. However, because of time constraints and 74 consecutive negative skin test results (followed by negative amoxicillin challenge), subsequent recruits bypassed skin testing and proceeded directly to amoxicillin challenge. If no reaction occurred, PCN allergy was removed from their record and they received intramuscular PCN G benzathine per the standard MCRD recruit prophylaxis protocol. In those who passed an amoxicillin challenge, there were no subsequent reactions to intramuscular PCN G benzathine (0 of 397). Recruits who reacted to skin testing or oral challenge were considered PCN allergic and were instructed to avoid PCN antibiotics, and they received azithromycin for prophylaxis. Recruits were excluded if they had a history of PCN-associated serious cutaneous reactions (excluding urticarial/angioedema), hepatitis, hemolytic anemia, or nephritis. However, there were no recruits presenting with this history. A small number of recruits were excluded because of refusal to consent (n = 12), of whom 2 had previously been evaluated for PCN allergy.

After approval from the Institutional Review Board at Naval Medical Center San Diego, we performed a retrospective chart review of the electronic medical record to assess the results of these PCN allergy evaluations done at MCRD. Candidates were identified by *International Classification of Diseases, Tenth Revision* code Z88.0 and *International Classification of Diseases, Ninth Revision* code V14.0, and by review of medical intake forms submitted at the beginning of recruit training. Demographic and medical information was collected on each recruit. The results of the skin testing and/or amoxicillin challenge were collected and analyzed as well to assess the frequency and severity of reactions.

A total of 402 recruits were included in the study. Background data on these recruits are presented in Table I. Seventy-four recruits underwent skin testing in addition to amoxicillin challenge. None of these recruits reacted to either skin testing or challenge. The remaining 328 recruits went directly to amoxicillin challenge without skin testing, and only 5 (1.5 %) had an acute objective challenge reaction. Thus, only 1.2% of all recruits evaluated were documented to have PCN allergy. There were no cases of anaphylaxis and all 5 were isolated cutaneous reactions except for 1, which included globus. All 5 recruits were treated with an oral antihistamine and with a single dose of intramuscular epinephrine to avoid reaction progression. None of them needed additional medication or transfer to a higher level of care. Table II summarizes the baseline characteristics of these

TABLE I. Characteristics of the recruits who underwent PCN allergy evaluation

Characteristic	N (%)
Inciting medication	
PCN	295 (73.5)
Amoxicillin	77 (19.2)
Cephalosporin	27 (6.7)
Azithromycin	1 (0.2)
Unknown	2 (0.4)
Reaction type	
Cutaneous	306 (76.1)
Respiratory	4 (0.9)
Gastrointestinal	6 (1.5)
Multisystem	7 (1.7)
Unknown	79 (19.8)
Age at reaction (y)	
<1	117 (29.1)
1-6	164 (40.8)
7-12	55 (13.7)
>12	21 (5.2)
Unknown	45 (11.2)
Exposure to PCN since initial reaction	
No	366 (91.0)
Yes	36 (9.0)
Reacted	9 (25.0)
Did not react	12 (33.3)
Unknown	15 (41.7)
Medical history	
Other medication allergies	34 (8.5)
History of "childhood asthma"	25 (6.2)
History of aeroallergy	109 (27.1)
Family history of medication allergy	105 (26.1)

TABLE II. Characteristics of recruits who reacted to amoxicillin challenge

Patient	Inciting drug	Age at rxn (y)	Type of rxn	Repeat exposure to a PCN	Fhx of drug allergy	Asthma history	Aeroallergy history	Other drug allergies
1	Augmentin	3	Rash	Y—No reaction	Y	N	Y	N
2	Amoxicillin	Unknown	Unknown	N	Y	N	N	Y
3	PCN	2	Rash	N	Y	N	Y	N
4	PCN	<1	Hives	N	Y	N	N	N
5	PCN	Unknown	Unknown	N	N	N	N	N

Fhx, Family history; *N*, no; *Rxn*, reaction; *Y*, yes.

5 recruits. No statistical analysis was performed given the small number of reactors.

In summary, most physicians would agree that IgE-mediated drug allergy can be life-threatening and must be taken seriously. However, most patients reporting PCN allergy are not allergic. Only 1.2% of the patients in our study turned out to have evidence of a clinically significant IgE-mediated PCN allergy. Given the negative consequences of mislabeling patients PCN allergic, allergists should evaluate those reporting such allergy to decide whether continued avoidance is necessary. PCN allergy evaluation must be done safely, but efficiency is also an important factor. This study suggests that low-risk populations, such as military recruits, may be appropriate candidates for direct oral challenge under the supervision of an allergist in a properly equipped facility. Such patients may otherwise never get an evaluation. Future studies are warranted to assess the long-term outcomes with future antibiotic use after tolerance of an oral amoxicillin challenge.

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REFERENCES

1. Lieberman P, Nicklas R, Oppenheimer J, Kemp SF, Lang DM, Bernstein DI, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. J Allergy Clin Immunol 2010;126:477-480.e1-42.
2. Solensky R, Khan DA, Bernstein IL, Bloomberg GR, Castells MC, Mendelson LM, et al. Drug allergy: an updated practice parameter. Ann Allergy Asthma Immunol 2010;105:259-73.
3. 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.
4. Picard M, Begin P, Bouchard H, Cloutier J, Lacombe-Barrios J, Paradis J, et al. Treatment of patients with a history of penicillin allergy in a large tertiary-care academic hospital. J Allergy Clin Immunol Pract 2013;1:252-7.
5. Macy E, Ngor E. Safely diagnosing clinically significant penicillin allergy using only penicilloyl-poly-lysine, penicillin, and oral amoxicillin. J Allergy Clin Immunol Pract 2013;1:258-63.
6. Macy E. Penicillin allergy: optimizing diagnostic protocols, public health implications, and future research needs. Curr Opin Allergy Clin Immunol 2015;15:308-13.
7. Caubet JC, Frossard C, Fellay B, Eigenmann PA. Skin tests and *in vitro* allergy tests have a poor diagnostic value for benign skin rashes due to β-lactams in children. Ped Allergy Immunol 2015;26:80-2.
8. Caubet JC, Kaiser L, Lemaitre B, Fellay B, Gervaix A, Eigenmann PA, et al. The role of penicillin in benign skin rashes in childhood: a prospective study based on drug rechallenge. J Allergy Clin Immunol 2011;127:218-22.
9. Bourke J, Pavlos R, James I, Phillips E. Improving the effectiveness of penicillin allergy de-labeling. J Allergy Clin Immunol Pract 2015;3:365-374.e1.