

Penicillin skin testing in the management of penicillin allergy in an outpatient pediatric population

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ABSTRACT

Background: Eight to ten percent of patients believe that they are allergic to penicillin, yet only 10% of those patients have evidence of an immunoglobulin E (IgE) mediated allergy upon penicillin skin testing (PST). In the adult population, a negative PST result is associated with a low risk of immediate reaction on oral challenge, but further studies are needed in the pediatric population.

Objective: To calculate the negative predictive value (NPV) of the current skin testing regimen of penicillin, benzylpenicilloyl-polylysine (the major determinant), and ampicillin in a pediatric outpatient population to assess the utility of adding the minor determinant mixture to the skin testing regimen.

Methods: A retrospective chart review was conducted of all pediatric patients seen in a single-center pediatric allergy/immunology outpatient clinic between January 1, 2010, and March 1, 2016, who underwent PST for presumed penicillin drug allergy.

Results: Only 38% of patients who underwent PST had a drug reaction history consistent with an IgE-mediated reaction. 28.8% of the patients had a positive PST result. The addition of ampicillin to the standard PST regimen of penicillin and benzylpenicilloyl-polylysine identified an additional 4.1% of patients. Two patients (3.2%) reacted on oral challenge with a minor rash. The NPV of the PST regimen was 98%. No significant predictive variables for a positive PST result were identified.

Conclusion: Given the high NPV of the current PST regimen, we do not recommend additional testing with the minor determinant mixture. Despite this high NPV, the utility of PST in the low-risk, low-pretest probability outpatient pediatric population was limited, and select patients may be able to proceed directly to oral challenge.

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Eight to ten percent of patients who visit subspecialty clinics, urgent cares, and hospitals believe themselves to be allergic to penicillin.^{1–3} However, only ~6–8%^{4,5} of these patients have evidence of an immunoglobulin E (IgE) mediated penicillin allergy when evaluated by penicillin skin testing (PST). Yet, many physicians on hearing of a patient's presumed penicillin allergy elect not to use penicillins or other lactam antimicrobials. This unnecessarily exposes patients to broad-spectrum antibiotics, which are associated with more adverse effects, may be less efficacious, contribute to multidrug resistant organisms, and are often of greater monetary cost.^{6,7}

Penicillin is metabolized into major and minor determinants. The majority of penicillin is converted into the major determinant penicilloyl, a small amount remains

as penicillin, and a very small amount is converted into the minor determinants penicilloate and penilloate. Most patients who are allergic to penicillin are allergic to penicillin metabolites, although some react to the core structure of penicillin and others react to the R-side chain on the aminopenicillins. Thus, PST is usually performed with penicillin G (PenG), the major determinant benzylpenicilloyl-polylysine (PrePen), and, if available, a minor determinant mixture (MDM) of penicilloate and penilloate and/or an aminopenicillin (ampicillin or amoxicillin).

The currently proposed negative predictive value (NPV) of PST with PenG and PrePen is very high, with an approximate 1–3%^{4,8} risk of immediate reaction on oral challenge, but studies suggest that the false negative rate may be higher in children⁹ and that testing with the full MDM panel can identify up to another 10% of patients who are allergic to penicillin.¹⁰ Skin testing with aminopenicillins is important in the pediatric population given the frequent use of amoxicillin. At our institution, we currently skin test with PenG, PrePen, and ampicillin but do not use MDM. The primary end point of this study was to calculate the NPV of our current PST regimen to assess if there is utility in adding MDM testing in our population to minimize the risk of allergic reaction on oral challenge. Secondary end points included assessing the additional value

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of aminopenicillin testing and identifying predictive variables for positive PST results.

METHODS

After institutional review board (University of California–San Diego) approval, a retrospective chart review was undertaken of all pediatric patients seen in the allergy/immunology outpatient clinic at Rady Children’s Hospital San Diego between January 1, 2010 and March 1, 2016, who underwent PST for presumed penicillin drug allergy. Standard skin testing procedure in the clinic includes percutaneous skin-prick testing (SPT), followed by intradermal testing (IDT), followed by oral challenge. The reagents used in SPT and IDT were PenG 10,000 units/mL (McKesson, San Francisco, CA) stored at 4°C and diluted in clinic, PrePen (Alk-Abello, Copenhagen, Denmark) in 0.25-mL single-use ampules, and ampicillin (McKesson) 10 mg/mL for SPT and 1 mg/mL for IDT reconstituted by the pharmacy and immediately diluted in the clinic.

Histamine (1 mg/mL) was the positive control, and normal saline solution was the negative control. All the patients refrained from using antihistamines for ≥ 1 week before skin testing. A positive SPT result was defined as a wheal of ≥ 5 mm with flare when the skin site was examined 15 minutes after the reagent was introduced. If the SPT result was negative, then IDT was undertaken by using 0.1 mL of the above solutions. A positive IDT result was defined as a wheal of ≥ 5 mm with flare when the skin site was examined 15 minutes after the reagent was introduced.

If the IDT result was negative, then oral challenge was undertaken with amoxicillin 50 mg/kg. The patients were given 10% of the total dose, and, if no reaction occurred after 15 minutes, then the remaining 90% was administered and the patient was observed for an additional 60 minutes. The patients who had inconclusive IDT results or declined IDT were allowed to undergo oral challenge, depending on the clinical history per the discretion of the attending physician. A failed oral challenge occurred when there was an adverse drug reaction (ADR) on ingestion, including symptoms of rash, angioedema, respiratory compromise, gastrointestinal (GI) upset, or hemodynamic instability. A patient was considered to not be allergic to penicillin only if he or she did not react upon oral challenge. No delayed reaction testing or challenge was performed.

A chart review was performed to collect data on the patient’s age, gender, history of atopy, time from the last penicillin reaction, reaction symptoms, offending drug, and penicillin drug testing results. From these data, the rates of skin test positivity to SPT, IDT, and oral challenge were calculated for each reagent. We

Table 1 Demographic characteristics

Characteristics	Patients, no. (%)
Gender	
Boys	44 (55)
Girls	36 (45)
Age at reaction, y	
<1 y	10 (14)
1–4 y	47 (64)
5–9 y	12 (16)
>10 y	5 (6.7)
Duration between reaction and testing	
<5 y	54 (71)
≥ 5 y	22 (29)
Atopy	46 (57.5)
Asthma	20 (27.5)
Allergic rhinitis	31 (36)
Eczema	15 (19)
Food allergy	11 (14)
Antibiotic	
Only amoxicillin or amoxicillin-clavulonate	61 (79)
Combined amoxicillin-cephalosporin	11 (14)
“Penicillin”	5 (6.4)

also calculated the NPV of our current PST protocol by using oral challenge to amoxicillin as the criterion standard. Statistical analysis was used to attempt to identify variables predicting positive PST results. Odds ratios for each variable of interest were calculated by using the maximum likelihood estimation (MLE). Logistic regression was performed for the continuous variables atopy (defined as the number of atopic diseases that a child had) and time from the last penicillin reaction.

RESULTS

Eighty patients were included in this cohort (Table 1). The mean age of the patients for PST was 7.3 years, with a mean age at reaction of 3.3 years, which indicated, on average, 4.0 years passed between the initial reaction and the PST. Fifty-eight percent had a history of atopy (28% asthma, 36% allergic rhinitis, 19% eczema, 14% food allergy). The most common reported offending antibiotic was amoxicillin (93%) either as pure amoxicillin or amoxicillin-clavulanate, with the remainder only able to identify a penicillin-type drug that caused a reaction. Fourteen percent of the patients reported a drug reaction to both amoxicillin and a cephalosporin. The most common immediate reaction to the drug was nonurticarial rash (65%), followed by urticaria (32%), and angioedema (9%) (Table 2). Thirty-

Table 2 Type of reaction

	Patients, no. (%)
Reaction	
Rash	50 (65)
Hives	25 (32)
Angioedema	7 (9.1)
Respiratory symptoms	1 (1.3)
Gastrointestinal symptoms	0
Hemodynamic instability	0
Joint symptoms	2 (2.6)
Possible immunoglobulin E mediated	29 (38)

eight percent of the patients had symptoms concerning for IgE mediated reaction, with hives or facial swelling or symptoms of anaphylaxis. Only one patient (1.3%) had a high-risk reaction associated with respiratory symptoms, GI upset, or hemodynamic instability.

SPT with PenG, PrePen, and ampicillin was performed on 80 patients and did not identify any patients with a wheal of ≥ 5 mm. Seventy-three of the 80 patients proceeded to IDT; 28.8% of the patients tested positive (Fig. 1). Of the 73 who underwent IDT, 19.2% reacted to PenG, 8.3% to PrePen, and 13.7% to ampicillin; 4.1% of the patients reacted to ampicillin alone. Sixty-two patients proceeded to oral challenge (50 patients with negative IDT results, 6 patients who declined IDT, 6 patients with positive IDT results); 96.8% had no reaction, 3.2% (2/62) had a mild reaction with rash. No patients had a severe reaction. The NPV was 98%. The positive predictive value was unable to be calculated because the majority of the patients who had a positive result on IDT did not proceed to oral challenge. However, none of the six patients with positive IDT results who elected to proceed with oral challenge had a reaction.

Statistical analysis was used to identify variables for predicting positive PST results. Variables of interest included a history of asthma, allergic rhinitis, eczema, food allergy, and the number of atopic conditions as well as the time since a reaction, IgE-mediated reaction history (urticaria, angioedema, respiratory symptoms, anaphylaxis), and a convincing reaction history (respiratory symptoms, GI symptoms, or hemodynamic instability). Conditional MLE analysis failed to identify any variables with a statistically significant odds ratio for predicting positive PST results (Table 3). Logistic regression performed on the continuous variables of atopy and time since reaction also failed to identify any predictive value for these variables (Table 4).

DISCUSSION

According to the Joint Task Force on Practice Parameters,¹³ PST is the most reliable method for evaluating

patients for IgE-mediated penicillin allergy and should ideally be performed in all patients with a history concerning for penicillin drug allergy with both major and minor determinants. This recommendation primarily comes from data in the adult population in which the NPV of PST for immediate reactions approaches 100%.^{12,13} We undertook this study to more closely examine the utility of PST in the outpatient pediatric population with particular attention to the different PST reagents.

Current skin testing at our institution includes penicillin, the major determinant, and an aminopenicillin but does not include MDM, which is not commercially available in the United States. Given the high NPV of 98% in our study, adding MDM to the PST protocol is unlikely to significantly reduce the number of ADRs on oral challenge in the pediatric outpatient population. Furthermore, the clinical significance of a positive PST result to MDM is unclear. There may be more utility in testing with MDM in populations with high pretest probability and in those patients who cannot afford to have an ADR, *e.g.*, patients in the inpatient setting.¹²

Because 85% of our retrospective cohort reported a reaction to amoxicillin or amoxicillin-clavulanate, the standard PST protocol at our institution includes an aminopenicillin despite there being no standardized formulations for aminopenicillin skin testing. Of the patients in the cohort, 4.1% had positive PST results only to ampicillin. Analysis of these data indicated that the addition of an aminopenicillin to the skin testing regimen in pediatric patients may be of value, but it is unclear whether a positive aminopenicillin skin test represents true allergy or merely sensitivity.

In this cohort, 28.8% of the patients had positive PST results, which was considerably higher than the 6–8.8% reported in other pediatric studies^{9,10,13} and the 3.6% rate in the adult population.^{14,15} Interestingly, the retrospective pediatric outpatient cohort in Jost *et al.*¹⁰ (1979–1992) had a positive PST result prevalence of 27%, which is similar to our data, but this dropped to 6% in their prospective cohort (1993–2003). Jost *et al.*¹⁰ theorized that this decline was due to changes in antibiotic prescribing patterns, which is unlikely to explain the findings in our study. Types of reagents used and population characteristics, including age, time since reaction, and gender, did not explain the discrepancies.

It is possible that differences in the PST protocol and reagent concentrations accounted for the higher positive PST rate in our study. For example, compared with Fox and Park,⁹ our institution uses a higher concentration of PenG (10,000 versus 6000 units/mL), although both concentrations are within the standard range. Furthermore, for IDT, we administered 0.1 mL of the reagent, whereas other studies in the pediatric population use as little as 0.02 mL.¹⁶ Other reasons for

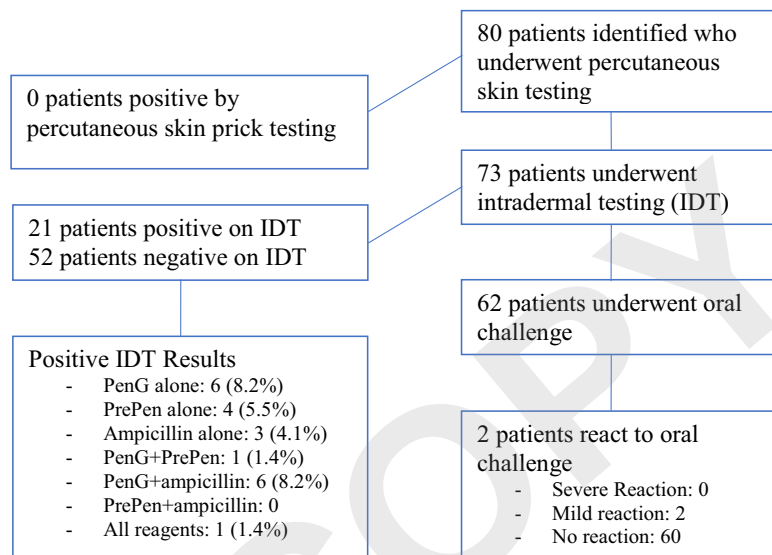


Figure 1. Penicillin skin testing and oral challenge results.

Table 3 Positive PST by variable of interest

	Positive PST, no. patients		OR (95% CI)*	p Value
	Negative	Positive		
Asthma			0.585 (0.123–2.224)	0.557
No	37	17		
Yes	15	4		
Allergic rhinitis			0.910 (0.275–2.870)	0.999
No	31	13		
Yes	21	8		
Eczema			1.705 (0.381–6.998)	0.501
No	44	16		
Yes	8	5		
Food allergy			0.279 (0.006–2.325)	0.432
No	44	20		
Yes	8	1		
High-risk reaction			0 (0–13.050)	0.999
No	49	21		
Yes	2	0		
IgE-mediated symptoms			0.389 (0.096–1.343)	0.115
No	27	16		
Yes	22	5		

PST = Penicillin skin test; OR = odds ratio; CI = confidence interval; IgE = immunoglobulin E.

*ORs were calculated by conditional maximum likelihood estimation.

false-positive results in PST include nonhistamine mediated reactions,¹⁷ hidden additives or irritant effect,¹⁸ and an increased rate of drug sensitivity when administered liquid penicillin that was not stored at -70°C .¹⁹

Statistical analysis failed to identify predictive variables for positive PST results. Other studies identified that having a shorter interval between reaction and testing^{20–22} and having a convincing reaction history^{22–25} are correlated with a higher rate of positive PST results. Whether we were unable to

detect these trends due to the small sample size or if this did not apply to the pediatric outpatient population is unclear. The lack of predictive values for atopy, age at reaction,^{22,25,26} and IgE-mediated reaction¹⁰ was consistent with previous studies.

The criterion standard for penicillin allergy is oral challenge. In this cohort, two patients (3.2%) had a minor ADR (rash) on taking amoxicillin after a negative PST result. This result was consistent with other pediatric and adult studies, which calculated the rate

Table 4 Logistic regression analysis to identify predictive variables for positive PST results

	Estimate	±SE	OR (95% CI)	p Value
Atopy	−0.143	0.263	0.867 (0.504–1.430)	0.586
Time since reaction	−0.037	0.056	0.964 (0.854–1.071)	0.513

PST = Penicillin skin test; SE = standard error; OR = odds ratio; CI = confidence interval.

of ADR to oral challenge as 1.4–3.8%^{9,13,27,28} in the pediatric population and 1.2–3.2% in the adult population.²⁹ A recent study by Han *et al.*³⁰ provided new insight into false-negative skin testing results by describing the role that histamine and the Rho/Rho-associated protein kinase (ROCK) pathway play in non-allergic non-IgE-mediated hypersensitivity reactions. These studies collectively demonstrated that PST is safe in the pediatric population.

It is interesting that none of our six patients with positive PST results reacted on oral challenge. Although there is likely selection bias because not all of the patients with positive PST results were challenged, this finding was inconsistent with previous data in the pediatric and adult populations. Caubet *et al.*²⁷ challenged 11 pediatric patients with positive PST results; 4 (36%) had an ADR. This inconsistency may be due to differences in the study population. Compared with other studies,¹⁰ the cohort in our study had a lower pretest probability of penicillin allergy because only 38% had symptoms concerning for an IgE-mediated reaction. Forty-seven percent of the patients in our cohort underwent PST for a drug reaction history, which consisted of a maculopapular non-urticarial rash to amoxicillin or amoxicillin-clavulanate, but results of a study indicate that 5–10% of all patients who receive amoxicillin or ampicillin develop a delayed maculopapular rash, which is not an IgE-mediated reaction.³¹

The Joint Task Force on Practice Parameters¹¹ still suggests that patients with vague or mild reaction histories undergo PST because a high percentage of patients do have positive PST results.^{32,35} In European studies, there is growing evidence that children with a mild history of penicillin allergy may be able to proceed directly to oral challenge without skin testing.^{4,5,34,35} In our cohort, >95% of the patients had a history of mild reactions, there was a high PST positivity rate yet a normal ADR rate on oral challenge, and a low positive predictive value (from a small subgroup). These data add to the growing body of literature that suggests that large multicenter studies to assess the safety of direct oral challenge without previous PST are needed.

We propose considering the utility of PST in the outpatient pediatric clinic based on two variables: whether the reaction history is concerning for an IgE-mediated process, and the severity of initial reaction.

Patients for whom the initial reaction was mild and the history was not consistent with an IgE-mediated process may be able to proceed directly to oral challenge in a controlled clinic setting as long as they are not medically fragile. In Mill *et al.*,³⁴ 818 children with a history of suspected drug allergy to amoxicillin proceeded directly to oral challenge, of whom 94% tolerated the drug and only 2.1% had immediate reactions, all of which were mild, consisting only of hives. There is also evidence in adult patients that, for patients at low risk of ADR due to remote and mild reaction histories, the rate of ADR to oral challenge is the same regardless of PST results.²⁴

However, patients with a history of reactions concerning for an IgE-mediated process or who had more severe drug reactions (angioedema, trouble breathing) should proceed to PST first and then oral challenge only if the PST result is negative. Those patients with histories consistent with a severe non-IgE-mediated reaction (Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis, Drug Reaction with Eosinophilia and Systemic Symptoms, serum sickness) should avoid the drug and do not need routine PST. In the inpatient setting, patients have a higher pretest probability of positive PST, a higher risk of having an ADR, and are more likely to be unable to afford an ADR; thus PST in the inpatient setting (ideally performed with all reagents including MDM) will continue to provide critical information in guiding antibiotic choices. (this statement should cite reference 13 at the end).

There were several limitations to this study. It was a retrospective chart review and, therefore, likely to underrepresent patients at high risk, with anaphylactic reactions, and who were unlikely to undergo PST. There may also have been selection bias because not all the patients with negative SPT results proceeded to IDT and not all the patients with negative IDT results proceeded to oral challenge. Also, this was a single-institution study, and larger prospective studies are needed in the ambulatory pediatric setting.

CONCLUSION

Given the high NPV of the current PST regimen in the outpatient pediatric population, we do not recommend additional testing with MDM. Despite this high NPV, the utility of PST in this low-risk, low-pretest

probability population was limited. Patients with mild reaction histories and no clear IgE-mediated symptoms may be able to proceed directly to oral challenge.

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REFERENCES

- Kerr J. Penicillin allergy: a study of incidence as reported by patients. *Br J Clin Pract.* 1994; 48:5–7.
- Albin S, Agarwal S. Prevalence and characteristics of reported penicillin allergy in an urban outpatient adult population. *Allergy Asthma Proc.* 2014; 35:489–494.
- Chan DS, Callahan CW, Moreno C. Multidisciplinary education and management program for children with asthma. *Am J Health System Pharm.* 2001; 58:1413–1417.
- Zambonino MA, Corzo JL, Munoz C, et al. Diagnostic evaluation of hypersensitivity reactions to beta-lactam antibiotics in a large population of children. *Pediatr Allergy Immunol.* 2014; 25:80–87.
- Marrs T, Fox AT, Lack G, du Toit G. The diagnosis and management of antibiotic allergy in children: Systematic review to inform a contemporary approach. *Arch Dis Child.* 2015; 100: 583–588.
- Lee CE, Zembower TR, Fotis MA, et al. The incidence of antimicrobial allergies in hospitalized patients: implications regarding prescribing patterns and emerging bacterial resistance. *Arch Intern Med.* 2000; 160:2819–2822.
- MacLaughlin EJ, Saseen JJ, Malone DC. Costs of beta-lactam allergies: selection and costs of antibiotics for patients with a reported beta-lactam allergy. *Arch Fam Med.* 2000; 9:722–726.
- Demoly P, Romano A, Botelho C, et al. Determining the negative predictive value of provocation tests with beta-lactams. *Allergy.* 2010; 65:327–332.
- Fox SJ, Park MA. Penicillin skin testing is a safe and effective tool for evaluating penicillin allergy in the pediatric population. *J Allergy Clin Immunol Pract.* 2014; 2:439–444.
- Jost BC, Wedner HJ, Bloomberg GR. Elective penicillin skin testing in a pediatric outpatient setting. *Ann Allergy Asthma Immunol.* 2006; 97:807–812.
- Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; and Joint Council of Allergy, Asthma and Immunology. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol.* 2010; 105:259–273.
- Geng B, Eastman JJ, Mori K, Braskett M, Riedl MA. Utility of minor determinants for skin testing in inpatient penicillin allergy evaluation. *Ann Allergy Asthma Immunol.* 2017; 119:258–261.
- Mendelson LM, Ressler C, Rosen JP, Selcow JE. Routine elective penicillin allergy skin testing in children and adolescents: study of sensitization. *J Allergy Clin Immunol.* 1984; 73:76–81.
- Park MA, Matesic D, Markus PJ, Li JT. Female sex as a risk factor for penicillin allergy. *Ann Allergy Asthma Immunol.* 2007; 99:54–58.
- Macy E, Schatz M, Lin C, Poon KY. The falling rate of positive penicillin skin tests from 1995 to 2007. *Perm J.* 2009; 13:12–18.
- Vyles D, Adams J, Chiu A, Simpson P, Nimmer M, Brousseau DC. Allergy testing in children with low-risk penicillin allergy symptoms. *Pediatrics.* 2017; 140: pii: e20170471.
- Tannert LK, Falkencrone S, Mortz CG, Bindslev-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.
- Grims RH, Kranke B, Aberer W. Pitfalls in drug allergy skin testing: false-positive reactions due to (hidden) additives. *Contact Dermatitis.* 2006; 54:290–294.
- Neftel KA, Walti M, Schulthess HK, Gubler J. Adverse reactions following intravenous penicillin-G related to degradation of the drug in vitro. *Klin Wochenschr.* 1984; 62:25–29.
- Goldberg A, Confino-Cohen R. Skin testing and oral penicillin challenge in patients with a history of remote penicillin allergy. *Ann Allergy Asthma Immunol.* 2008; 100:37–43.
- Blanca M, Torres MJ, Garcia JJ, et al. Natural evolution of skin test sensitivity in patients allergic to beta-lactam antibiotics. *J Allergy Clin Immunol.* 1999; 103:918–924.
- Ponvert C, Perrin Y, Bados-Albiero A, et al. Allergy to betalactam antibiotics in children: results of a 20-year study based on clinical history, skin and challenge tests. *Pediatr Allergy Immunol.* 2011; 22:411–418.
- Adkinson NF Jr, Thompson WL, Maddrey WC, Lichenstein LM. Routine use of penicillin skin testing on an inpatient service. *N Engl J Med.* 1971; 285:22–24.
- Van Dellen RG, Gleich GJ. Penicillin skin tests as predictive and diagnostic aids in penicillin allergy. *Med Clin North Am.* 1970; 54:997–1007.
- Rubio M, Bousquet PJ, Gomes E, Romano A, Demoly P. Results of drug hypersensitivity evaluations in a large group of children and adults. *Clin Exp Allergy.* 2012; 42:123–130.
- Wong BB, Keith PK, Wasserman S. Clinical history as a predictor of penicillin skin test outcome. *Ann Allergy Asthma Immunol.* 2006; 97:169–174.
- 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; 127:218–222.
- Macy E, Ngor EW. Safely diagnosing clinically significant penicillin allergy using only penicilloyl-poly-lysine, penicillin, oral amoxicillin. *J Allergy Clin Immunol Pract.* 2013; 1:258–263.
- Macy E, Mangat R, Burchette RJ. Penicillin skin testing in advance of need: multiyear follow-up in 568 test result-negative subjects exposed to oral penicillins. *J Allergy Clin Immunol.* 2003; 111:1111–1115.
- Han J, Yi Y, Li C, et al. Involvement of histamine and RhoA/ROCK in penicillin immediate hypersensitivity reactions. *Sci Rep.* 2016; 6:33192.
- Shapiro S, Siskind V, Slone D, Lewis GP, Jick H. Drug rash with ampicillin and other penicillins. *Lancet.* 1969; II:969–972.
- Solensky R, Earl HS, Gruchalla RS. Penicillin allergy: prevalence of vague history in skin test-positive patients. *Ann Allergy Asthma Immunol.* 2000; 85:195–199.
- Stember RH. Prevalence of skin test reactivity in patients with convincing, vague, unacceptable histories of penicillin allergy. *Allergy Asthma Proc.* 2005; 26:59–64.
- 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:e160033.
- Moral L, Caubet JC. Oral challenge without skin tests in children with non-severe beta-lactam hypersensitivity: Time to change the paradigm? *Pediatr Allergy Immunol.* 2017; 28:724–727. □

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