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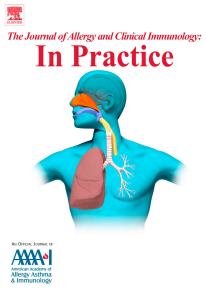

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Safety and Outcomes of Oral Graded Challenges to Amoxicillin without Prior Skin Testing

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Abstract

Background: Unconfirmed penicillin allergy poses substantial public health consequences. The most widely accepted protocol to evaluate penicillin allergy is skin testing followed by amoxicillin challenge.

Objective: To evaluate the safety of direct oral graded challenges to amoxicillin.

Methods: Prospective single-blind clinical trial with historical controls of patients ≥ 7 years old with historical non-life-threatening reactions to penicillin. Patients received placebo followed by a 2-step graded challenge to amoxicillin. The allergic reaction rate was compared to the rate observed in our previous study that included skin testing and to the currently reported penicillin allergy prevalence in the US population.

Results: Of the 155 participants who completed an amoxicillin challenge, 120 patients (77.4%) experienced no reaction while 31 patients (20%) experienced non-allergic reactions to either placebo (n=16) or amoxicillin (n=15). Four patients (2.6%) developed mild allergic reactions. Significantly (p=0.03) fewer patients [4/155, 2.6%, 95% CI (1.0%, 6.5%)] were determined to be allergic compared to 14/170 subjects [(8.2%, 95% CI (5.0%, 13.4%)] in our previous study where patients were determined to be allergic based on either positive skin tests (n=11) or allergic challenge reactions after negative skin tests (n=3). This 2.6% reaction rate was also significantly less than the 10% reported US prevalence of penicillin allergy (p=0.003).

Conclusions: Placebo-controlled oral graded challenges to amoxicillin without prior skin testing may be safe for patients ≥ 7 years old with non-life-threatening historical reactions to penicillin. Amoxicillin can be tolerated by the majority of patients with self-reported penicillin allergy.

ClinicalTrials.gov Registration: NCT03158831

Highlights Box

1. What is already known about this topic?

Penicillin allergy is reported by approximately 10% of the United States population. The most widely accepted protocol to evaluate penicillin allergy is skin testing followed by amoxicillin challenge.

2. What does this article add to our knowledge?

This study demonstrates that placebo-controlled oral graded challenges to amoxicillin without prior penicillin skin testing may be safe for patients ≥ 7 years old with non-life-threatening historical reactions to penicillin.

3. How does this study impact current management guidelines?

If confirmed by larger studies, skin testing to penicillin prior to an oral amoxicillin challenge is unlikely to be necessary in patients ≥ 7 years old with non-life-threatening historical reactions to penicillin.

Key Words: Penicillin allergy; graded challenge; drug provocation test; adverse drug reaction; hypersensitivity reaction; placebo

Abbreviations

ANOVA: analysis of variance

CI: confidence interval

IgE: Immunoglobulin E

IQR: interquartile range

mg: milligram

ml: milliliter

NPV: negative predictive value

SEM: standard error of the mean

US: United States

Background

Penicillin allergy is reported by approximately 10% of the United States (US) population, which is equivalent to over 32.7 million people.[1,2] Patients labeled with penicillin allergy often receive suboptimal treatment for infectious diseases with second-line, broad-spectrum antibiotics that tend to be less effective, more costly, and associated with an increased risk of antibiotic-resistant infections.[3-5] The substantial public health consequences of unconfirmed penicillin allergy have led numerous societies and agencies, including the Centers for Disease Control and Prevention, Infectious Diseases Society of America, the American Academy of Allergy, Asthma, and Immunology, and the Choosing Wisely initiative of the American Board of Internal Medicine Foundation, to recommend testing for penicillin allergy as an essential component of antibiotic stewardship.[6-10] After a comprehensive evaluation, recent studies have demonstrated that greater than 94% of patients who report penicillin allergy can tolerate the antibiotic.[11-13]

The most widely accepted protocol to evaluate penicillin allergy consists of skin testing followed by an oral amoxicillin challenge in skin test-negative individuals.[11,13-17] In the US, skin testing is typically performed using the major determinant (benzylpenicilloyl polylysine) and penicillin G dilutions due to the lack of commercial access to the full panel of minor determinants, which also includes penicilloate and penilloate.[11] Skin testing with these reagents has a negative predictive value (NPV) around 95%, which increases to nearly 100% when followed by an oral amoxicillin challenge.[1,11,18] In a study conducted at our center using this approach, 8.2% of 170 patients were determined to beallergic based on either a positive skin test or an allergic challenge reaction to a beta-lactam after negative skin tests.[13] While most positive challenge reactions after negative skin tests are mild and self-limited, systemic reactions to

amoxicillin have been reported, including immediate life-threatening reactions involving hypotension and bronchospasm.[19]

Recent studies in patients with historical cutaneous reactions to amoxicillin have also demonstrated that positive skin tests do not necessarily predict challenge reactions. For example, skin testing was shown to have poor diagnostic value for benign skin rashes due to beta-lactams in children with an overall sensitivity of 50% for immediate-reading intradermal tests in one study.[20] In another study, only one of 17 children who developed an immediate reaction during an amoxicillin graded challenge subsequently had a positive penicillin skin test.[12] Of 34 patients with a history of non-immediate penicillin allergy associated with positive skin tests, only two patients experienced allergic challenge reactions to penicillin.[21] One-hundred-sixty-nine patients with a remote non-life-threatening reaction to penicillin were challenged regardless of the results of penicillin skin testing. Mild rashes to oral challenges were observed in 6.6% of 137 challenges associated with a positive skin test and 3.7% of 135 challenges associated with a negative skin test result (p=0.29).[22] Therefore, the gold standard for verifying penicillin tolerance is an oral challenge to a therapeutic dose of amoxicillin.[15,23]

Recent studies have begun to explore the safety of direct oral challenges without preceding skin tests in limited populations with low-risk histories of penicillin allergy.[12,21,24] Direct challenges were found to be safe in children with amoxicillin-induced rashes with a NPV of 89.1%.[12] Ninety-four percent of children tolerated challenges while the remainder developed mild reactions.[12] In a cohort limited to male Marine recruits, only 5 (1.5%) recruits had immediate reactions during direct amoxicillin challenges.[24] Five-day oral penicillin challenges without antecedent skin testing have also been found to safely exclude clinically significant

delayed-onset hypersensitivity reactions in patients with previous nonimmediate reactions to penicillin.[21]

These studies have demonstrated the safety of direct beta-lactam challenges in patient populations limited to well-defined cohorts with a history of low-risk penicillin allergy. The present study sought to evaluate the safety of a direct oral graded challenge to amoxicillin without prior skin testing in a broader cohort of patients ≥ 7 years old who reported a history of penicillin allergy that was non-life-threatening.

Methods

Trial Design and Setting

We conducted a prospective single-blind clinical trial with historical controls between January 2016 and December 2017 at an outpatient drug allergy clinic affiliated with a single, tertiary-care academic center in Bronx, NY. This study was approved by the Institutional Review Board at Montefiore Medical Center/Albert Einstein College of Medicine and was registered on ClinicalTrials.gov (NCT03158831). No funding was obtained to support this study.

Inclusion/Exclusion Criteria

Patients ≥ 7 years old with historical non-life-threatening reactions to penicillin were eligible for inclusion. Exclusion criteria included reactions to penicillin with the following features: bronchospasm or laryngeal edema requiring intubation; anaphylactic shock; or severe non-IgE-mediated reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, interstitial nephritis, hepatitis, hemolytic anemia, drug reaction with eosinophilia and systemic symptoms, cutaneous and/or mucosal blisters, hypersensitivity vasculitis, pneumonitis, pulmonary fibrosis, and serum sickness). Pregnancy and antihistamine use within three days of enrollment were also exclusion criteria.

Recruitment Methods

Consecutive patients with reported penicillin allergy who presented to our outpatient drug allergy clinic were screened for enrollment. We also utilized a decision support tool at our institution to identify patients who had penicillin allergy documented in their electronic medical record. Recruitment letters were sent to these patients, who were subsequently screened for eligibility. Informed consent was obtained for all patients.

Intervention

Patients were challenged with placebo followed by a two-step oral graded challenge to amoxicillin, as described in our previous study.[13] Patients were informed they would receive a placebo, but were not told when it would be administered. Study investigators followed the same protocol for all patients, who first received placebo followed by a 30-minute observation period. An oral challenge was subsequently performed with 80 mg (1 ml of 400 mg/5 ml suspension) of amoxicillin followed by 30 minutes of observation and subsequent administration of a full therapeutic dose (500 mg) of amoxicillin. Patients were observed for 60 minutes after the therapeutic dose. Amoxicillin was supplied in liquid formulation and mixed in the same yogurt and pharmaceutical sweetener used for placebo. Vital signs and physical examination were performed at baseline and every 30 minutes. If a subjective reaction occurred, vital signs and physical examination were repeated. If no objective signs of an allergic reaction were observed and vital signs were stable, the patient was given the option of discontinuing the challenge with or without treatment or continuing the challenge without treatment. If a patient experienced an objective reaction to amoxicillin, the challenge was discontinued and treatment was administered, if warranted. All challenges were performed in an outpatient allergy clinic equipped to handle anaphylactic reactions.

Non-allergic challenge reactions were defined as reactions to placebo or amoxicillin comprised solely of subjective symptoms that resolved spontaneously with no change in vital signs and no objective signs of a reaction when examined by a study investigator. Patients with non-allergic reactions were advised that they had no restrictions on future penicillin use. Allergic reactions were defined as reactions with either objective signs observed by the study investigator that did not resolve spontaneously within an hour or subjective symptoms experienced by the subject that did not resolve spontaneously. Avoidance of beta-lactams was

advised for all patients determined to be allergic. All patients were instructed to call the principal investigator if a delayed reaction occurred. All participants were also called within one month to assess for delayed reactions and again within one year to determine tolerability of subsequent treatment with penicillin.

Primary Outcome

We compared the proportion of allergic challenge reactions to amoxicillin in our study to the following proportions observed in our previous study of oral beta-lactam challenges with antecedent penicillin skin testing: 1) the proportion of patients determined to be allergic to beta-lactams based on skin testing or objective challenge reactions (14/170=8.2%) and 2) the proportion of patients determined to be allergic to beta-lactams based on objective challenge reactions only (3/170=1.8%).[13]

Secondary Outcomes

We assessed the safety of our protocol by determining the number of patients who had life-threatening allergic challenge reactions defined as follows: 1) bronchospasm or laryngeal edema requiring intubation 2) use of epinephrine for anaphylaxis or 3) severe non-IgE-mediated reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, interstitial nephritis, hepatitis, hemolytic anemia, drug reaction with eosinophilia and systemic symptoms, cutaneous and/or mucosal blisters, hypersensitivity vasculitis, pneumonitis, pulmonary fibrosis, and serum sickness). We also compared the proportion of allergic reactions in our study to the currently reported penicillin allergy prevalence of 10% in the US population.[1]

Statistical Analysis

Comparisons were made among three groups of patients: those who had no reaction to either placebo or amoxicillin, those who had non-allergic reactions to either placebo or

amoxicillin, and those who had allergic reactions to amoxicillin (none had allergic reactions to placebo). One-way ANOVA or Kruskal-Wallis rank test (if data were non-normally distributed) were used for analysis of continuous variables. Categorical data were analyzed with Chi-square test or Fisher exact test, as appropriate. **S**ummary statistics were expressed as means ± standard error of the mean (SEM), medians and interquartile range (IQR), or proportions, as appropriate. The proportion of allergic reactions in this study was compared with Chi-square to both the proportion of patients determined to be allergic based on skin testing or allergic challenge reactions and to allergic challenge reactions alone observed in our previous study.[13] Allergic reaction rate was also compared to the reported 10% prevalence of penicillin allergy in the US population with a one-sample test of proportions. All statistical analyses were performed with SPSS (Version 24) and STATA 14.2 software (StataCorp, College Station, Texas). P values <0.05 were considered statistically significant.

Results

Patients' Characteristics

One hundred sixty-five patients were screened with enrollment of 159 patients, of whom 3 discontinued the challenge and 1 withdrew (Figure 1). Of the 155 patients included in the analysis, the majority were female (n=120, 77.4%) and Latino (n=58, 37.4%) with a mean age of 51.1 years (Table 1). Both White (n=43, 27.7%) and Black (n=41, 26.5%) patients were well-represented. Historical reactions were predominantly reported as urticaria (n=61), rash (n=43), or unknown reaction as a child (n=23) (Tables 1 and 2).

Outcomes of Graded Challenges

One hundred twenty patients (77.4%) experienced no reaction while 31 patients (20%) experienced non-allergic reactions to either placebo (n=16) or amoxicillin (n=15) and 4 patients (2.6%) developed allergic reactions (Table 1, Figure 1). One patient had a distinct reaction to placebo with a subjective sensation of a "funny feeling" in his throat that spontaneously resolved and was subsequently followed by an allergic reaction to amoxicillin with a nonimmediate rash several hours later; this patient's reaction is included in the analysis only as an allergic reaction. No patients developed life-threatening challenge reactions.

Patients who developed allergic reactions had a significantly greater number of baseline reported drug allergies/intolerances [median: 3, IQR 2.5-3.5] compared with patients with non-allergic reactions (median 2, IQR 1-4) and no reaction (median 1, IQR 1-2.5) (p=0.02) (Table 1). Significant differences in symptoms reported during historical reactions were present (p=0.03) with urticaria as the most common historical symptom in patients with no reaction (n=46, 38.3%) or with non-allergic reactions (n=15, 48.3%) (Tables 1 and 2). No patients with a history of urticaria or isolated rash to penicillin experienced allergic challenge reactions. While a higher

298 percentage of women (22.5%) experienced non-allergic challenge reactions as compared to men
299 (11.4%), the finding was not statistically significant (p=0.14).

300 **Characteristics of Challenge Reactions**

301 The majority of patients who experienced non-allergic challenge reactions had subjective
302 symptoms predominantly characterized by pruritus (n=10), oropharyngeal symptoms (n=9; one
303 patient underwent laryngoscopy, which was unremarkable), or a combination of these two
304 symptoms (n=3) (Figure 2). Four female patients experienced objective signs/symptoms after
305 receiving placebo, including urticaria, vomiting, cough, and a decrease in peak flow associated
306 with subjective oropharyngeal and oculonasal symptoms. All symptoms resolved spontaneously
307 with subsequent completion of amoxicillin challenges without reactions.

308 Four patients experienced challenge reactions that were determined to be allergic (Figure
309 2). Three patients reported mild nonimmediate rashes within 24 hours of the challenge. Only
310 one patient required treatment with antihistamines with resolution within 24 hours. A patient
311 who experienced intractable pruritus was determined to be allergic with symptom resolution
312 within 1 hour of antihistamine treatment.

313 **Relationship of Historical Reactions to Challenge Reactions**

314 The majority of patients who experienced non-allergic challenge reactions (n=31) had
315 historical reactions associated with urticaria (n=15) (Tables 1 and 2, Figure 3). These patients
316 experienced various non-allergic challenge reactions, mostly pruritus (n=8), and subjective
317 oropharyngeal symptoms (n=5). One patient with a historical urticarial reaction subsequently
318 experienced urticaria after receiving placebo, which resolved spontaneously. She completed her
319 amoxicillin challenge without reaction. Pruritus (n=7) and oropharyngeal symptoms (n=6) were

also common non-allergic challenge symptoms experienced by patients with historical reactions of rash, unknown reaction as a child, and angioedema or oropharyngeal symptom.

Three patients determined to be allergic who experienced nonimmediate rashes had distinct historical reactions: 1) unknown reaction as a child, 2) nausea/vomiting, and 3) angioedema associated with a rash (Tables 1 and 2). The fourth allergic patient who had severe intractable pruritus during the challenge also had a historical reaction of pruritus.

Comparison of Outcomes of Graded Challenges

Significantly (p=0.03) fewer patients [(4/155, 2.6%, 95% CI (1.0%, 6.5%)] were determined to be allergic compared to 14/170 subjects [(8.2%, 95% CI (5.0%, 13.4%)] in our previous study where patients were determined to be allergic based on either positive skin tests (n=11) or allergic challenge reactions after negative skin tests (n=3). [13] There was no significant difference in the proportion of allergic challenge reactions observed in our current study (4/155=2.6.%) compared to our prior study (3/170=1.8%) (p=0.59). This 2.6% reaction rate was also significantly less than the 10% reported US prevalence of penicillin allergy (p=0.003).[1]

Results of Follow-Up Phone Calls

We reached 96 patients (61.9%) within one month of amoxicillin challenges to assess for delayed reactions. Nineteen patients completed a subsequent course of amoxicillin, of whom five patients reported mild, delayed symptoms [cutaneous symptoms (n=4) and subjective oropharyngeal symptom (n=1)] that self-resolved and did not preclude completion of their amoxicillin course.

Sixty-nine patients (44.5%) patients were eligible for one-year follow-up phone calls, of whom 19 patients were reached. One of the five patients who subsequently completed a course

of amoxicillin reported a subjective symptom of “inflamed skin” that self-resolved and did not preclude completion of a 10-day treatment course.

Discussion

To our knowledge, this is the first study to assess the safety and outcomes of direct oral amoxicillin challenges without prior skin testing in patients ≥ 7 years old who reported a history of penicillin allergy that was non-life-threatening. Our study demonstrates that direct challenges were safe in this broad population with only 2.6% of patients determined to be allergic, all of whom experienced mild, non-life-threatening symptoms. Three of four allergic patients developed mild nonimmediate rashes, which cannot be accurately predicted by skin testing as these reactions are likely T-cell-mediated rather than IgE-mediated.[1,21,24] The reaction rate observed in our study is in range with the reaction rates of 1.5-6.1% reported in three recently published studies regarding the safety of direct amoxicillin challenges in children with penicillin allergy, patients with nonimmediate historical reactions, and male Marine recruits with historical reactions to penicillin.[12,21,24] The percentage of our study population determined to be allergic is also significantly lower than the 8.2% of patients in our prior study who were determined to be beta-lactam-allergic based on either positive skin testing or positive oral challenges.[13] It is possible that some of the 11 skin test-positive patients in our prior study may have tolerated the culprit beta-lactam if challenged, as demonstrated by results of a recent study of 34 skin test-positive patients with historical cutaneous reactions to penicillin who overwhelmingly tolerated amoxicillin.[21] These findings suggest that not only is skin testing prior to oral challenges in patients with non-life-threatening historical reactions unlikely to be necessary, but also that, in some cases, it may actually overdiagnose penicillin allergy. Therefore, the gold standard for evaluating penicillin allergy should remain an oral challenge.[15,23]

The safety of direct oral challenges in our study is further demonstrated by the comparable proportion of allergic challenge reactions observed both with and without antecedent

skin testing.[13] Furthermore, the allergic reaction rate in our study was significantly less than the estimated 10% US prevalence of penicillin allergy, which suggests that the majority of patients labeled with penicillin allergy would tolerate penicillin. By extrapolation, it is possible that the true percentage of patients allergic to penicillin in the US is likely closer to 0.3%.

There are several possibilities why most patients in our study tolerated amoxicillin. Both amoxicillin and ampicillin have been associated with the development of non-IgE-mediated, nonimmediate maculopapular exanthems in approximately 5-10% of patients potentially due to the presence of concomitant underlying viral infections or other cofactors, which were not present during the challenge.[1,12,25-28] It is also possible that some patients with historical reactions gained tolerance to penicillin over time due to the loss of sensitization through IgE antibodies.[29] One study also demonstrated that the rate of positive penicillin skin tests was lower in older patients and in those with a longer time since reaction, further supporting this notion.[16]

Recent studies have also found that the overwhelming majority of patients who report penicillin allergy have negative skin testing.[11,13,16] While skin testing is considered a low-risk procedure, it can be expensive. A base-case penicillin allergy evaluation including skin testing followed by oral challenge is estimated to cost $220.[18] Evaluation of all Americans who report penicillin allergy would cost over $7 billion using this protocol.[1,2,18] However, lower cost estimates of $84 per evaluation could potentially be achieved by eliminating skin testing in patients with non-life-threatening historical reactions.[18] Forgoing skin testing would also result in decreased utilization of time and resources.

The absence of skin testing in our study protocol could potentially expand its usability to physicians other than allergists. If evaluation of penicillin allergy is limited to board-certified allergists, each allergist would need to evaluate over 5000 patients in the US.[2,30] To begin to

tackle the substantial public health burden of unconfirmed penicillin allergy in the US, it would be beneficial if more physicians were trained to perform these evaluations. Recent studies have demonstrated that inpatients with reported beta-lactam allergies can be assessed by providers other than allergists for a direct graded challenge using standardized guidelines based solely on the characteristics of the historical reaction.[31,32] One study demonstrated that implementation of these guidelines resulted in an almost 7-fold increase in inpatient graded challenges to beta-lactams without increased adverse reactions as compared to patients who underwent prior skin testing.[32] The feasibility, safety, and potential value of training non-allergists to use our challenge protocol would need to be further studied.

Although the current standard of care does not include the use of placebo during oral graded drug challenges, we believe the addition of placebo can be helpful, especially when patients experience subjective symptoms. The double-blind, placebo-controlled food challenge is currently recognized as the gold standard for evaluating food allergy.[33] In our prior study that focused on the utility of placebo prior to graded drug challenges, we found that patients who reacted to placebo prior to beta-lactam challenges had an increased number of baseline reported drug allergies as compared with those who both did and did not react to beta-lactams.[13] In our current cohort of patients, those with allergic reactions during amoxicillin challenges and patients with nonallergic reactions both had a higher median number of drug allergies as compared with those who did not react. Therefore, the use of placebo should particularly be considered in patients who report more than one drug allergy or intolerance. Placebo should also be considered when challenging female patients given the majority of patients who reacted to placebo both in our current study and prior study were female.[13]

Our study has some potential limitations. Despite a study population well-represented with Latino, White, and Black patients, our patients were enrolled at a single, academic center, which may reduce generalizability. Our study also did not include children under the age of 7 or pregnant women and, therefore, results cannot be generalized to these patient populations. Given we evaluated patients who were generally healthy at the time of challenge, we were unable to investigate the potential for a drug-virus interaction leading to a reaction or the presence of other potential co-factors. Since we did not perform a randomized controlled trial, there is also a possibility of confounding due to our comparison with historical controls. Finally, we were unable to calculate NPV since only 27.5% of patients eligible for 1-year follow-up phone calls were reached, of whom only 5 patients completed a subsequent course of amoxicillin.

Our study suggests that placebo-controlled oral graded challenges to amoxicillin without prior skin testing may be safe in the evaluation of patients ≥ 7 years old who report a history of penicillin allergy that was non-life-threatening. However, our study protocol should be further validated at other centers to confirm its safety and generalizability. Our findings also support earlier reports that amoxicillin can be tolerated by the vast majority of those with self-reported penicillin allergy. The absence of skin testing can potentially increase the usability of this protocol beyond allergists to other specialists, which can expand the national effort to address the vast public health consequences of underuse of penicillin due to unconfirmed allergy in the US.

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548 **Figure Legends**

549 Figure 1. Outcomes of evaluation. *Two patients discontinued the challenge after placebo
550 reactions: 1. subjective oropharyngeal symptom with an unremarkable laryngoscopy and 2.
551 severe retching/coughing. One patient had an upper respiratory tract infection and elected to
552 discontinue the challenge after the test dose due to personal reasons.

553 Figure 2. Characteristics of reactions during challenges.

554 Figure 3. Relationship of historical reactions to non-allergic challenge reactions. Each bracket
555 with arrows represents one patient who experienced multiple symptoms during his/her non-
556 allergic challenge reaction.

Table 1. Characteristics of patients by outcome of challenge (N = 155)

Characteristic	No Reaction (n=120, 77.4%)	Non-Allergic Reactions (n=31, 20%)	Allergic Reactions (n=4, 2.6%)	*p*-values*
Age (y), mean ± SE	51.8 ±1.85	48.3 ±3.0	54.3 ±13.3	0.6
Female patients, n (%)	91 (75.8)	27 (87)	2 (50)	0.15
Race/Ethnicity, n (%)				0.8
Latino**	48 (40)	9 (29)	1 (25)	
White	30 (25)	12 (38.7)	1 (25)	
Black	31 (25.8)	8 (25.8)	2 (50)	
Multiracial	3 (2.5)	1 (3.2)	0	
Other/Unknown	8 (6.7)	1 (3.2)	0	
No. of reported drug allergies/intolerances, median (IQR)	1 (1-2.5)	2 (1-4)	3 (2.5-3.5)	**0.02**
Age at time of historical reaction (y), mean ± SE	24.4 ±1.9	21.5 ±3.7	20.3 ±14.8	0.8
No. of years between historical reaction and challenge, mean ± SE	27.2 ±1.8	26.2 ±3.3	32.2 ±3.9	0.9
Historical Reactions, n (%)				**0.03**
Urticaria	46 (38.3)	15 (48.3)	0	
Rash	37 (30.8)	6 (19.4)	0	
Unknown historical reaction	16 (13.3)	6 (19.4)	1 (25)	
Angioedema or oropharyngeal symptom	6 (5)	3 (9.7)	1 (25)	
Other***	15 (12.5)	1 (3.2)	2 (50)	

* P values are for comparisons of the 3 columns and derived from analysis of variance or Kruskal-Wallis rank test for the continuous variables reported as mean ±SE or medians and IQR, respectively, or from Chi-square analysis for categorical variables presented as n (%). Bolded p-values are statistically significant ($p < 0.05$). Bolded p-values are statistically significant ($p < 0.05$).

**48 of 58 patients categorized as Latino provided further details of their ethnicity. The majority of patients were Puerto Rican (n=20), Dominican (n=17), or Central/South American (n=7).

***For patients with no reaction, other includes no historical reaction (n=4), pruritus (n=3),

gastrointestinal symptom (n=2), dyspnea (n=2), stupor (n=1), seizure (n=1), vasovagal syncope (n=1), and anaphylaxis to beta-lactam with unrelated side chain (n=1). Other refers to pruritus in one patient with a non-allergic challenge reaction. For patients with allergic reactions, other refers to pruritus (n=1) and gastrointestinal symptom (n=1).

52

53 **Table 2. Detailed characteristics of historical reactions to beta-lactams by outcome of**

54 **challenge**

55

Historical Reactions*	**No Reaction (n=120)**	**Non-Allergic Reactions (n=31)**		**Allergic Reactions (n = 4)**
		Placebo Reactions (n=16)	**Challenge Reactions (n=15)**	
Urticaria	46 (38.3)	7 (43.8)	8 (53.3)	0
Immediate urticaria	28 (23.3)	4 (25)	7 (46.7)	0
Urticaria and angioedema	8 (6.7)	1 (6.3)	1 (6.7)	0
Nonimmediate urticaria	8 (6.7)	0	0	0
Nonimmediate urticaria and vomiting	1 (0.8)	0	0	0
Urticaria and respiratory symptom	1 (0.8)	1 (6.3)	0	0
Urticaria and oropharyngeal symptom	0	1 (6.3)	0	0
Rash	37 (30.8)	3 (18.8)	3 (20)	0
Unspecified details	18 (15)	2 (11.1)	2 (13.3)	0
Nonimmediate rash	13 (10.8)	0	1 (6.7)	0
Immediate non-urticarial rash	6 (5)	1 (6.3)	0	0
Unknown historical reaction	16 (13.3)	3 (18.8)	3 (20)	1 (25)
Angioedema	5 (4.2)	1 (6.3)	0	1 (25)
Isolated angioedema	2 (16.7)	1 (6.3)	0	0
Angioedema and unspecified rash	1 (0.8)	0	0	1 (25)
Angioedema and dyspnea	1 (0.8)	0	0	0
Ocular angioedema and subjective oropharyngeal symptom	1 (0.8)	0	0	0

Oropharyngeal symptom	1 (0.8)	2 (11.1)	0	0
Isolated oropharyngeal symptom	1 (0.8)	0	0	0
Oropharyngeal symptom and palpitations	0	1 (6.3)	0	0
Oropharyngeal symptom and pruritus	0	1 (6.3)	0	0
No historical reaction	4 (3.3)	0	0	0
Pruritus	3 (2.5)	0	1 (6.7)	1 (25)
Gastrointestinal symptom	2 (1.7)	0	0	1 (25)
Nausea and vomiting	0	0	0	1 (25)
Nausea and dizziness	1 (0.8)	0	0	0
Nausea, vomiting, diarrhea	1 (0.8)	0	0	0
Other**	6 (5)	0	0	0

Values represent n (%).

*If the patient's historical reaction affected more than one system, the reaction was grouped under the more prominent reported system.

**Includes dyspnea (n=2), stupor (n=1), seizure (n=1), vasovagal syncope (n=1), and anaphylaxis to beta-lactam with unrelated side chain (n=1).

Figure 1

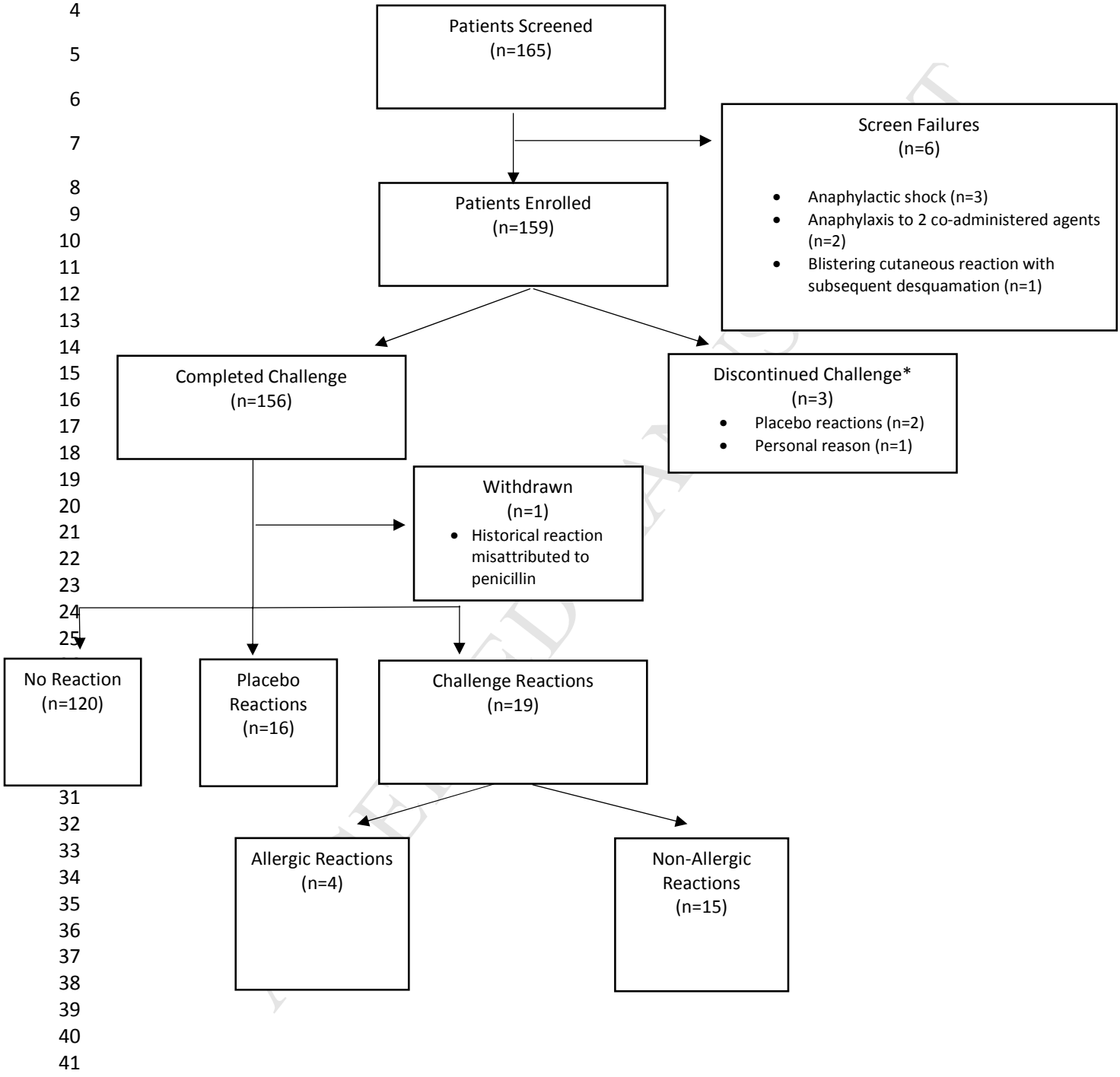
Patients Screened
(n=165)
Screen Failures
(n=6)
Anaphylactic shock (n=3)
Anaphylaxis to 2 co-administered agents (n=2)
Blistering cutaneous reaction with subsequent desquamation (n=1)
Patients Enrolled
(n=159)
Completed Challenge
(n=156)
Discontinued Challenge*
(n=3)
Placebo reactions (n=2)
Personal reason (n=1)
Withdrawn
(n=1)
Historical reaction misattributed to penicillin
No Reaction
(n=120)
Placebo Reactions
(n=16)
Challenge Reactions
(n=19)
Allergic Reactions
(n=4)
Non-Allergic Reactions
(n=15)

Figure 2

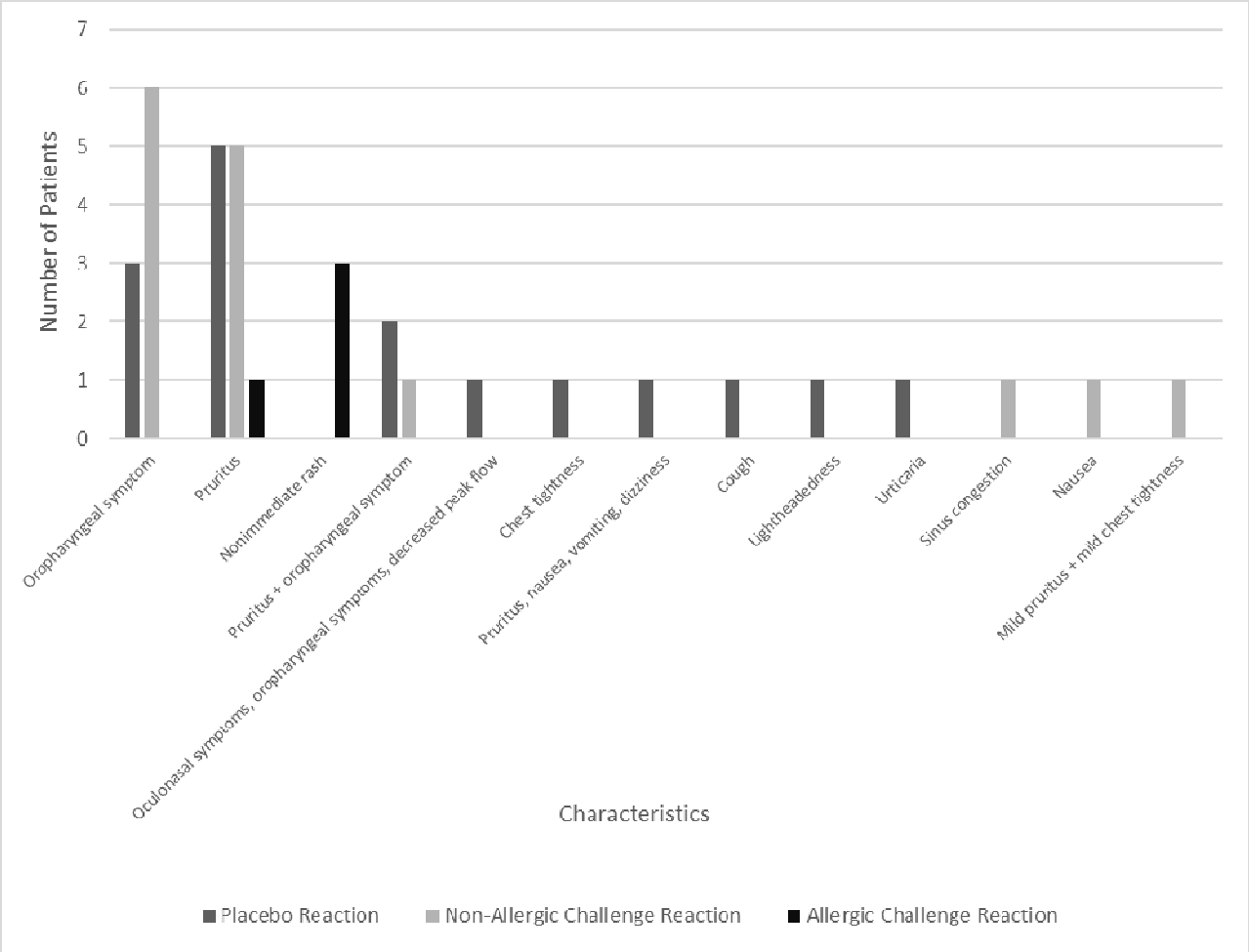

Figure 3