



Skin testing and drug challenge outcomes in antibiotic-allergic patients with immediate-type hypersensitivity

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ABSTRACT

Background: The evaluation of antibiotic immediate-type hypersensitivity is intricate because of non-standardized skin testing and challenge method variability.

Objective: To determine the safety outcomes and risk factors for antibiotic challenge reactions in patients reporting a history of antibiotic immediate-type hypersensitivity.

Methods: A 5-year retrospective review of patients evaluated for immediate-type antibiotic allergy was conducted. Data analyzed included patient demographics, index reaction details, and outcomes of skin testing and challenges, classified as single-step or multistep.

Results: Antibiotic hypersensitivity history was identified in 211 patients: 78% to penicillins, 10% to fluoroquinolones, 7.6% to cephalosporins, and 3.8% to carbapenems. In total, 179 patients completed the challenges (median age 67 years, range 50–76 years, 56% women), and compared with nonchallenged patients, they reported nonanaphylactic ($P < .001$) and remote index ($P = .003$) reactions. Sixteen patients (8.9%) experienced challenge reactions (5 of 28 for single-step challenge, 11 of 151 for multistep challenge), and 11 of these patients had negative skin testing results before the challenge. Challenge-reactive patients were significantly younger ($P = .007$), more often women ($P = .036$), and had additional reported antibiotic allergies ($P = .005$). No correlation was detected between the reported index and observed challenge reaction severities ($\kappa = -0.05$, 95% confidence interval -0.34 to 0.24). Anaphylactic rates were similar during single-step and multistep challenges (3.6% vs 3.3%).

Conclusion: In the present population, younger women with multiple reported antibiotic allergies were at greatest risk for challenge reactions. Negative skin testing results did not exclude reactions, and index severity was not predictive of challenge outcome. The multistep and full-dose methods demonstrated a comparable reaction risk for anaphylaxis.

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Introduction

Importance of the Evaluation Antibiotic Drug Allergy

Performing a comprehensive antibiotic allergy evaluation is essential in the diagnosis of antibiotic hypersensitivity and ensures that patients receive cost-conscious and appropriate medications for the treatment of infections.¹ However, hospitalized patients who report adverse antibiotic reactions are infrequently evaluated and thus might receive more expensive, less effective, and newer generation regimens. Administration of broad-spectrum antibiotics can have detrimental consequences, including the propagation of

microbial antibiotic resistance, in addition to the economic impact of direct consumer costs. Patients labeled as “penicillin allergic” tend to receive alternative antibiotics, placing them at greater risk for developing *Clostridium difficile* or microbial-resistant infections, resulting in longer hospital stays.^{2,3} This label also contributes to an estimated 63% increase in overall antibiotic costs.⁴ The Centers for Disease Control and Prevention has recently advocated for the evaluation of penicillin allergy by providing recommendations on appropriate clinical history gathering, allergic skin testing, and drug challenges.⁵

Role of Skin Testing and Drug Challenge in Antibiotic Hypersensitivity Evaluations

Thus, the evaluation of antibiotic hypersensitivity represents a unique opportunity for allergists to decrease health care costs by

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providing optimal antibiotic options. The movement to appropriately remove the penicillin-allergic label from patients is certainly gaining recognition.⁶ However, the assessment of nonpenicillin antibiotics is complex because of nonstandardized skin testing reagents and challenge method variability in clinical practice.^{7–10} Skin testing is well validated for penicillin and to a lesser degree for cephalosporins and carbapenems.^{1,7,9–12} Fluoroquinolone skin testing is deemed of little value, in part because of discrepant irritating test doses, producing high false-positive rates.^{13–15} Antibiotic drug challenge is instrumental in the evaluation of antibiotic immediate-type hypersensitivity in addition to comprehensive clinical history and data collection.^{1,8,11,16,17} If the skin testing result is negative, then performing an antibiotic challenge is recommended in patients with a low likelihood of experiencing a reaction.^{1,8,11}

Protocol Variability in Antibiotic Drug Challenge Methods

Although considered the gold standard for a diagnosis of hypersensitivity, there is some variability in how drug challenges are performed.^{8,10,16–18} The Joint Task Force on Practice Parameters for Drug Allergy, most recently updated in 2010, provides general guidelines on drug challenge protocols.⁷ Depending on the clinical circumstances, physicians can use a single-step (full test dose) approach or opt to administer an incremental graded-dose challenge with 2 or 3 steps.¹ Compared with single-step challenges, multiple steps are believed to offer increased safety, but data are limited in this regard.^{1,19} Reactions to partial doses theoretically could be less severe and therefore impart a lower risk to the patient.¹ Rates of antibiotic challenge reactions in patients reporting prior antibiotic hypersensitivity vary from approximately 1% to 15% in the available literature, and although challenges are typically performed in patients deemed at low risk for reactions, harmful adverse outcomes can unpredictably occur.^{18–25}

Objectives of This Study on Antibiotic Drug Allergy Evaluations

The primary objective of this retrospective review was to investigate the relation between patient self-reported antibiotic hypersensitivity history and subsequent skin testing results and/or challenge outcomes during an allergy consultation. Through a descriptive analysis, we aimed to (1) identify putative risk factors for antibiotic drug challenge reactions, (2) analyze the relation between the reported index reaction severity and the observed challenge reaction severity, and (3) examine the safety and outcomes of single-step and multistep challenge methods. This review investigated specific challenge reaction rates, tolerance within and among different antibiotic classes, induction of tolerance outcomes, and the use of alternative antibiotic agents in patients at our institution.

Methods

Study Design and Patient Selection

We conducted a 5-year institutional review board–approved retrospective review of adult patients (≥ 18 years old) who were evaluated for a history of immediate-type antibiotic allergy. These patients were evaluated by allergists-immunologists at our 591-bed university-affiliated hospital or outpatient office practice from 2009 through 2014. Most patients were identified through an inpatient and outpatient billing query of *Current Procedural Terminology* codes for percutaneous and intradermal drug skin testing (95018 and 95017), drug challenge (95076), and drug induction of tolerance (95180), with additional patients identified by a manual search through an allergy-immunology consultation log book. Only patients reporting a clinical history consistent with a prior antibiotic immediate-type hypersensitivity reaction were included.

Patients were excluded if they provided any self-reported history that was not consistent with an immediate-type hypersensitivity reaction (delayed hypersensitivity reactions and/or histories suggestive of Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, or drug rash with eosinophilia and systemic symptoms).

Data Collection

Data reviewed and gathered from the health record included patient demographics and clinical characteristics, including age, sex, atopic disease (self-reported history of asthma, atopic dermatitis, allergic rhinitis, and/or food allergy) and, if applicable, other reported antibiotic drug allergy. We also examined the antibiotic index reaction history for its remoteness (number of years ago that the reaction occurred from the time of the allergy evaluation), reaction severity including the signs and symptoms developed, route of administration, treatments received for the reaction, and overall time course of the reaction and its resolution. All reactions described were consistent with type I immediate hypersensitivity reactions except for those patients who had an unknown index reaction.

Outcomes Measured and Challenge Method Definitions

The outcomes of skin prick and/or intradermal antibiotic testing and of antibiotic drug challenges were reviewed. Skin testing was performed with the major determinant Pre-Pen (benzylpenicilloyl polylysine; ALK Abellø, Round Rock, Texas) according to the manufacturer's instructions, the minor determinant Pfizerpen (penicillin G potassium [PenG], 10,000 U/mL; Pfizer, New York, New York) according to the Drug Allergy Practice Parameter guidelines,¹ and challenge-specific agents at recommended nonirritating concentrations with histamine-positive (1 mg/mL for skin prick and 0.1 mg/mL for intradermal testing) and glycerinated phenol saline–negative controls.^{7,15,26–31} (Table 1).

Challenges were categorized as single-step (full dose administered) or incremental multistep using 2 steps (1/10th dose administered, followed by the remaining dose) or 3 steps (1/100th dose administered, followed by 1/10th dose administered, followed by the remaining dose). Intervals between subsequent doses were 30 to 60 minutes, based on the Joint Task Force on Practice Parameters recommendations and clinician assessment.⁷ The number of challenge steps was determined by the clinician's review of the index reaction history, the patient's current clinical status, and skin test results if available. For analysis, 2-step and 3-step challenges were combined to compose a multistep challenge group. For patients with a positive challenge result, we noted the reaction severity and the dose and challenge step at which the reaction occurred. In these patients, we also reviewed whether an induction of tolerance for

Table 1

List of Skin Test Concentrations for Antibiotics Used

Skin test agent	Concentration (SP)	Concentration (ID)
Ampicillin	20 mg/mL	20 mg/mL
Nafcillin	250 mg/mL	25 μ g/mL
Piperacillin-tazobactam	20 mg/mL	20 mg/mL
Cefazolin	330 mg/mL	33 mg/mL
Cefepime	20 mg/mL	2 mg/mL
Ceftriaxone	100 mg/mL	10 mg/mL
Cefuroxime	100 mg/mL	10 mg/mL
Ertapenem	1 mg/mL	1 mg/mL
Meropenem	1 mg/mL	1 mg/mL
Levofloxacin	1–2.5 mg/mL	0.025 mg/mL
Moxifloxacin	0.5 mg/mL	N/A

Abbreviations: ID, intradermal; N/A, not applicable; SP, skin prick.

the preferred antibiotic was performed or whether the patient received an alternative antibiotic.

Definition of Reaction Severity

The reported index reaction severity and observed antibiotic challenge reaction severity were graded based on increasing severity and organ system involvement as adapted from Iammatteo et al¹⁹: grade 0, no reaction; grade 1, cutaneous findings only; grade 2, mucocutaneous, respiratory, or gastrointestinal involvement; and grade 3, anaphylaxis (as defined by Sampson et al³²). Anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled: (1) acute onset of an illness (minutes to several hours) with involvement of the skin and/or mucosal tissue (eg, generalized hives, pruritus or flushing, or swollen lips, tongue, or uvula) and at least 1 of the following: (a) respiratory compromise (eg, dyspnea, wheeze and bronchospasm, stridor, decreased peak expiratory flow, or hypoxemia) or (b) decreased blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, or incontinence); (2) at least 2 of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours): (a) involvement of the skin and mucosal tissue (eg, generalized hives, itch and flush, or swollen lips, tongue, or uvula), (b) respiratory compromise (eg, dyspnea, wheeze and bronchospasm, stridor, decreased peak expiratory flow, or hypoxemia), (c) decreased BP or associated symptoms (eg, hypotonia [collapse], syncope, or incontinence), or (d) persistent gastrointestinal symptoms (eg, crampy abdominal pain or vomiting); or (3) decreased BP after exposure to a known allergen for that patient (minutes to several hours). In adults, a systolic BP lower than 90 mm Hg or a decrease greater than 30% from that person's baseline BP was labeled grade 4 (cardiopulmonary arrest). If the details of the index reaction severity could not be adequately recalled by the patient or were unknown, thus preventing its classification as an immediate-type hypersensitivity reaction, then it was labeled grade 5 (unknown).

Statistical Analysis

Clinical characteristics and patient demographics were summarized using median (interquartile range) and frequency (percentage) and compared using the Wilcoxon rank-sum test and Pearson χ^2 with exact *P* values computed. The κ statistics were used to estimate the agreement between the patient-reported index severity and observed challenge reaction severity and to estimate the agreement between the number of steps expected to be completed in the challenge and the number of steps actually completed. The Cochran-Armitage trend test was used to determine the relation between the challenge outcome and the challenge dose received. Results with a *P* value less than .05 were considered statistically significant. All analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina).

Results

Baseline Patient Clinical Characteristics

In total, 211 adult patients with an antibiotic immediate-type hypersensitivity history undergoing an allergy evaluation were identified (median age 67 years, age range 50–76 years, 58% women). Patients reported reactions to multiple antibiotic classes, including 165 (78%) to penicillins (penicillin, amoxicillin, or piperacillin-tazobactam), 22 (10%) to fluoroquinolones (ciprofloxacin, levofloxacin, or moxifloxacin), 16 (7.6%) to cephalosporins (first generation: cephalexin, cefadroxil, or cefazolin; second generation: cefaclor or cefprozil; third generation: cefdinir or ceftriaxone; fourth generation: cefepime; fifth generation: ceftaroline), and 8 (3.8%) to carbapenems (meropenem, ertapenem, or

Table 2

Demographics and Clinical Characteristics of Antibiotic Challenged and Non-challenged Patients

	Challenged	Nonchallenged	All patients	<i>P</i> value
Patients, n	179	32	211	
Age (y) ^a	67 (50–76)	67 (51–75)	67 (50–76)	.660
Women, n (%)	100 (56)	22 (69)	122 (58)	.243
Index reaction occurrence (number of years since evaluation) ^a	40 (20–40)	15 (14–30)	40 (15–40)	.003
Additional self-reported antibiotic allergies (n) ^a	0 (0–0)	0 (0–1)	0 (0–1)	.085
Self-reported atopic history, n (%)	47 (26)	6 (19)	53 (25)	.392
Medication allergy by history, n (%)				<.001
Penicillin class	151 (84)	14 (44)	165 (78)	
Cephalosporin class	15 (8.4)	1 (3.1)	16 (7.6)	
Carbapenem class	6 (3.4)	2 (6.3)	8 (3.8)	
Fluoroquinolone class	7 (3.9)	15 (47)	22 (10)	
Index reaction severity, n (%)				<.001
Grade 1	84 (47)	17 (53)	101 (48)	
Grade 2	44 (25)	5 (16)	49 (23)	
Grade 3	8 (4.5)	9 (28)	17 (8.1)	
Grade 4	1 (0.6)	1 (3.1)	2 (1.0)	
Grade 5 (unknown)	42 (24)	0 (0)	42 (20)	
Antibiotic skin testing result, n (%)				<.001
Negative	125 (70)	9 (28)	134 (64)	
Positive	1 (0.6)	5 (16)	6 (2.8)	
Not tested	53 (30)	18 (56)	71 (34)	

^aAge, index reaction occurrence, and additional reported antibiotic allergies are reported as median (interquartile range).

imipenem). For the index reaction, most patients reported an oral route of antibiotic administration (44%) and a nonanaphylactic (71%) reaction (grade 1 or 2). Approximately 25% of patients had a self-reported history of atopic disease. The index reaction history was remote (median 40 years previously). Baseline clinical characteristics are listed in Table 2. Figure 1 shows a comparison of the number of patients with drug allergy to a particular class of antibiotics with the antibiotic class evaluated at the time of consultation.

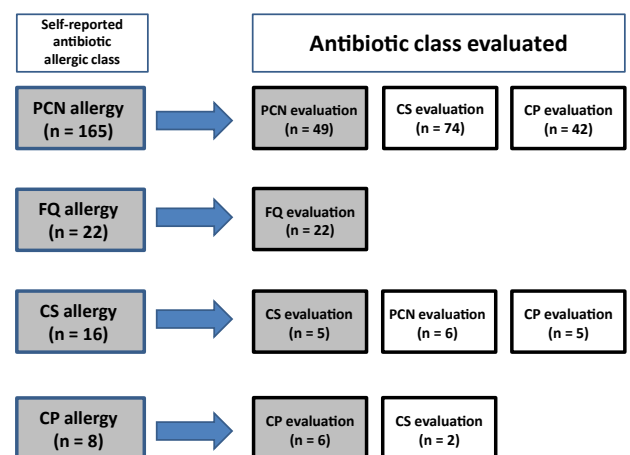


Figure 1. Distribution of patients evaluated for antibiotic allergy, represented by the self-reported antibiotic allergic class (left of arrow) and the evaluated antibiotic class at the time of consultation (right of arrow). Shaded boxes represent evaluations for similar antibiotic classes. CP, carbapenem class; CS, cephalosporin class; FQ, fluoroquinolone class; PCN, penicillin class.

Table 3
Characteristics and Outcomes of Patients With Positive Skin Testing Results

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age (y)	54	33	29	67	91	74
Sex	female	female	female	female	female	female
Self-reported atopic disease history	AD	AS, AR	none	none	none	none
Self-reported allergy antibiotic	amoxicillin + clavulanate	amoxicillin	penicillin	penicillin	ciprofloxacin	levofloxacin
Index reaction severity grade	2	3	1	1	1	3
Agent with positive skin testing results	Pre-Pen (SP), PenG (SP)	Pre-Pen (SP), PenG (SP)	Pre-Pen (SP), PenG (SP)	Pre-Pen (ID)	moxifloxacin	levofloxacin
Antibiotic drug challenge agent (outcome)	amoxicillin (tolerated)					
Induction of tolerance agent (outcome)			nafcillin (tolerated)			levofloxacin (tolerated)
Alternative agent administered		vancomycin aztreonam		no antibiotic therapy given	meropenem	

Abbreviations: AD, atopic dermatitis; AR, allergic rhinitis; AS, asthma; ID, intradermal; PenG, penicillin G potassium; SP, skin prick.

Skin Testing Outcomes

Skin prick and/or intradermal testing to the antibiotic of treatment were performed in 141 patients. Results of skin testing (positive vs negative reactions) were 4 vs 49 for penicillins, 1 vs 52 for cephalosporins, 0 vs 31 for carbapenems, and 2 vs 2 for fluoroquinolones. The patient with the positive cephalosporin skin test had a history of penicillin allergy and was challenged to augmentin, and thus was considered as part of the nontested group, as he did not have penicillin testing performed. Most patients with negative skin testing results (125 of 134) underwent further evaluation with antibiotic challenge. Characteristics and clinical outcomes of patients with positive skin testing results are presented in Table 3.

Clinical Characteristics of Challenged Patients

Antibiotic drug challenges were performed in 179 patients (median age 67 years, range 50–76 years, 56% women): 48 to penicillins, 76 to cephalosporins, 48 to carbapenems, and 7 to fluoroquinolones. Challenged and nonchallenged patients had comparable characteristics, including age, sex, self-reported atopic disease history, and number of other self-reported antibiotic allergies. Challenged patients compared with nonchallenged patients had more remote index reactions (40 vs 15 years, $P = .003$), which were mainly not anaphylaxis (4.5% vs 28%) or cardiopulmonary arrest (0.6% vs 3.1%) but were more likely to have been unknown reactions (24% vs 0%, $P < .001$). In challenged individuals, 125 had negative skin testing results. Clinical characteristics of challenged and nonchallenged patients are listed in Table 2.

Antibiotic Challenge Outcomes and Clinical Characteristics of Challenge-Reactive Patients

Sixteen patients (8.9%) had positive challenge results resulting in hypersensitivity reactions. Of these patients, 11 had negative skin testing results and 5 were not skin tested to the challenge agent. All challenge reactions were observed by medical staff, with the exception of 1 female outpatient with a nonurticarial rash that developed 5 days after the challenge completion. Antibiotic-specific reaction rates were 43% to fluoroquinolones (3 of 7), 10% to penicillins (5 of 48), 10% to carbapenems (5 of 48), and 3.9% to cephalosporins (3 of 76). Challenge reactions were treated with oral or intravenous antihistamines, inhaled albuterol, and/or intravenous or oral corticosteroids. Epinephrine was administered for anaphylactic reactions. Table 4 presents the specific treatment of each challenge-reactive patient. Patients with positive challenge results were younger (median age 52 vs 68 years, $P = .007$), more often women (81% vs 53%, $P = .036$), and had additional reported antibiotic allergies (median 0.5 vs 0, $P = .005$) compared with those

who tolerated their challenges. Challenge-reactive and challenge-tolerant patients exhibited comparable spectra of index reaction severities. Clinical characteristics of the challenge-reactive and challenge-tolerant patients are listed in Table 5. Eleven patients with reported penicillin class allergy had negative skin testing results to Pre-Pen, PenG, and their challenge-specific β -lactam agent, but still experienced challenge reactions. Anaphylaxis occurred in 6 patients (4 with negative skin testing results) who received piperacillin-tazobactam ($n = 2$), cefepime ($n = 1$), ciprofloxacin ($n = 1$), or meropenem ($n = 2$). Table 4 presents a detailed summary of the characteristics and outcomes of the challenge-reactive patients.

Induction of Tolerance and Alternative Antibiotic Treatment Regimens

Of the 32 nonchallenged patients, 16 received alternative treatment regimens, 8 underwent successful induction of tolerance to the preferred antibiotic, and the other 8 underwent skin testing but not a challenge during outpatient elective evaluations. Of the group of 16 challenge-reactive patients, 2 underwent induction of tolerance and 9 received alternative agents. The other 5 patients received no further antibiotic therapy. Induction-of-tolerance agents included ampicillin, nafcillin, piperacillin-tazobactam, cephalexin, ceftriaxone, meropenem, and levofloxacin. A wide variety of alternative antibiotics were administered; however, the most common agents were tigecycline ($n = 5$); levofloxacin and vancomycin ($n = 4$); aztreonam, meropenem, and ceftriaxone ($n = 3$); and azithromycin and linezolid ($n = 2$).

Tolerability Rates Among Antibiotic Classes

Of all the challenges completed, patients with reported penicillin allergy exhibited high tolerability to other penicillins (88%), cephalosporins (96%), and carbapenems (90%), whereas patients with fluoroquinolone allergy demonstrated poor tolerability to other fluoroquinolone antibiotics (57%). Figure 2 displays the tolerability rates of antibiotic challenges for all antibiotic classes.

Drug Challenge Reaction Severity and Reported Index Reaction Severity

Index reaction severities varied among challenge-positive patients: grade 1 in 9, grade 2 in 4, grade 3 in 2, and grade 5 in 1. Nine patients had challenge reactions to medications in the same class as their reported index reaction. Excluding the grade 5 (unknown) index reaction case from statistical analysis, drug challenge reaction severity was similar to index reaction severity in approximately 38% of patients, whereas 50% experienced more severe reactions and approximately 13% experienced less severe

Table 4
Antibiotic Drug Challenge-Reactive Patient Clinical Characteristics and Outcomes Data

Age (y)/sex	Self-reported antibiotic allergy	Other antibiotic allergies, n	Pre-Pen and PenG skin test result	Additional skin test agent (result)	Challenge agent	Index and challenge reaction severity grades	Reaction step (dose at challenge reaction)	Treatment(s) administered	Induction of tolerance agent	Alternative agent received
44/M ^c	penicillin	0	neg	piperacillin-tz (neg)	piperacillin-tz	2 → 3	2 (1/10th dose)	Epi, AH, CS		cefepime; linezolid
51/F ^c	penicillin	0	neg	piperacillin-tz (neg)	piperacillin-tz	1 → 3	3 (remaining dose)	norepinephrine ^a		
52/F ^c	penicillin	1	neg	ampicillin (neg)	amoxicillin	2 → 1	1 (full dose)	AH		ceftriaxone
67/F ^c	penicillin	1	neg	ampicillin (neg)	amoxicillin	1 → 2	1 (full dose)	AH, CS		
50/F ^c	amoxicillin	1	neg	ampicillin (neg)	amoxicillin-clav	1 → 1 ^b	1 (full dose)	AH		
46/F	amoxicillin	2	neg	cefazolin (neg)	cephalexin	1 → 1	3 (remaining dose)	AH		
57/F	penicillin	0	neg	ceftriaxone (neg)	ceftriaxone	2 → 1	3 (remaining dose)	AH		
34/F	penicillin	3	neg (SP only)	cefepime (neg; SP only)	cefepime	3 → 3	3 (remaining dose)	Epi, AH, CS		levofloxacin; gentamicin
67/M	penicillin	0	neg	N/A	meropenem	1 → 3	1 (1/10th dose)	Epi, AH, CS		vancomycin; tigecycline
75/F	penicillin	0	neg	meropenem (neg)	meropenem	3 → 3	2 (1/10th dose)	Epi, AH, CS		fosfomycin
44/M	penicillin	0	neg	ertapenem (neg)	ertapenem	1 → 2	2 (remaining dose)	AH, CS		tigecycline
69/F	penicillin	0	neg	meropenem (neg)	meropenem	2 → 2	2 (1/10th dose)	AH, SABA		levofloxacin; tigecycline
36/F ^c	ertapenem	4	neg	N/A	meropenem	1 → 1	2 (remaining dose)	AH, CS	meropenem	
46/F ^c	levofloxacin	1	neg	N/A	ciprofloxacin	1 → 3	1 (full dose)	Epi, AH, CS		meropenem
60/F ^c	ciprofloxacin	0	N/A	N/A	moxifloxacin	1 → 1	1 (full dose)	AH, CS		metronidazole
65/F ^c	levofloxacin	4	N/A	N/A	levofloxacin	5 → 1	1 (1/100th dose)	AH	levofloxacin	

Abbreviations: AH, antihistamine; clav, clavulanate; CS, corticosteroid; Epi, epinephrine; F, female; M, male; ID, intradermal; N/A, not available or performed; neg, negative; PenG, penicillin G potassium; SABA, inhaled short-acting β -agonist; SP, skin prick; tz, tazobactam.

All patients had negative skin testing results (SP and ID) unless specified otherwise.

^aPatient was on norepinephrine before and during the challenge and required an increased dose of the norepinephrine drip for the hypotension challenge reaction (tryptase level 25.1).

^bDelayed-type reaction.

^cPatients challenged to a similar antibiotic class as their reported antibiotic allergy class.

reactions. Half the patients with a history of cutaneous-only reactions experienced more severe reactions during the challenge. There was very low statistical agreement between the reported index reaction severity and the observed challenge reaction severity ($\kappa = -0.05$, 95% confidence interval -0.34 to 0.24), indicating no correlation between the prior and current reactions.

Outcomes of Single-Step and Multistep Antibiotic Challenge Methods

The outcomes of single-step (full dose) and multistep (incremental dose) challenges were reviewed. The multistep method was applied in 151 patients ($n = 96$ for 2-step and $n = 55$ for 3-step challenges) and a single-step administration was performed in 28 patients. Patients had comparable demographics and index reaction severity, except that patients with the single-step challenge had additional reported antibiotic allergies ($P = .001$). There were larger proportions of penicillin and fluoroquinolone single-step challenges ($P < .001$) compared with the other drug classes. Reactions occurred in 5 of 28 single-step and 11 of 151 multistep challenges (18% and 7.3%, respectively). Nine of 11 patients (82%) who underwent multistep challenges reacted to doses beyond the initial step. There was a significant trend in the proportion of patients with positive challenge outcomes and increasing cumulative dose received because 6.3% of patients with challenge-positive reactions reacted to the 1/100th dose, 25% reacted to the 1/10th dose, and 69% reacted to the full dose (exact $P < .001$). Anaphylactic reactions occurred in 3.6% ($n = 1$ of 28) of single-step and 3.3% ($n = 5$ of 151) multistep challenges. Anaphylaxis occurred in 1.0% ($n = 1$ of 96) of the 2-step challenges and 7.3% ($n = 4$ of 55) of the 3-step challenges. Of 6 total anaphylactic reactions, 4 occurred during a 3-step challenge but none occurred at the 1/100th dose.

Discussion

This retrospective study is unique in its design because it examined antibiotic challenge parameters such as index reaction severity in relation to challenge outcomes. Risk factors for antibiotic hypersensitivity include a history of allergic reaction; female sex; adults 20 to 50 years old; topical, intramuscular, and intravenous routes of administration; and recurrent antibiotic exposures, especially in patients with cystic fibrosis or other recurrent infections and patients with immunodeficiency states.^{7,8,11,33–37} In our population, younger women with multiple self-reported antibiotic hypersensitivities were at significantly greater risk for challenge reactions.

Of the patients with reported penicillin allergy and negative skin testing results to Pre-Pen, PenG, and their challenge-specific β -lactams, 11% ($n = 11$ of 98) experienced challenge reactions, including 4 anaphylactic reactions to piperacillin-tazobactam, cefepime, and meropenem. Anaphylaxis to piperacillin-tazobactam despite negative piperacillin-tazobactam skin testing results has been reported.³⁸ Approximately 12% of patients (3 of 25) with negative skin testing results to Pre-Pen, PenG, and carbapenems had carbapenem challenge reactions. This is in contrast to Gaeta et al³⁹ who reported that patients with positive penicillin skin testing results but negative carbapenem skin testing results tolerated carbapenem challenges (211 of 212 patients accepted and tolerated challenges). Likewise, 6.0% of patients (3 of 47) with negative skin test results to the penicillin determinants and cephalosporins experienced cephalosporin challenge reactions. Bousquet et al²² found that approximately 17% of patients with a β -lactam allergy history had positive penicillin and cephalosporin challenge reactions, including anaphylaxis, despite negative major and minor determinant penicillin skin testing. In another study by Messaad et al,²³ 8.4% of patients were diagnosed with β -lactam

Table 5
Demographics and Clinical Characteristics of Challenge-Reactive and Challenge-Tolerant Patients

	Challenge-reactive patients	Challenge-tolerant patients	All patients challenged	P value
Patients, n	16	163	179	
Age (y) ^a	52 (45–66)	68 (51–77)	67 (50–76)	.007
Women, n (%)	13 (81)	87 (53)	100 (56)	.036
Index reaction occurrence (number of years since evaluation) ^a	17 (10–40)	40 (20–40)	40 (20–40)	.152
Additional self-reported antibiotic allergies (n) ^a	0.5 (0–1.5)	0 (0–0)	0 (0–0)	.005
Self-reported atopic history, n (%)	6 (38)	41 (25)	47 (26)	.370
Medication allergy by history, n (%)				.021
Penicillin class	12 (75)	139 (85)	151 (84)	
Cephalosporin class	0 (0)	15 (9.2)	15 (8.4)	
Carbapenem class	1 (6.3)	5 (3.1)	6 (3.4)	
Fluoroquinolone class	3 (19)	4 (2.5)	7 (3.9)	
Index reaction severity, n (%)				.224
Grade 1	9 (56)	75 (46)	84 (47)	
Grade 2	4 (25)	40 (25)	44 (25)	
Grade 3	2 (13)	6 (3.7)	8 (4.5)	
Grade 4	0 (0)	1 (0.6)	1 (0.6)	
Grade 5 (unknown)	1 (6.3)	41 (25)	42 (24)	
Antibiotic skin testing result, n (%)				.999
Negative	11 (69)	114 (70)	125 (70)	
Positive	0 (0)	1 (0.6)	1 (0.6)	
Not tested	5 (31)	48 (29)	53 (30)	

^aAge, index reaction occurrence, and additional antibiotic allergies are reported as median (interquartile range).

hypersensitivity by challenge after negative penicillin skin testing results. Furthermore, an extensive prospective study demonstrated a significant decrease in β -lactam hypersensitivity diagnosed by skin testing in patients with confirmed allergy to β -lactams by a positive challenge or basophil activation test result.²⁰ Our data support that negative testing with the Pre-Pen and PenG might not completely exclude challenge reactions.

Although challenges are performed in low-risk patients, they could cause adverse reactions and safety is of utmost importance. Challenge-reactive patients did not have a history of more severe index reactions compared with the challenge-tolerant patients in our study; 2 patients with a history of anaphylaxis tolerated challenges to antibiotics of the same class as their index reaction. However, a nonanaphylactic index reaction history ought not to mislead physicians that anaphylaxis will not occur during a challenge. In the challenge-reactive patients, we found that approximately 88% of patients had similar or more severe challenge reactions compared with their index reaction severity when drugs

of the same antibiotic class were administered. This is in contrast to previous data that challenge reactions are reproducible or less severe compared with patient-reported reactions; however, that study included antibiotic (24%) and nonantibiotic challenge reactions.²³ Although various studies have reported different outcomes, challenges are generally considered a safe method in appropriately selected patients, but anaphylaxis can still be an untoward, potential risk.

The observed cross-reactivity (and tolerability) across different antibiotic classes was similar to published retrospective data.^{1,40–42} This was especially notable for patients with reported penicillin class hypersensitivity undergoing challenges to cephalosporins and carbapenems with respective cross-reaction rates of 4.3% and 10%. No patients with reported cephalosporin hypersensitivity ($n = 15$) reacted to any cephalosporins or β -lactams during the challenge. In patients labeled as having a penicillin allergy, 88% ($n = 37$ of 42) could tolerate penicillins, supporting previous data stating that approximately 90% of patients so labeled can tolerate penicillins.¹ Furthermore, 98% of patients ($n = 41$ of 42) with an unknown index reaction history tolerated any challenge. Only 1 patient with unknown index reaction experienced a delayed-type cutaneous exanthem.

The available data on fluoroquinolone hypersensitivity trends are increasing but remain rather limited. It is postulated that the increased use of fluoroquinolones, especially in communities with β -lactam resistance patterns, has contributed to an increased incidence of reactions to this class.^{15,20} Blanca-López et al³⁵ found a strong association between prior confirmed β -lactam hypersensitivity and fluoroquinolone hypersensitivity. In our study, 2 of 3 patients who reacted to fluoroquinolone challenges also reported a history of penicillin allergy. Although fluoroquinolones comprised the smallest subgroup in our review, patients challenged to this class demonstrated high cross-reactivity to other fluoroquinolones. Fluoroquinolones also had the highest overall reaction rate (43%) among all antibiotic class-specific challenges. In another similarly designed study, a relatively larger proportion of patients (27.3%, $n = 9$ of 33) with a history of fluoroquinolone allergy challenged to fluoroquinolones reacted compared with patients allergic to and challenged to β -lactams.²³ With the increasing prevalence of fluoroquinolone hypersensitivity, new data regarding risk factors and cross-reactivity will likely emerge in the near future.

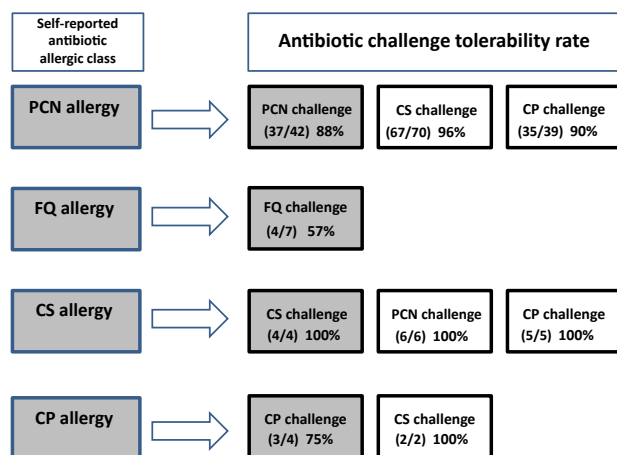


Figure 2. Antibiotic drug challenge tolerability rates of all challenged patients, with the patient self-reported antibiotic allergic class (left of arrow) and the antibiotic challenge class (right of arrow). Shaded boxes represent similar antibiotic classes. CP, carbapenem class; CS, cephalosporin class; FQ, fluoroquinolone class; PCN, penicillin class.

Most of our challenged patients reacted after the final (full or remaining) administered dose. The single-step challenge reaction rate was higher at 18% compared with multistep challenges, but this could be skewed because of a larger number of patients who underwent multistep antibiotic challenges. In our population, performing a 2-step method for the multistep challenges would have captured all anaphylactic reactions. No patients experienced anaphylaxis at the first step (1/100th dose) of a 3-step challenge. Single-step and multistep challenge anaphylaxis rates were nearly identical (~3%). There were no differences in reaction severity between the methods. These findings suggest an overall comparable risk between the single-step and multistep methods, which has been similarly concluded in another retrospective review.¹⁹

Our study had several limitations, such as its retrospective design at a single center. We also recognized the potential for patient recall bias of antibiotic allergy history details because most reactions were remote. As previously alluded to, there were relatively small nonpenicillin antibiotic class sample sizes that prevented the sub-analysis of these groups for class-specific risk factors and cross-reactivity. The small sample also limited the analysis of data for comparing 2-step with 3-step positive challenge results.

To conclude, our study found that younger women with multiple antibiotic allergy histories were at greater risk for challenge reactions. Negative skin testing results with the major and 1 minor penicillin determinants and with antibiotic-specific agents did not completely exclude challenge reactions for β -lactams. Reported index reaction severity did not offer predictive value for the challenge outcome most of the time. Practically all patients with unknown index histories tolerated their challenges. Consistent with current drug allergy practice guidelines, we recommend performing challenges in a select population of individuals with low potential for reactions. Larger studies would help confirm or dispute the lack of index severity as a stratification factor for challenge risk. In our population, all but 1 of the challenge-reactive patients had symptoms with the 1/100th dose, suggesting that a challenge dose of 1/10th will capture most reactions. Further research is required to decisively determine the speculative safety benefits of multistep challenges, particularly for 3-step challenges. Allergists should proceed cautiously during antibiotic challenges regardless of the method used because reactions, including anaphylaxis, remain an established risk for patients.

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