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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.

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 Abellò, 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 μg/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.