Clinical Commentary Review

Practical Management of Antibiotic Hypersensitivity in 2017

Eric Macy, MD, MS[a], Antonino Romano, MD[b,c], and David Khan, MD[d] *San Diego, Calif; Rome and Troina, Italy; and Dallas, Texas*

Antibiotics are the most common class of medications that individuals report *allergy* or intolerance to. Adverse reactions are reported at a predictable rate with all antibiotic use that vary by antibiotic. Antibiotic *allergy* incidence rates are sex dependent, higher in females than in males. Most of these events are not reproducible or immunologically mediated. Antibiotic *allergy* prevalence increases with increasing age and is more common in hospitalized populations and in populations that use more antibiotics. Determining potential mechanisms for the observed symptoms of the adverse reactions is the starting point for effective management of antibiotic hypersensitivity. Skin testing and direct challenges are the primary tools used to determine acute tolerance in 2017. Commercially available *in vitro* testing is not currently clinically useful in determining antibiotic hypersensitivity, with rare exceptions. Desensitization can be used when acute-onset immunologically mediated hypersensitivity is confirmed to safely administer a needed antibiotic. Desensitization is not possible when clinically significant T-cell–mediated delayed-type hypersensitivity is present. Effective management of antibiotic *allergy* is an important part of a comprehensive antibiotic stewardship program. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

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Why another review on antibiotic hypersensitivity? Why would you want to reexpose an individual to an antibiotic they think already gave them a problem? We all know that antibiotics are significantly overused and the pattern of overuse varies widely across countries and across continents, wherever antibiotics are available.[1,2] We also recognize that there are no side effect–free drugs and that all antibiotic use is associated with a certain predictable rate of adverse reactions. Multiple drug-resistant infections are becoming more common.[3] Developing effective antibiotic stewardship programs is taking on new importance and urgency.[4] New information on the risks of avoidance of antibiotics, particularly narrow-spectrum penicillins, when they are the drugs of choice has made it important for specialists in Allergy and Clinical Immunology and Infectious Disease along with hospitalists and other primary care providers to be able to safely and efficiently evaluate and/or refer individuals with reported antibiotic intolerances and know when to do diagnostic testing, drug challenge, or desensitize.[5]

This review is meant to provide a practical approach to managing the clinical care of individuals who have reported adverse reactions to antibiotics. In this article, we use the term "intolerance" to encompass any reaction that is typically listed as an *allergy* in the medical record, recognizing that most of these are not true immunologic reactions and many may be perceived symptoms unrelated to the drug. The literature on evaluating antibiotic-associated adverse drug reactions has evolved dramatically over the past 80 years, since sulfonamide antibiotics became clinically available. The cumulative literature is very confusing, often apparently contradictory, and almost impossible to reconcile in its entirety.[6-8] Nonimmunologically mediated reactions are commonly referred to as "*allergy*" in the electronic health record (EHR), which adds to the confusion in both patients and many physicians.[9] Given this, it is not surprising that current antibiotic hypersensitivity management and testing practices vary widely.[10]

Most reported antibiotic intolerance or *allergy* is from direct pharmacologic effects of the antibiotic or antibiotic-independent sequela of the underlying bacterial or viral infection being treated, or often mistreated, with the implicated antibiotic.[11] These nonimmunologically mediated sequelae can include headaches, fevers, benign rashes, hives with or without angioedema, gastrointestinal symptoms including upset stomach, nausea, and vomiting, serious drug-resistant infections including methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococcus, and *Clostridium difficile*, and other somatic symptoms.[12] Antibiotic-associated immunologically mediated hypersensitivity only accounts for a small subgroup of reported intolerances or *allergy*.[11] Immunologically mediated symptoms can vary from relatively common, but benign, hives or delayed-onset exanthems, to serious and potentially life-threatening reactions such as IgE-mediated anaphylaxis, serious cutaneous adverse drug reactions (SCARs), hepatitis, serum sickness,

[a]Department of Allergy, Kaiser Permanente San Diego Medical Center, San Diego, Calif
[b]Allergy Unit, Presidio Columbus, Catholic University of Sacred Heart, Rome, Italy
[c]Istituti di Ricovero e Cura a Carattere Scientifico (IRCCS) Oasi Maria S.S., Troina, Italy
[d]Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas

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Corresponding author: Eric Macy, MD, MS, Kaiser Permanente Department of Allergy, 7060 Clairemont Mesa Blvd, San Diego, CA 92111. E-mail: eric.m.macy@kp.org.

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Abbreviations used
EHR- Electronic health record
DRESS- Drug eruption with eosinophilia and systemic symptoms
SCARs- Serious cutaneous adverse reactions
SJS- Stevens-Johnson syndrome
SSLR- Serum sickness-like reaction
TEN- Toxic epidermal necrolysis

hemolytic anemia, cytopenias, pneumonitis, or nephritis.[11] We will provide a general framework on how to address the management of individuals presenting with antibiotic *allergy*, safely identify those with clinically significant immunologically mediated hypersensitivity, and enable most of them to use the needed antibiotic or the least morbid alternative.

EPIDEMIOLOGY OF ANTIBIOTIC HYPERSENSITIVITY

The reference standard for a clinically significant antibiotic-associated adverse event is currently what is reported in the drug *allergy* field of the EHR.[13] In most EHRs there is only a drug *allergy* field and no other place to note drugs that should not be used, used with caution, or were associated with an adverse reaction. If there is no notation made in the EHR, then any adverse reaction that may have occurred cannot affect future antibiotic choice, and an inaccurate notation, or unconfirmed *allergy*, in the EHR will greatly reduce future exposure to that antibiotic. When one reviews the EHR, the time after the antibiotic exposure can make a significant difference in the adverse reaction incidence rate observed. Not all reports are made in a timely fashion. Checking 1 month after an exposure results in significantly lower reported rates of antibiotic *allergies* than checking 1 year after.[14] There are limited comprehensive population-based data on the incidence and prevalence of reported antibiotic intolerances (*allergies*). The prevalence of drug intolerance reports varies around the world, apparently dependent on the most commonly used antibiotics. In a study of 2,375,424 Kaiser Permanente Southern California healthplan members, who had at least 11 months of coverage in 2009, at least 1 visit during 2009, and essentially a representative sample of about 1% of the US population that uses health care, the prevalences of *allergy* to specific antibiotics were as follow: penicillins 186,630 (7.9%), sulfonamides 101,952 (4.3%), macrolides 28,275 (1.2%), cephalosporins 25,956 (1.1%), tetracyclines 16,555 (0.70%), quinolones 18,815 (0.46%), nitrofurantoin 5,809 (0.24%), clindamycin 4,745 (0.20%), metronidazole 3,623 (0.15%), with only rare reports to other antibiotics.[15] See Table I. There was a marked female predominance for all reported antibiotic intolerances, with the highest ratios noted for nitrofurantoin (0.43% females, 0.02% males, ratio, 21.5) and metronidazole (0.25% females, 0.04% males, ratio, 6.25). Overall, there were 216,192 (16.7%) females who reported at least 1 antibiotic intolerance, compared with only 94,576 (8.8%) of the males. Similar data were obtained from 1,766,328 hospitalized patients in Boston between 1990 and 2013, with the expected higher rates of drug intolerances noted in relatively older hospitalized patients compared with the entire population.[16] In contrast, in a study of an academic general practice in the Netherlands in 2014, less than 2% of the 8288 patients reported penicillin intolerance.[17]

New antibiotic intolerance reporting incidence is higher in females than in males for all antibiotic families.[18] It is also higher for all antibiotic families, except penicillins, in individuals with any reported drug intolerance compared with individuals with no reported drug intolerances. About 1 in 200 penicillin antibiotic courses results in a new penicillin intolerance report, independent of drug intolerance history.[15] Individuals receiving penicillins after negative penicillin allergy testing note reactions about 1% to 3% of the time, but only rarely convert to allergy test positive.[19] Individuals with multiple drug intolerance syndrome rarely have any underlying immunologically mediated mechanism responsible for their reactions because most listed reactions are predictable side effects.[20]

CLINICAL PRESENTATIONS

Clinically, hypersensitivity reactions to antibiotics are classified as immediate and nonimmediate according to the time interval between the first dose of the last administration and their onset.[21,22] *Immediate reactions* are defined as those occurring within 1 hour and up to 6 hours after the first dose of the last administration.[21,23] Immediate reactions usually manifest as isolated symptoms, such as urticaria, angioedema, conjunctivitis, respiratory symptoms (rhinitis, bronchospasm, cough, dyspnea), gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pain), or rarely as anaphylaxis.[22] *Nonimmediate* reactions are defined as those occurring at any time greater than 6 hours after the initial drug administration,[22] often starting 2 to 5 days later. The most common nonimmediate reactions are maculopapular or morbilliform exanthems and delayed-appearing urticaria/angioedema. Rarely, SCARs occur, which include acute generalized exanthematous pustulosis, drug-induced hypersensitivity syndrome or drug rash (or reaction) with eosinophilia and systemic symptoms (drug eruption with eosinophilia and systemic symptoms [DRESS]), and severe bullous exanthems such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).[24] In addition, nonimmediate reactions can be manifest by interstitial nephritis, pneumonitis, hemolytic anemia, cytopenias, hepatitis, and/or vasculitis with or without signs of serum sickness occurring up to several weeks after the first dose of the last administration.

If there is a recent history of antibiotic-associated anaphylaxis, specifically within 3 months of testing, the probability of clinically significant IgE-mediated allergy will be high, 20% to 50%.[25] If there is a distant history of benign index symptoms, specifically more than 10 years ago, the risk of clinically significant IgE-mediated allergy will be very low, 1% to 2%.[26] For individuals with a distant history of anaphylaxis, the risk is lower than for more recent reactions and many reported episodes of anaphylaxis do not meet the clinical criteria for true anaphylaxis, making the repeat risk even lower. Testing strategies need to consider the pretest probability of a positive test result. There are also frequent false-positive test results for most skin testing protocols and *in vitro* testing methods.[27] If these are relied on solely to determine acute tolerance and the reference standard of a drug challenge is not used to confirm, then many more individuals will suffer morbidity from the inability to use the preferred antibiotic they could safely tolerate.

TABLE I. Intolerance prevalence and immunogenicity of common antibiotics

Antibiotic or antibiotic family	Intolerance prevalence	IgE-mediated allergy	T-cell–mediated delayed hypersensitivity	Intrafamily immunologic cross-reactivity
Penicillins	7.9%	Possible	Possible	Common
Sulfonamides	4.3%	Unlikely	Possible	Unlikely
Macrolides	1.2%	Unlikely	Unlikely	Unknown
Cephalosporins	1.1%	Possible	Possible	Unlikely
Tetracyclines	0.70%	Unlikely	Unlikely	Unknown
Quinolones	0.46%	Possible	Unknown	Common
Nitrofurantoin	0.24%	Unlikely	Unlikely	NA
Clindamycin	0.20%	Unlikely	Possible	NA
Metronidazole	0.15%	Unlikely	Possible	NA

NA, Not applicable/available.

MECHANISMS OF IMMUNOLOGICALLY MEDIATED ANTIBIOTIC HYPERSENSITIVITY

The immunologic mechanism involved in most immediate reactions is classically antigen-specific IgE-dependent mast cell activation. It is also possible for antigen-specific IgG to activate complement that results in acute rashes and non–IgE-mediated mast cell activation. Nonimmediate reactions are even more heterogeneous. Most confirmed immunologically mediated maculopapular exanthems are T-cell–mediated. Cytotoxic and IL-5–producing, drug-specific CD4 T cells migrate into the skin and kill keratinocytes presenting the drug on MHC class II molecules through a perforin-dependent mechanism.[24,28] SCARs are frequently mediated through antigen-specific T cells.[29] Antigen-specific IgG and complement can be responsible for reactions as varied as delayed serum-sickness reactions, hemolytic anemias and cytopenias, and anaphylactic reactions.[30] It is possible that a prolonged antibiotic course results in the new production of antibiotic-specific IgE and results in delayed-onset urticaria.[31]

ELEMENTS FOR PROPER DOCUMENTATION OF DRUG INTOLERANCES/ALLERGY

Table II outlines the 3 essential elements of a drug intolerance entry in the EHR: the date of the reaction, the time between the first dose of the last course and the onset of the symptoms, and the specific symptoms.[32] There needs to be enough information listed in the drug intolerance entry to enable future treating physicians to determine whether any of the following is possible or probable: IgE-mediated allergy, IgG and complement-mediated hypersensitivity, T-cell–mediated delayed-type hypersensitivity, or any SCAR (including DRESS, TEN, SJS, or acute generalized exanthematous pustulosis) or serum sickness-like reaction (SSLR).

TABLE II. The 3 essential elements of a drug intolerance entry in the EHR

1. Date of the index adverse reaction
2. Time to onset of the index adverse reaction after the first dose of the last course
3. Specific clinical characteristics of the index adverse reaction (note 1 or more of the following in as much detail as possible)
   a. Anaphylaxis or shortness of breath*
   b. Hives*
   c. Other benign rashes*
   d. Gastrointestinal symptoms*
   e. Other benign symptoms*
      i. Headaches
      ii. Cough
      iii. Other
      iv. Unknown
   f. SCARs or other serious systemic symptoms‡
      i. Biopsy proven T-cell–mediated severe cutaneous eruption
      ii. DRESS
      iii. SJS
      iv. TEN
      v. Hepatitis/pneumonitis/nephritis
      vi. Hemolytic anemia/cytopenias
      vii. Other severe nonimmunologically mediated symptoms
         A. Angioedema
         B. Tendon rupture
         C. Other

*OK to consider testing, drug challenge, or desensitization if indicated.
‡Do not consider testing or drug challenge outside of a research protocol. Desensitization is not possible.

DIAGNOSIS AND TESTING CONCERNS RELATED TO SPECIFIC ANTIBIOTICS OR ANTIBIOTIC FAMILIES

Penicillins

Needless avoidance of penicillin because of an unconfirmed penicillin *allergy* has been shown to be a significant public health risk.[33,34] Any effective testing strategy needs to rapidly, inexpensively, and safely test individuals and minimize false-positive test results.[35] There is a significant level of IgE-mediated immunologic cross-reactivity among penicillins based on the shared core structures.[36] Aminopenicillins typically have higher rates of IgE-mediated adverse reactions compared with other penicillins.[37] There are individuals specifically reactive only to amoxicillin, a phenomenon apparently more common in Europe than in North America.[38,39] The reference standard test to document acute penicillin class antibiotic tolerance is an oral challenge, usually with amoxicillin, the most commonly used penicillin.[40] Low-risk individuals, including those with benign delayed-onset nonurticarial rashes, gastrointestinal upset, or headaches, can be safely evaluated with direct oral challenge without any preliminary skin testing.[41] Skin testing is done to minimize the number of serious acute oral challenge reactions. There is no consensus approach to what testing reagents are necessary or sufficient when penicillin skin testing, but simpler protocols appear to be safe and effective in most clinical settings.

In North America, where penicillin minor determinants are not commercially available, skin testing with benzylpenicilloyl-polylysine (PRE-PEN) and penicillin G, and when negative followed by a single dose of amoxicillin 250 mg, has been shown to be a safe and effective method for determining tolerance to penicillin.[42] Penicillins can also induce T-cell—mediated delayed hypersensitivity reactions.[43] Delayed reading of intradermal testing or patch testing has been used to try to predict clinically significant T-cell—mediated reactions, but results have not been consistent and the predictive value is uncertain; therefore, an oral challenge remains the reference standard test.[44] Multiday challenges do not appear to be any safer or clinically more useful than single-day challenges.[45] If there is a clinically significant T-cell—mediated, non-SCAR, delayed- type hypersensitivity to amoxicillin, it will typically be manifest within 5 days of an oral 250 mg amoxicillin challenge.[46] *In vitro* antipenicillin IgE tests are not useful outside of the setting of evaluating individuals who recently had penicillin-associated anaphylaxis.[47,48] When both skin tests and *in vitro* tests are highly positive, the risk of repeat anaphylaxis with an oral challenge is high.[49] Those rare individuals with penicillin-associated SCARs should not be tested or rechallenged outside of a research setting.[50]

Sulfonamide antibiotics

Sulfonamide antibiotics (eg, sulfamethoxazole, sulfadoxin, and sulfapyridine) are sulfonyl arylamines, characterized by a sulfonamide (SO2—NH2) moiety directly attached to a benzene ring, which carries an unsubstituted amine (-NH2) at the N4 position.[51,52] There is no cross-reactivity between antibiotic and nonantibiotic sulfonamides. Sulfonamides are most commonly associated with nonimmediate manifestations, such as maculopapular rashes and fixed drug eruptions. SCARs have been reported.[52,53] The risk of SJS/TEN is higher for sulfonamide antibiotics than for most other antibiotics. Most immunologically mediated sulfonamide-associated adverse reactions appear to be T-cell—mediated.[54] Sulfonamide antibiotics have the highest benign rash rate of all antibiotics.[15] The rash rate is even higher in individuals with active untreated or acutely treated HIV infection with low CD4 T-cell counts.[55] Prolonged treatment of the HIV with highly effective antiretroviral therapy then often results in tolerance.[56] There is no useful skin or *in vitro* test available to gauge the acute risk of reexposure.[57] Patch testing and the delayed reading of intradermal tests have been used to help gauge the delayed-onset risk of reexposure, but clinically drug challenge is still the reference standard test.[58] Dapsone does not appear to significantly cross-react with sulfamethoxazole.[59] Single-dose challenges appear to be just as safe as multiple dose challenge/desensitizations for proving tolerance to sulfonamides in HIV-infected patients.[60,61] Whether this is true for non-HIV patients is unknown but multistep single-day challenges have been shown to be as safe and effective as multistep multiday challenges.[58]

Macrolides

Macrolides are classified according to the number of carbon atoms in their lactone ring: 14 membered (erythromycin, troleandomycin, roxithromycin, dirithromycin, and clarithromycin), 15 membered (azithromycin), and 16 membered (spiramycin, rokitamycin, josamycin, and midecamycin).[62] Azithromycin is the most widely overused antibiotic in the United States.[63] Macrolide antibiotics reversibly bind bacterial 50S ribosomal subunits. They are too small to be directly immunogenic. It is unknown whether they are able to haptenate serum proteins. They are promotility agents and can be directly irritating to the gastrointestinal tract. Data on the utility of skin testing with macrolides is conflicting and although several studies have evaluated clarithromycin skin tests using a lyophilized form, this is not available in the United States. Because of several potential reasons including their direct irritant effect on the skin, their small size, and their lack of covalently binding to serum proteins, on the basis of the available evidence, the authors believe that macrolide skin testing is generally not useful due to the potential for false-positive skin test results at concentrations below the published nonirritating concentrations.[64,65] There does not appear to be any clinically significant class intolerance noted with macrolides.[66] If one macrolide is not tolerated, select another if indicated. If a specific macrolide is needed again, a drug challenge is safe and effective.[66,67]

Cephalosporins

About 3% of individuals exposed to a third- or higher-generation cephalosporin develop *Clostridium difficile* infection within 90 days.[68] First- and second-generation cephalosporins have *Clostridium difficile* infection incidence rates an order of magnitude lower.[68] Cephalosporins in general do not have clinically significant levels of immunologic cross-reactivity with penicillins, except for rare individuals who mount specific responses to shared side chains.[69] Penicillin allergy testing is not useful in evaluating the risk of cephalosporin-associated reactions.[70] Individuals with a history of intolerance to one cephalosporin typically tolerate other cephalosporins.[71] Skin testing and *in vitro* testing are not well enough validated, or even needed, for routine use in the clinical management of cephalosporin *allergy*.[72] Typically, just selecting an alternative cephalosporin, which ideally does not share a side chain with the implicated cephalosporin, is a safe and commonly used approach.[68] In patients with anaphylaxis to cephalosporins, negative skin tests to cephalosporins with disparate R1 groups predicted tolerance.[72] Cephalosporins are only extremely rarely uniquely associated with SCARs.[68]

Tetracyclines

Tetracyclines can induce photosensitive dermatitis and esophageal irritation.[73] They have not been convincingly shown to induce clinically significant IgE-mediated allergy or T-cell—mediated hypersensitivity. Drug challenge is generally successful.

Quinolones

Quinolones can be classified according to their generation: first (cinoxacin and nalidixic acid), second (ofloxacin, norfloxacin, ciprofloxacin, and enoxacin), third (levofloxacin), and fourth (gemifloxacin and moxifloxacin). Clear patterns of immunologically mediated cross-reactivity among quinolones have not been well established.[74] Skin testing with quinolones is not clinically useful because of direct mast cell activation through the Mrgprb2 receptor.[75,76] Levofloxacin-mediated histamine release is closely linked to activation of pertussis toxin-sensitive G proteins.[77] IgE-mediated hypersensitivity has been suggested using *in vitro* testing. Apparent T-cell—mediated SCARs have been rarely identified. Clinically the reference standard test for acute tolerance remains drug challenge. Nonimmunologically mediated adverse reactions predominate. Both hypoglycemia and

TABLE III. Suggested drug challenge protocols based on risk factors

Risk factors	Direct full-dose challenge (oral if possible, 1 h of observation after dose if history of acute reaction and 5 d of follow-up if history of delayed-onset reaction)	Graded challenge (1/10th and then a full dose with 1/2 h of observation after first dose and 1/2-1 h of observation after the final dose)	Graded challenge (1/100th, 1/10th, and then a full dose with 1/2 h of observation after the first 2 doses and 1/2-1 h of observation after the final dose)
Low-probability medication Hives or other benign index reaction	X		
Low-probability medication Possible anaphylaxis		X	
High-probability medication Hives or other benign index reaction		X	
High-probability medication Comorbid disease (eg, severe chronic obstructive pulmonary disease)			X

TABLE IV. Penicillin oral desensitization protocol[99]

Step	Penicillin V (units/mL)	Dose (mL)	Dose (units)	Cumulative dose
1	1000	0.1	100	100
2	1000	0.2	200	300
3	1000	0.4	400	700
4	1000	0.8	800	1,500
5	1000	1.6	1600	3,100
6	1000	3.2	3200	6,300
7	1000	6.4	6400	12,700
8	10,000	1.2	12,000	24,700
9	10,000	2.4	24,000	48,700
10	10,000	4.8	48,000	96,700
11	80,000	1.0	80,000	176,000
12	80,000	2.0	160,000	336,700
13	80,000	4.0	320,000	656,700
14	80,000	8.0	640,000	1,296,700

Administer penicillin V orally every 15 min per step. Each dose can be diluted in 30 mL water for patient to ingest. Total time: 3 h 45 min.

hyperglycemia have been noted among elderly hospitalized patients who received gatifloxacin.[78] Quinolones have been associated with tendon rupture.[79]

Nitrofurantoin

Nitrofurantoin has not been convincingly associated with IgE- or benign T-cell–mediated reactions. Serious nitrofurantoin-induced pulmonary toxicity is well described and rechallenge is contraindicated. Reproducible nitrofurantoin-induced hepatic injury is also well described and rechallenge is contraindicated. Recurrence has been documented as long as 17 years after the index reaction.[80] Benign rashes can be safely rechallenged.

Clindamycin

Clindamycin is associated with much high rates of *Clostridium difficile* infection infections than are penicillins.[81] Clindamycin has been associated with T-cell–mediated delayed-onset hypersensitivity that may be predicted by patch testing.[82]

Metronidazole

Metronidazole has not been convincingly associated with IgE- or benign T-cell–mediated reactions. Drug challenge is generally successful.[83]

Other betalactams

Other betalactams, including monobactams, carbapenems, and clavulanate, do not tend to have clinically significant levels of immunologic cross-reactivity with penicillins or cephalosporins, with the exception of rare individuals who mount specific responses to shared side chains.[84-88] Individuals with IgE-mediated allergy to betalactamase inhibitors such as clavulanate have been identified.[89]

Aminoglycosides

Aminoglycosides are classified into 2 groups: the streptidine group (streptomycin) and the desoxystreptamine group (kanamycin, amikacin, gentamicin, tobramycin, and neomycin).[90] Aminoglycosides can rarely cause both immediate and nonimmediate hypersensitivity reactions. Skin testing and patch testing have been rarely used. Cross-reactivity among aminoglycosides is common, approaching 50% or more among those belonging to the desoxystreptamine group.[91] Aminoglycosides are directly nephrotoxic and ototoxic.

Vancomycin

Vancomycin can directly activate mast cells and is associated with a "red man syndrome." Premedication with antihistamines, slowing the infusion rate, and avoidance of concomitant mast cell secretagogues (eg, opiates) are helpful in patients with red man syndrome. Vancomycin has been associated with rare cases of T-cell–mediated delayed-type hypersensitivity, linear IgA bullous dermatosis, DRESS, acute interstitial nephritis, and SJS/TEN.[92,93] Patch testing and skin testing have been used to help gauge the risk of reexposure.[94]

TABLE V. Example intravenous drug desensitization protocol

Preparation of solutions			
	Volume of diluent (eg, 0.9% sodium chloride)	Total amount to be injected in each solution	Final concentration
Solution 1	250 mL	10 mg	0.04 mg/mL
Solution 2	250 mL	100 mg	0.4 mg/mL
Solution 3	250 mL	1000 mg	4 mg/mL

Drug desensitization protocol					
Step	Solution	Rate (mL/h)	Time (min)	Administered dose (mg)	Cumulative dose (mg)
1	1	2	15	0.02	0.02
2	1	5	15	0.05	0.07
3	1	10	15	0.1	0.17
4	1	20	15	0.2	0.37
5	2	5	15	0.5	0.87
6	2	10	15	1	1.9
7	2	20	15	2	3.9
8	2	40	15	4	7.9
9	3	10	15	10	18
10	3	20	15	20	38
11	3	40	15	40	78
12	3	80	15	80	158
13	3	160	15	160	318
14	3	320	15	320	638
15	3	640	9	362	1000
Total time = 219 min.					

Full dose = 1000 mg.

DRUG CHALLENGES

Drug challenges are considered the reference standard for confirming acute tolerance to an antibiotic. Even in the case of penicillin allergy where skin testing has a good negative predictive value, an oral challenge is recommended to confirm acute tolerance and convince the patient that the antibiotic can be safely used. For most antibiotics, skin testing is not as well standardized and clinically useful and drug challenges are relied on to confirm tolerance. Many terms are used to describe drug challenge procedures including graded dose challenges, test doses, and provocation. The term provocation implies that the intention of this procedure is to provoke a reaction when in fact the purpose is quite the opposite. In clinical practice, the purpose of drug challenge is to confirm tolerance to an antibiotic and in carefully selected patients serious reactions are uncommon.[95,96] Pretreatment with antihistamines is not generally recommended for antibiotic drug challenge.

A negative drug challenge typically indicates that the patient may be considered acutely tolerant to that antibiotic. However, false-negative drug challenges may occur because of several factors including inadequate dosing, inadequate duration of the drug challenge, or a missing cofactor (eg, no concurrent infection). There is also a certain rate of adverse reactions that occur with all antibiotic use, even in individuals with no previous reactions. In the case of betalactam antibiotics, false-negative results occur infrequently as evidenced by a report by Demoly et al[97] that determined a negative predictive value of 94%. Of these false-negative reactions, none was serious, most were delayed, and all were cutaneous (mostly urticaria or exanthems) and some patients with self-reported reactions had subsequent negative drug challenges.

In clinical practice, drug challenges for antibiotic allergy are intended for patients who are deemed to be at low risk for being allergic to the given drug.[98] They are typically performed after skin testing, such as the case for penicillin, or may be performed without skin testing. Nonirritating concentrations are not well established for quinolones and some antibiotics may be irritating even at very dilute concentrations; therefore, drug challenges remain the only option for the initial evaluation of a patient. Challenges may also be used to exclude cross-reactivity. For example, most IgE-mediated cephalosporin allergy is apparently directed against R1-specific side-chain determinants. Patients who have negative skin tests to other cephalosporins with disparate R1 side chains have been shown to tolerate drug challenges with cephalosporins.[99] Many patients may have vague or subjective symptoms that are mild and not convincing for an IgE-mediated drug allergy (eg, headache or nausea) and a drug challenge can help confirm tolerance of these individuals. Drug challenges are contraindicated in antibiotic-induced lupus, vasculitis, organ-specific drug reactions causing cytopenias, hepatitis, nephritis, or pneumonitis and severe cutaneous adverse reactions including SJS and DRESS. Drug challenges are generally avoided in patients with SSLR; however, there are some data suggesting that children with SSLR to amoxicillin may tolerate amoxicillin challenges.[41,100] Whether this approach is safe for other antibiotics has not been studied. However, it should be noted that SSLRs to cefaclor are typically

cefaclor-specific and these patients tolerate other cephalosporins with no greater risk than average patients.[101]

There are multiple published protocols for antibiotic challenges, all with some fairly common approaches. Drug challenges for patients with immediate reactions should always be performed in a setting capable of treating anaphylactic reactions, although these are rarely encountered with good patient selection criteria. Determining the starting dose for an antibiotic challenge depends primarily on the pretest probability of the patient being truly allergic to that antibiotic.[102] See Table III. The key is using at least a 10-fold dose increment during multidose drug challenges. The lower the likelihood the patient will have a serious acute reaction, the higher the starting dose. Typical starting doses range from 1/100th of the final dose to a full therapeutic dose. More than 3 steps are virtually never indicated. For patients with histories of immediate reactions, doses are commonly administered every 30 to 60 minutes and typically patients are observed for 1 hour following the final dose. Drug challenges using these approaches have been found to be safe and effective methods for determining tolerance. If an acute IgE-mediated reaction occurs during a drug challenge, desensitization should be performed if that antibiotic is needed in the future.

Although some allergists use multistep challenges involving 3 or more graded doses, when compared with either a single-step or a 2-step challenge, reaction rates and severity are similar and there appears to be no advantage to these more expensive and time-consuming approaches.[102] Furthermore, using multiple steps, particularly with less than 10-fold dosing increments, may inadvertently desensitize the patient, which is not the goal of a drug challenge.

For delayed reactions, a single therapeutic dose with 2 to 5 days of home follow-up is generally sufficient. Patients can report the reactions and then return to the clinic for observation, treatment, and/or a skin biopsy if needed. The drug can be readministered every several days to allow time for a reaction to develop, if there is concern. For patients with a history of nonimmediate benign cutaneous reactions, challenges can be performed at home, but the first dose may be given under supervision if there is uncertainty.

For patients with purely subjective symptoms or with a history of multiple drug intolerance syndrome, one should strongly consider performing single-blind placebo-controlled challenges because these patients frequently have symptoms with placebo.[102] For oral challenges, inert fillers such as methylcellulose can be inserted into opaque gelatin capsules for use as placebos.

ANTIBIOTIC DESENSITIZATION

Antibiotic desensitizations have been performed since the 1940s, initially with gradually increasing doses of penicillin concomitant with antihistamine and epinephrine injections.[103] However, it was not until the early 1980s when a safer desensitization protocol was developed by Sullivan et al[104] and most antibiotic desensitization protocols are quite similar to this. See Table IV. Oral desensitizations should be performed whenever possible, even before the parenteral use of the same antibiotic. The basic principle of an antibiotic desensitization is to start with about double the dose used to produce the positive skin test result that confirmed the presence of clinically significant amounts of antibiotic-specific IgE. This is generally about 1/10,000th of the final therapeutic dose, with doubling doses every 15 minutes. If a reaction occurs during the desensitization, treat the reaction, stabilize the patient, then repeat the dose that was last tolerated, and complete the desensitization. Desensitizations can be done even in pregnant patients.[105] Castells[106] has developed a protocol using 3 different dilutions of a parenteral antibiotic starting with a 1:100 dilution, then a 1:10 dilution, and then the full concentration with advances in dosing made by increasing the rate of infusion[106] (Table V). Adverse reactions to antibiotic drug desensitizations are generally less frequent, and no more severe, than with other desensitizations. They can be safely performed in an outpatient setting that routinely performs oral food challenges. Individuals performing antibiotic desensitizations need to be well trained and comfortable in the management of acute anaphylaxis. In one of the early studies by Sullivan et al[104] using oral penicillin desensitizations, about 30% had delayed-onset reactions, none had immediate or anaphylactic reactions. Desensitization should be attempted only in the setting of well-documented IgE-mediated antibiotic allergy. Desensitizations are not clearly effective for T-cell—mediated reactions, such as benign delayed-onset rashes, and are contraindicated for more serious T-cell—mediated reactions.[107] Desensitizations are not possible for other nonimmunologically mediated reactions.[108]

MAINTENANCE OF ACUTE TOLERANCE AFTER DESENSITIZATION

It is critical to have continual exposure to the antibiotic after desensitization until the therapeutic course is completed. If more than 5 half-lives of the antibiotic expire without further dosing, then it will be necessary to repeat the desensitization. In certain settings, reactions can be noted with delayed redosing after as little as 2 half-lives, but reactions are also common in desensitized individuals even with continual dosing. In the setting of long-acting benzathine penicillin used for syphilis therapy, patients appear to be capable of maintaining a desensitized state for as long as 3 weeks and repeat desensitization is typically not needed.[104]

CONCLUSIONS

The effective management of antibiotic hypersensitivity starts with the accurate documentation of the index reaction. It is necessary to determine the likely mechanism(s) compatible with the clinical symptoms observed. After a thorough evaluation, the vast majority of patients with reported antibiotic allergy can be shown to be tolerant of the drug. Perform skin testing or *in vitro* testing when indicated and/or possible to screen out individuals at high risk for IgE-mediated anaphylaxis. Drug challenge, orally when possible, remains the reference standard test to determine acute tolerance. New reactions are always possible with repeat therapeutic administrations, even in drug challenge negative individuals. Always consider the risks of continued antibiotic avoidance, particularly when a narrow-spectrum antibiotic is the antibiotic of choice for a documented bacterial infection, in relation to the risks of reexposure when managing antibiotic intolerance.

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