

Review

Direct challenges are the gold standard for most antibiotic allergy evaluations



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Key Messages

- Graded challenges should be performed for penicillin allergy in adults with cutaneous-only reaction histories more than 5 years ago.
- Graded challenges should be performed for penicillin allergy in pediatric patients with cutaneous-only reaction histories.
- Graded challenges to penicillins can be done outside the allergy/immunology setting and have cost and time savings associated with them.
- Cephalosporin-graded challenges are indicated for cephalosporins with different R-group side chains.
- Graded challenges to other antibiotic classes including sulfamethoxazole, fluoroquinolones, tetracyclines, macrolides, metronidazole, carbapenems, and aztreonam should be performed in patients with mild reaction histories more than 5 years ago.

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ABSTRACT

Antibiotic allergies are frequently encountered in clinical practice, and delabeling of these allergies has individual and public health benefits. This review focuses on the evidence supporting graded challenges without preceding skin testing in adult and pediatric patients to the major groups of antibiotics including penicillins, cephalosporins, sulfamethoxazole, fluoroquinolones, tetracyclines, macrolides, metronidazole, carbapenems, and aztreonam. The cost savings, time savings, and evidence for performing graded challenges outside of an allergy/immunology office are also reviewed for graded challenges to penicillins.

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Introduction

Antibiotic allergies are frequently encountered in clinical practice. Accumulation of allergy labels may preclude use of appropriate antibiotics and adversely affect outcomes. Direct challenges (DCs) are an effective tool to evaluate low-risk (Fig 1) or unclear reaction histories to antibiotics and offer advantages over skin testing (ST). Of course, DCs are not indicated for histories suggestive of severe cutaneous adverse reactions, where continued drug avoidance is necessary, or those suggestive of recent anaphylaxis, where a temporary induction of drug tolerance may be indicated for a needed drug. This article reviews the evidence supporting DCs for penicillins, cephalosporins,

trimethoprim/sulfamethoxazole, fluoroquinolones, tetracyclines, macrolides, carbapenems, and aztreonam, including pediatric data where they exist. Of note, dosing for these DCs is not standardized and a number of steps vary. Often, a two-step challenge may be used for billing purposes.¹ Practical recommendations, including evidence supporting DCs for penicillin-based antibiotics outside of the allergy/immunology purview, are emphasized (Fig 2).

Penicillin Direct Challenges

Direct Challenges in Adults

Studies Supporting Direct Challenges to Penicillin in Adults

The public health and individual risks of a penicillin allergy label include increased risk of resistant organisms, more costly care, adverse effects from second-line antibiotics, and increased mortality.^{1–4} Penicillin

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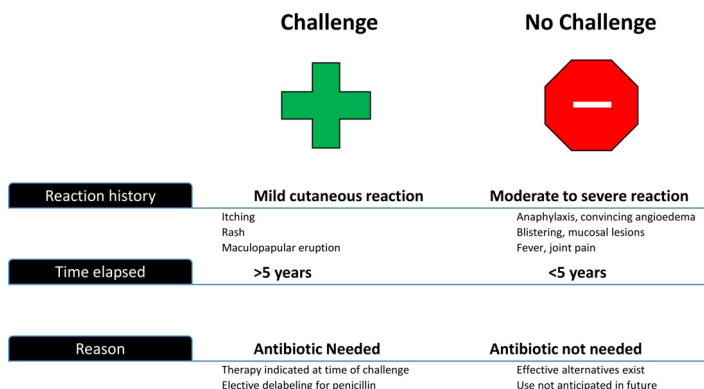


Figure 1. Indications for graded challenge or graded challenge avoidance.

skin testing (PST) with a dose of amoxicillin after a negative testing result was historically used to prove or disprove penicillin allergy¹; however, a growing body of literature favors direct challenge (DC, without prior PST) to penicillin in patients with low-risk reaction histories. One of the first articles to demonstrate this approach in adults retrospectively described the military experience of 328 Marine recruits who underwent DC to amoxicillin.⁵ Most of these recruits had cutaneous-only or unknown reactions and only 5 (1.5%) experienced mild reactions.⁵

Iammatteo et al⁶ conducted a prospective, placebo-controlled study in which patients received placebo followed by a 2-step DC to amoxicillin. Most patients reported historical reactions of urticaria, rash, swelling, or unknown reaction details. Of 156 patients, 120 (77%) tolerated the challenge. Only 4 patients (2.6%) experienced an allergic reaction.⁶ A unique aspect of this article was the placebo challenge, in which 16 patients experienced symptoms. An additional 15 patients experienced “non-allergic” subjective symptoms, with the most common symptoms of oropharyngeal symptoms, pruritus, or both during the amoxicillin challenge.⁶ The results of this study illustrate the psychological components of DC to consider when symptoms are reported.

Mustafa et al⁷ conducted a randomized, 1:1, prospective study comparing PST with DC in low-risk (cutaneous-only symptoms, >10 years ago in adults, >1 year ago in children) children and adults. There were 79 patients in the DC group, and all but 3 tolerated the DC. These 3 patients experienced mild, nonanaphylactic symptoms.⁷ The authors concluded that in their study population, PST carried a higher risk of false positives in low-risk patients in that 10 of 80 patients in the PST group were positive compared with only 3 in the DC group.⁷ This raises the concern that PST may hinder the goal of delabeling given the risk of “over-calling” true penicillin allergy.

The definition of “low risk” adults was heterogeneous in the studies cited previously. Trubiano et al⁸ developed and validated a penicillin allergy clinical decision tool, PEN-FAST, for use in adult patients. Other clinical decision rules^{9–11} are less generalizable than PEN-FAST. The goal of PEN-FAST was to identify patients who do not require PST and would be appropriate for DC.⁸ There were 622 patients in the prospective internal derivation and validation cohort and a retrospective external validation cohort of 945 patients. “PEN” represents anyone reporting a penicillin allergy, F represents 5 years or less since a reaction (2 points), A represents anaphylaxis or angioedema (2 points), S represents a severe cutaneous adverse reaction (2 points), and T represents the need for medical treatment (1 point).⁸ A score of 0 represents a very low risk of a positive penicillin/penicillin-based antibiotic (PCN) evaluation result, a score of 1 to 2 represents a low risk of a positive PCN evaluation result, a score of 3 represents a moderate risk of a positive PCN evaluation result, and 4 to 5 represents a high risk of a positive evaluation result. The negative predictive value of a score of 3 or less was 96.3%.⁸ Further validation of the PEN-FAST rule is underway with a larger randomized study comparing PST with the PEN-FAST identified DC group.¹²

Ensuring safety with DCs remains of primary concern. A Bayesian meta-analysis conducted by Cardoso-Fernandes et al¹³ helps to allay these concerns. This analysis included 112 studies of 26,595 subjects and calculated a pooled frequency of severe reactions to DC at 0.06%, with anaphylaxis as the most frequent severe reaction.¹³ The authors caution that their data are limited by included study heterogeneity and exclusion of patients with a history of life-threatening reactions and positive skin test results.¹³ For comparison, the estimated rate of new penicillin-induced anaphylaxis is 1 to 4 cases per 10,000 administrations, which is 0.04% for the higher end of the estimate.^{14,15}

General Guide to Antibiotic Challenge

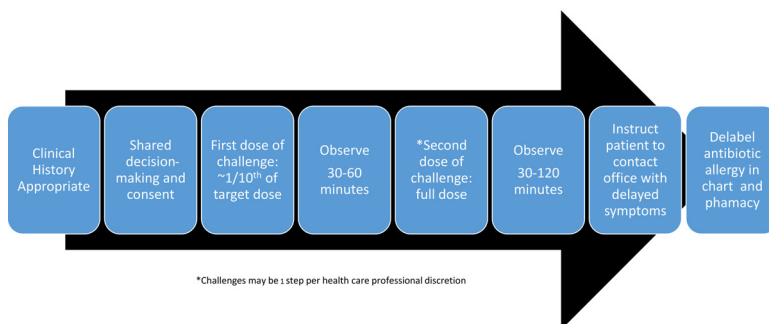


Figure 2. Schematic of graded challenge process.

Advantages of Direct Challenges in Adults

Generalizability outside the allergy/immunology office to inpatient settings and the emergency department. Although a uniform definition of a low-risk patient is evolving, the above-mentioned studies provide guidance for the implementation of DC in place of PST. A distinct advantage of a DC over a PST is generalizability without the need for specialized PST training. This generalizability has been revealed in the inpatient, primary care, emergency department (ED), and intensive care unit settings. Ramsey et al¹⁶ used DCs for 48 inpatients with appropriate histories with telemedicine allergy support. One patient with a mild reaction to DC was treated with antihistamines alone. This approach obviated the need for an on-site allergist to perform PST.¹⁶ Another inpatient challenge PCN allergy delabeling protocol describes 81 patients who underwent inpatient amoxicillin challenge initiated by nonallergists. Two patients experienced a positive challenge result, both cutaneous reactions.¹⁷ An evaluation of ED DCs was part of an institution-wide guideline at the Massachusetts/Brigham health system. Patients with a history of nonurticarial rash, delayed hypersensitivity rash, or unknown reaction underwent DC in the ED. Of 310 total DCs, 37 were to penicillin. Three patients of 37 reacted to a penicillin-based antibiotic, with symptoms of throat swelling or hives, requiring only antihistamine treatment.¹⁸ Koo et al¹⁹ reported their experience with DCs for low-risk patients in the intensive care unit. They challenged 205 patients, with only 2 patients experiencing a delayed rash. Inclusion criteria included patients with a low-risk history, able to provide a history, and hemodynamic stability.¹⁹ If DCs move outside of the purview of allergy/immunology, any setting in which they are used should be equipped to handle anaphylaxis.

Cost and Time Savings of Penicillin Direct Challenges

The study by Mustafa et al⁷ compared the cost savings of DC with that of PST in a randomized outpatient trial. The per-patient direct cost savings for a DC was \$340.00. In a formal economic evaluation study by Sousa-Pinto et al²⁰ the net benefit for DC in the outpatient setting was \$3122 compared with \$2849 for PST. Blumenthal et al²¹ also conducted a cost analysis for PCN evaluations, where the cost estimate for DC was \$84 compared with a cost range of \$168 to \$537 depending on the PST model. Regarding time savings, the analysis by Mustafa et al⁷ revealed a time savings in minutes with DC as compared with PST (66.7 minutes vs 72.7 minutes). In the study of e-consultation in the inpatient setting, Mustafa et al²² found a significant time savings in turnaround time to complete the consult recommending a DC as compared with in-person PST (1 hour vs 7 hours).

Direct Challenges in Children

Studies Supporting Direct Challenges to Penicillin in Children

A robust literature base exists supporting DC to penicillin in children leading to the recommendation in the recent Drug Allergy Practice Parameter Update against PST in pediatric patients with a history of benign cutaneous reactions.¹ Mill et al²³ published a foundational study in which 777 of 818 pediatric patients with a history of a cutaneous-only reaction tolerated a DC, with 17 experiencing mild immediate reactions (hives, rash, angioedema, or recurrent vomiting) and 31 experiencing delayed reactions (hives, rash, angioedema, serum sickness-like reaction). All immediate and delayed reactions were mild. Interestingly, PST conducted 2 to 3 months after the observed immediate reactions did not correlate with the immediate reactions, with only 1 child having a positive PST result.²³ In a larger cohort from the same research group, 1811 of 1914 (94.6%) patients tolerated a DC, with 42 (2.2%) developing mild immediate reactions and 61 (3.2%) experiencing mild delayed reactions.²⁴ A positive DC result was associated with a historical reaction occurring within 5 minutes

of exposure. A history of a reaction lasting more than 7 days increased risk for a delayed reaction to the DC.²⁴

Advantages of Direct Challenges in Children

Generalizability of direct challenges to penicillin in pediatric population.

There are limited data for pediatric DC in the inpatient setting, but there was an ED study in which 82 low-risk patients were randomized to receive either a DC or no challenge. There were 38 patients who tolerated DC.²⁵ The number of patients who participated in the study vs those who were eligible reveals the difficulty of a DC in this environment: 133 patients were not interested, the treating physician declined 11, and 8 did not consent.²⁵ Another study looking at a system-wide pediatric inpatient PCN allergy delabeling program was able to disprove 80 of 701 penicillin allergy labels without any adverse events.²⁶

Tolerability, cost, and time. An obvious advantage to DC in the pediatric population is the lack of prick and intradermal testing. This enormously increases the acceptability of a penicillin allergy evaluation in this population. The cost-savings advantage of DC should hold in the pediatric population.²¹ There are less data on time savings of DC in the pediatric population as compared with PST, although the study of Mustafa et al⁷ did include pediatric patients.

Cephalosporin Direct Challenges

Direct Challenges to Cephalosporins With Dissimilar Side Chains

Cephalosporin allergy is less common than PCN allergy, and 1% to 2% of the population reports a cephalosporin allergy.²⁷ Hypersensitivity to cephalosporins is due to the R-group side chain, so cephalosporins with dissimilar side chains are likely to be tolerated in patients with true cephalosporin hypersensitivity.¹ The recently updated drug allergy practice parameters recommend proceeding with a DC to cephalosporins in patients with nonanaphylactic reaction histories.¹ The parameter also recommends that ST should be performed to a cephalosporin with a dissimilar side chain in patients with a history of anaphylaxis to a cephalosporin.¹ It has been difficult to establish the testing characteristics of cephalosporin ST because of varied concentrations used in testing and an unknown positive predictive value of positive cephalosporin skin test results because most studies have not challenged positive cephalosporin skin test results.²⁸ This section will highlight a few recent studies evaluating cephalosporin allergy and their supporting evidence for DCs to dissimilar side chains.

Romano et al²⁹ published a landmark study in 2015 looking at the tolerability of cephalosporins with dissimilar side chains in the case of an immunoglobulin (Ig)E-mediated reaction in 102 subjects. All these patients had positive ST result to the index cephalosporin. Although these subjects underwent additional ST in this study, the salient point is that all 102 subjects challenged to a cephalosporin with a dissimilar side chain to the index cephalosporin tolerated the DC.²⁹

Stone et al³⁰ reported a large retrospective review of 2 cohorts of patients reporting a PCN allergy, cephalosporin allergy, or both. There were 328 patients reporting a cephalosporin allergy, 245 with an immediate history and 83 with a delayed history. Patients in these cohorts underwent ST, with 22 of 328 patients having positive ST result to any of the following cephalosporins: cefazolin, cefuroxime, ceftriaxone, ceftazidime, and cefepime, with 18 patients with a positive ST result tolerating a challenge to cephalexin or cefuroxime. These patients were told to avoid cephalosporins sharing the same R-group side chain. There were 243 patients with negative ST result to cefazolin and ceftriaxone and the cephalosporin implicated in their reaction, and 139 proceeded to cephalosporin challenge, all of which

were tolerated.³⁰ This analysis reveals that skipping the ST and proceeding to DC to a cephalosporin with a dissimilar side chain is safe and effective.

Further work reviewed whether risk stratification criteria applied for DC to PCNs works for cephalosporins in adults. The study defined the following 3 risk groups based on their retrospective analysis of cephalosporin allergy evaluations: low risk, high risk (anaphylaxis within 5 years or symptoms suggestive of an IgE-mediated reaction occurring within 1 hour of administration), and highest risk (SCAR, serum sickness, liver or kidney injury).³¹ They defined a low-risk reaction history as isolated urticaria more than 5 years ago, self-limited cutaneous rash at any point without other organ involvement, gastrointestinal symptoms only, remote childhood reaction without details, family history of cephalosporin allergy, known tolerance of a cephalosporin since the index reaction, and symptoms not suggestive of an allergy. These criteria resulted in a negative predictive value of 100% for patients treated with an oral cephalosporin. The authors caution that a historical reaction to an intravenous cephalosporin may carry an increased risk.³¹ This particular work provides more structure and information for proceeding directly to a DC to a cephalosporin.

Penicillin and Cephalosporin Cross-Reactivity

The historical concern surrounding this question has mostly dissipated based on accruing data, allowing use of cephalosporins without a formal DC in the case of an unverified penicillin allergy.¹ Even in patients with a history of anaphylaxis to penicillin, a cephalosporin with a dissimilar side chain may be used without special precautions.¹ A “real world” analysis of the removal of the PCN/cephalosporin cross-reactivity alert at Kaiser Permanente revealed that cephalosporin use increased by 47% after removal of the alert. There was no increased risk of anaphylaxis or new allergy entries.³²

Trimethoprim/Sulfamethoxazole

Direct Challenges in the Adult Population

Sulfonamide antibiotic allergy is the second most reported drug allergy in the United States,³³ frequently presenting as a benign delayed maculopapular eruption.³⁴ Hypersensitivity is to the N1 heterocyclic ring or N4 aromatic amine of the sulfonamide moiety unique to sulfa antimicrobials, and therefore, cross-reactivity between sulfa nonantimicrobials such as diuretics or celecoxib in a patient with sulfa antimicrobial allergy is unlikely.³⁴

Immediate and delayed skin tests in addition to patch tests have been used to evaluate sulfa antimicrobial hypersensitivity but fail to reliably predict reactions.^{35,36} Management of sulfa antimicrobial hypersensitivity has relied heavily on temporary induction of tolerance protocols, based on studies focusing on human immunodeficiency virus patient populations.^{37,38} Several studies have found similar reaction rates between individuals who were desensitized and rechallenged,^{39–41} and one small study suggests that IgE-mediated hypersensitivity to TMP-SMX may wane.^{34,42}

There is growing evidence that a single-dose or 2-dose challenge to TMP-SMX is safe and effective.^{43–46} A single-dose challenge with TMP-SMX 80 to 400 mg followed by 1-hour observation and telephone follow-up was conducted in adults with a history of benign cutaneous or unknown reactions more than 5 years ago. Of these patients, 96% (171 of 179) successfully passed a single-dose challenge.⁴³ This study also looked at a 2-step challenge with 8 to 40 mg with 1-hour observation followed by 80 to 400 mg with 2-hour observation and telephone follow-up. Historical reactions included benign cutaneous reactions within the past 5 years, anaphylaxis, more than or equal to 2 IgE-mediated reactions in the past, or patient

anxiety with a single-dose challenge. Of these patients, 80% (20 of 25) tolerated the 2-dose challenge. For the challenge failures, 8 (61%) had nonsevere cutaneous reactions, 3 (23%) reported fever, 1 (7.6%) had immediate-onset throat itching and chest tightness, and 1 reported immediate left arm pain and malaise. Patients with nonimmediate and remote index reactions were more likely to tolerate single- or 2-dose challenges.⁴³

Another study revealed that 95.6% (43 of 45) of the patients with a history of a nonsevere cutaneous reaction to TMP-SMX or its components tolerated either 1- or 2-step DC.⁴⁴ Two patients had positive challenge results with minor cutaneous reactions. One patient with index reaction of urticaria developed urticarial rash, which resolved with antihistamines, and the other patient who reported a history of delayed rash developed a mild maculopapular rash. Motoa et al⁴⁷ found preserved safety with a 1- or 2-step challenge (26 patients each) as compared with a 6-day challenge (54 patients) to TMP-SMX, with cost savings in the shortened challenges.

Direct Challenges in the Pediatric Population

There are limited data on the safety and efficacy of DC for TMP-SMX allergy in the pediatric population. One small study reported successful DC with TMP-SMX in 10 pediatric patients though dose and manner of drug challenge were not reported.⁴⁶ Most patients (n = 9) had non-IgE-mediated/indeterminate index reactions. Further research is needed in pediatric populations.

On the basis of the above-mentioned studies, single-dose oral challenge to TMP-SMX should be considered for adults with nonsevere cutaneous reactions more than 5 years ago. Two-dose DC can be considered for patients with history of anaphylaxis more than 5 years ago. For patients with more recent anaphylaxis reactions less than 5 years ago, who require TMP-SMX, either drug desensitization or DC can be considered. TMP-SMX should be avoided for individuals who have had severe cutaneous adverse reactions.

Fluoroquinolones

Hypersensitivity to fluoroquinolones has been increasing⁴⁸ and usually presents as immediate reactions from urticaria to anaphylaxis.^{49,50} Delayed reactions including maculopapular rash and severe cutaneous adverse reactions also occur.^{51,52} ST has not been found to be reliable,^{49,50} especially because fluoroquinolones at higher doses have the capacity to induce direct mast cell degranulation through binding to the MRGPRX2 receptor.^{51,53,54} Cross-reactivity among fluoroquinolones is unclear,^{48,55} but a DC to a fluoroquinolone in appropriate cases may allow for use of an alternative fluoroquinolone. Patients with fluoroquinolone hypersensitivity may have a tendency for concurrent beta-lactam hypersensitivity,⁵⁶ which limits antimicrobial options. On the basis of these factors, direct DC remains the gold standard for evaluation of nonsevere fluoroquinolone hypersensitivity.^{1,48} Seitz et al⁵¹ found that 88% (45 of 51) of patients reporting immediate hypersensitivity to fluoroquinolones, 42 patients with a negative ST result and 3 patients with a positive ST result, successfully tolerated oral challenge. In this same cohort, 93% (26 of 28) of patients reporting delayed hypersensitivity to fluoroquinolones tolerated DC. Although 4- or 5-step DCs starting with one-tenth to full therapeutic dose with 30- or 60-min intervals have been described in the literature,^{51,57} these require more time. A single-dose or 2-step challenge to index fluoroquinolone in patients with remote history of nonsevere cutaneous-only reaction more than 5 years ago should be considered.¹ For more recent or higher risk index reactions, single- or 2-dose DC to alternative fluoroquinolone can be considered as overall cross-reactivity seems to be low. Induction of tolerance to index fluoroquinolones can be used for patients with positive drug challenge results or those with recent, high-risk

reactions such as anaphylaxis in need of index fluoroquinolone without acceptable alternative.⁵⁸

Fluoroquinolone Pediatric Considerations

Fluoroquinolones are generally avoided in pediatric populations because of their association with cartilage abnormalities, tendonitis/tendon rupture, resulting in a Food and Drug Administration–issued blackbox warning for this drug class. However, they are occasionally indicated for patients without acceptable alternatives. There is a dearth of information regarding fluoroquinolone hypersensitivity in pediatric populations. In rare cases where an alternative antibiotic does not exist, it may be reasonable to extrapolate from recommendations for adults and consider 2-dose challenges with an alternative or index fluoroquinolone in pediatric patients with remote, nonsevere cutaneous-only reactions.

Tetracyclines

Tetracycline hypersensitivity is more rare compared with other classes of antibiotics. Tetracycline, minocycline, and doxycycline are the most used drugs in this class.^{59,60} Although prescribed less frequently, minocycline is more often implicated in adverse drug and hypersensitivity reactions.⁶¹ Delayed hypersensitivity reactions ranging from benign rash to severe cutaneous adverse reactions are more frequently reported with tetracyclines than immediate hypersensitivity reactions, particularly with minocycline. Doxycycline overall has better safety profile within this class; however, case reports of urticaria, anaphylaxis, fixed drug eruptions, and Stevens-Johnson syndrome have been published.^{61–65} Cross-reactivity between tetracyclines has not been established, and this needs further investigation. ST for immediate hypersensitivity has not been validated.⁴⁸ Maciag et al⁶⁶ reported a case series of 10 patients, including 7 pediatric and 3 adult patients with hypersensitivity to 1 or more tetracyclines. Index reactions included benign cutaneous reactions for 6 patients, immediate-type reactions in 3 patients, and 1 patient with reported history of drug reaction with eosinophilia and systemic syndrome unlikely related to tigecycline. Five patients with mild index reactions tolerated DC after a negative ST result. Five patients underwent induction of tolerance because of a positive ST result or lack of ST. This seems to be one of the few recent studies addressing tetracycline hypersensitivity, and although the negative predictive value to ST in this small cohort was good, DC without preceding ST may have resulted in similar outcomes.⁶⁶

In line with the approach for other drug hypersensitivity reactions where validated testing is lacking, it is reasonable to consider 2-dose challenges to tetracyclines in individuals with remote history of benign cutaneous-only reactions greater than 5 years ago. Future studies should aim to evaluate this area. For more recent higher risk index reactions such as anaphylaxis within the last 5 years, induction of tolerance may be a safer option. Tetracyclines should strictly be avoided for severe cutaneous adverse reactions.

Macrolides

True hypersensitivity to macrolides is uncommon. One US health care system reported prevalence of 3.8 per 10,000 for macrolide-induced anaphylaxis, with erythromycin as the most common culprit.^{58,60} Self-reported adverse reactions to macrolides were 3.5% and occurred predominantly in outpatient medicine clinics. The prevalence of self-reported macrolide allergy in children ranges from 0.3 to 0.8%.^{59,67} True prevalence may be lower as many studies do not confirm hypersensitivity or differentiate hypersensitivity from adverse effects. Published hypersensitivity reactions include both immediate and delayed reactions, with urticaria and angioedema being the most frequently described symptoms. Maculopapular

exanthema, fixed drug eruptions, and bullous skin reactions have been described.^{58,68} Although macrolides are often avoided if reaction is reported, multiple studies have revealed that clinical history alone is insufficient to confirm allergy. ST for macrolides remains controversial and is not validated, with unknown predictive values.⁵⁸ Given this, DC remains the gold standard to establish or exclude hypersensitivity.^{1,69}

In one series of single, blinded DC among 107 patients, 8 of 107 (7.5%) had true hypersensitivity reactions. In this study among adults with reported reactions ranging from cutaneous reaction to anaphylaxis, oral DCs were performed with increasing doses of the index macrolide antibiotic every 30 minutes, starting with 1 mg, for a total of 6 doses, until cumulatively reaching the daily therapeutic dose. Seven patients had a reaction to spiramycin and one to roxithromycin. Most of those who reacted to the DCs have a history of an index reaction less than 24 hours after exposure.⁷⁰ In another investigation among patients ranging from ages 5 to 86 years, macrolide hypersensitivity was excluded in 109 of 125 patients (87.2%) with DC.⁷¹ In this study, patients underwent DC with standardized macrolide doses of erythromycin, clarithromycin, roxithromycin, and azithromycin. The authors note that their skin and intradermal macrolide test results were all negative. All 47 patients undergoing oral provocation tests had negative results. Six patients did not undergo the DC because of refusal or contraindication. In a subset analysis of patients presenting after eradication treatment for *Helicobacter pylori*, only 1 patient was diagnosed with having clarithromycin hypersensitivity after DC. The authors noted the importance of the temporal relationship of macrolide exposure and symptom manifestation. ST and in vitro testing alone are not sufficient to identify macrolide hypersensitivity, and after risk-benefit discussion, DCs should be offered in appropriate patients.^{60,72,73}

Metronidazole

Hypersensitivity reactions to metronidazole are uncommon, yet both immediate and delayed reactions have been reported, ranging from urticaria, angioedema, allergic contact dermatitis, fixed drug eruption, drug reaction with eosinophilia and systemic syndrome, and acute generalized exanthematous pustulosis.⁷⁴ A small number of case studies describe skin testing (SPT) to metronidazole, yet sensitivity to SPT is thought to be low, and the validity is unclear.⁷⁵ In one study of 4 patients with cutaneous exanthema caused by metronidazole, skin prick testing and patch testing were performed. ST result was positive in one patient and patch testing result was negative in all.⁷⁶ DC result was positive in 3 cases, resulting in delayed generalized exanthema and itching in 1 case and immediate itching and rash in the other 2 cases.⁷⁶ Given the low sensitivity of the SPT and patch testing, DC was an essential tool in this study to determine hypersensitivity.⁷⁶ One important note is that DCs were not performed in patients thought to have initial anaphylaxis to metronidazole. In patients with history of systemic reaction to metronidazole, oral desensitization protocols are available.⁷⁵

Carbapenems and Aztreonam

The reported incidence of carbapenem allergy is 0.3% to 3.7%.⁷⁷ In a clinical trial of more than 9000 patients treated with imipenem/cilastatin, there was no reported anaphylaxis. In a safety profile of meropenem in more than 6000 patients, rash and pruritus occurred in 1.4% and 0.3% of cases, respectively, with no reports of anaphylaxis. Similarly, in clinical trials with ertapenem use, only ertapenem-related pruritus and rash were reported in 0.5% to 1.2% and 1.1% to 1.6%, respectively, with no cases of anaphylaxis reported.⁷⁷ The most robust literature for carbapenem DCs is in patients with a PCN allergy in which carbapenem has been found to be safe,⁷⁸ leading to the

practice parameter recommendation that in patients with penicillin or cephalosporin allergy, a carbapenem may be administered with no additional testing.¹ Aztreonam allergy is rarely reported. In 1 case series of patients reported with having either aztreonam or ceftazidime allergy, challenge of aztreonam was tolerated in most patients.⁷⁹

Conclusion

DCs should be performed in patients with an antibiotic allergy with low-risk reaction histories, with most current data supporting their use in an allergy/immunology office. In children, DC may facilitate delabeling of reported antibiotic allergies more routinely. Some advantages of DC include future generalizability outside allergy/immunology clinics, potential cost and time savings, and transition to appropriate antibiotics in a timely manner for patients. The evidence summarized in this review supports the safe, effective, and key role DCs can play in antibiotic allergy delabeling.

Disclosures

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