

Recommendations for the Management of Beta-Lactam Intolerance

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Abstract Beta-lactam intolerance, most of which is not IgE or even immunologically mediated even though it is commonly called an “allergy,” can be safely managed using the following seven steps:

1. Avoid testing, re-challenging, or desensitizing individuals with histories of beta-lactam associated toxic epidermal necrolysis, Stevens–Johnson syndrome, drug reaction with eosinophilia and systemic symptoms syndrome, severe hepatitis, interstitial nephritis, or hemolytic anemia.
2. Avoid unnecessary antibiotic use, especially in the setting of viral infections.
3. Expect new intolerances to be reported after 0.5 to 4 % of all antibiotic utilizations, dependent on gender and the specific antibiotic used.
4. Expect a higher incidence of new intolerances in individuals with three or more medication intolerances already noted in their medical records.
5. For individuals with an appropriate penicillin class antibiotic intolerance based on a history of anaphylaxis, urticaria, macular papular rashes, unknown symptoms, or symptoms not excluded in step one, proceed with penicillin skin testing. Skin test with penicilloyl-polylysine and native penicillin. If skin test is negative, proceed with an oral amoxicillin challenge. If skin test and oral challenge are negative, penicillin class antibiotics may be used. If skin test or oral challenge is

positive, avoid penicillin class antibiotics. If skin test or oral challenge is positive, non-penicillin-beta-lactams may be used, unless there is a history of intolerance to a specific non-penicillin-beta-lactam, then avoid that specific non-penicillin-beta-lactam. If there is life-threatening infection that can only be treated with a penicillin class antibiotic, proceed with oral penicillin desensitization prior to any oral or parenteral penicillin use.

6. For individuals with an appropriate non-penicillin-beta-lactam intolerance, avoid re-exposure to the beta-lactam implicated. An alternative beta-lactam may be used, ideally with different side chains. Penicillin allergy testing is not useful in the management of non-penicillin-beta-lactam intolerance. Non-penicillin-beta-lactam skin testing is not clinically useful and should not be done outside of a research setting. If the non-penicillin-beta-lactam implicated is needed to treat a life-threatening infection, proceed with desensitization.
7. Be ready to treat anaphylaxis with all parenteral beta-lactam use.

Keywords Allergy · Adverse drug reaction · Beta-lactam · Carbapenem · Cephalosporin · Cross-reaction · Intolerance · Monobactam · Oral challenge · Penicillin · Skin test

Beta-Lactam Chemistry, Immunogenicity, and Potential for Causing Adverse Reactions

Beta-lactams are the most commonly used antibiotic family in the USA. Based on data collected by the Center for Disease Dynamics, Economics, and Policy (CDDEP.org), there were about 362 courses of beta-lactams dispensed per 1,000 individuals in 2010, with a large state-by-state variation. Nationwide, there was an average of about 247 courses of penicillins, about 114 courses of cephalosporins,

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and only about one course of monobactams and carbapenems combined dispensed per 1,000 individuals in 2010. Macrolides are the second most commonly used antibiotic family in the USA with about 211 courses dispensed per 1,000 people in 2010. Penicillins are still widely and inappropriately used for respiratory tract infection symptoms, most commonly caused by viruses [1]. In this review, the word “allergy” will only be used when an IgE-mediated adverse reaction has been confirmed. The words “intolerance” or “allergy” will be used synonymously to describe what is reported in the allergy field of the electronic medical record after a clinically significant adverse drug reaction is noted.

Beta-lactams account for a large fraction of the antibiotic intolerances, often called allergies, noted in the medical records of patients in North America, Europe, and around the world. Beta-lactam antibiotics, originally the penicillins, followed by the introduction of cephalosporins, monobactams, and carbapenems, are widely used, not only therapeutically in humans, but also in industrial agriculture as growth promoters. They are remarkably nontoxic to mammalian cells [2]. Beta-lactams bind to a catalytic serine residue on bacterial penicillin-binding proteins and prevent cell wall cross-linking. The weakened bacterial cell wall then is unable to keep the osmotic pressure inside the bacteria from rupturing the cell wall and killing the bacteria. In addition to serine residues, beta-lactams can bind to lysine residues on human serum proteins and haptenate them. Haptenation can produce foreign immunogens that on occasion induce antigen-specific IgE, IgG, and/or T cell production. Potentially, this can result in clinically significant immunologically mediated hypersensitivity reactions with re-exposures. Death from probable IgE-mediated anaphylaxis has been reported with parenteral beta-lactam use [3]. Death from anaphylaxis associated with oral beta-lactam use is extremely rare [4]. Early reports continue to have a great effect on the way beta-lactam allergies are currently perceived by many physicians [2]. We now know that only a small fraction of the beta-lactam associated adverse reactions reported are IgE-mediated or true allergy. The vast majority of individuals with a history of beta-lactam intolerance can tolerate beta-lactams with future adverse reaction rates no greater than random individuals in the population when corrected for gender and other underlying significant clinical factors such as other drug allergy history.

Based on immunochemistry, skin testing, and challenges, the immunologically important structures in penicillins appear to be related to the beta-lactam core [5–7]. For cephalosporins, monobactams, and carbapenems, the side chains may predominate as a target for anti-beta-lactam immune responses [8–10]. The side chain cross-reactivity hypothesis is primarily based on immunochemistry and has not been validated in large clinical trials [11–13]. There have been no

well-characterized groups of patients documented to have clinically significant IgE-mediated reactions to two beta-lactams that share side chains such as aztreonam and ceftazidime, amoxicillin and cephalexin, or penicillin and cephalothin despite multiple publications warning of such a theoretical possibility [14–17].

All drugs have side effects. A number of the potentially serious non-immunological adverse reactions associated with beta-lactam use have been well reviewed recently by Lagace-Wiens and Rubenstein [18]. Some broad spectrum beta-lactams, particularly certain cephalosporins, are associated with significantly increased rates of clostridium difficile infections. This may be exacerbated by the preferential biliary secretion that occurs with some cephalosporins, including cefixime, cefpiramide, cefoperazone, and cephtriaxone, which can result in higher GI concentrations. Cephalosporins with 3-methyl thiotetrazole side chains, including cefotetan, cefamandole, cefoperazone, and moxalactam, can reduce prothrombin synthesis and cause bleeding, along with causing a disulfiram-like reaction.

Most adverse reactions, commonly rashes, associated with beta-lactam use are not immunologically mediated, but may have underlying virolocal, microbiological, biochemical, or idiopathic causes [19]. Only reported and recorded reactions can significantly influence future prescribing. What is recorded in the drug intolerance, or allergy, field of the electronic health record is becoming the gold standard for clinically significant adverse drug reactions.

Many factors can influence the rate at which beta-lactam intolerances or allergies are reported. There is a baseline incidence of new intolerance reports that occur in populations with all antibiotic use [20] (see Table 1). This incidence varies

Table 1 New intolerance reports per therapeutic antibiotic class exposure based on the antibiotics used in 411,543 patients cared for by the Kaiser Permanente health care program in San Diego County during 2007

	Males (95 % CI)	Females (95 % CI)	P values
Sulfonamides	2.23 % (1.91, 2.59)	3.42 % (3.13, 3.74)	<0.0001
Penicillins	1.11 % (1.01, 1.24)	1.45 % (1.34, 1.57)	<0.0001
Tetracyclines	0.47 % (0.36, 0.62)	1.27 % (1.11, 1.46)	<0.0001
Cephalosporins	0.60 % (0.49, 0.72)	1.08 % (0.96, 1.21)	<0.0001
Macrolides	0.52 % (0.38, 0.72)	1.34 % (1.13, 1.58)	<0.0001
Quinolones	0.52 % (0.42, 0.65)	1.01 % (0.89, 1.14)	<0.0001

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significantly by gender, medical history, and the specific antibiotic used. Females report more drug allergies than males. Women will report new drug allergies at about twice the rate as men after each therapeutic antibiotic use, about 2 % per course for penicillins and about 1 % per course for cephalosporins. The incidence of reported drug intolerance increases with the number of drug allergies already reported by an individual. Individuals with multiple drug intolerance syndrome, a history of three or more unrelated medication class intolerances, or allergies, noted in their medical records, will report new adverse reactions after all antibiotic use at higher rates than individuals with no reported drug intolerances [21]. The prevalence of reported drug intolerance increases with increasing age. The rate of positive penicillin skin test results decreases with increasing time since the index reaction. Immunological hyper-reactivity tends to decrease with age. The incidence of reported adverse reactions can be higher when antibiotics are used inappropriately in the setting of certain viral infections [22]. The advent of completely electronic medical records covering large populations has enabled new insights into the epidemiology and natural history of adverse drug reactions associated with beta-lactam antibiotics. It is now possible to look at all antibiotic use and all new adverse reactions reported in millions of individuals in almost real time.

In the largest study published to date covering over 2 million people, about 9.5 % of females and 6 % of males had penicillin intolerance noted in their electronic medical record [20]. In the same study, only about 1.5 % of females and 0.7 % of males had cephalosporin intolerance noted. Sulfonamide antibiotics had the next highest prevalence of intolerance noted, 6.2 % of females and 2 % of males, after penicillins. All other antibiotic classes had intolerance prevalence rates of less than 2 % for females and less than 1 % for males.

The Clinical Evaluation of Beta-Lactam Intolerance

There have been a number of recent reviews on the diagnosis and management of beta-lactam allergy [23–25]. Much of the primary literature in this field is produced by specialized centers dedicated to the study of drug allergy. These groups often fail to critically evaluate the natural history of drug intolerance in large unselected populations and just concentrate on studying the patients referred to them. They are often referred outliers or extremely sensitive individuals. In vitro tests are often used in the evaluation of these individuals without adequate clinical correlation to re-challenge [26–28]. The same individuals may get repetitively studied [29–31]. Taken together, these factors can result in recommendations, though perhaps valid for the exceptional groups studied, which are not generalizable to entire populations.

When critically reviewing the drug intolerance literature, it is important to know how the individuals studied were selected and how they compare to random individuals in the same population with a history of the same drug intolerance. Clinicians rightfully may be paralyzed by increasingly complex published practice guidelines on drug allergy that do not seem to correlate with what they see clinically [32]. They may just elect to continue unnecessary avoidance of narrow spectrum penicillin G or amoxicillin when a simple and safe skin test or oral challenge may be indicated. This inaction potentially drives excessive use of antibiotics with potentially worse side effects, such as clindamycin, vancomycin, quinolones, and broad spectrum third-generation cephalosporins. The intermittent lack of commercially available penicilloyl-poly-lysine over the past decade made it difficult to safely test for penicillin allergy. The net result is that very few individuals with a beta-lactam antibiotic intolerance have their diagnosis verified.

There have been falling rates of positive skin test results to penicillin major and minor determinants reported over the past 50 years [33, 34]. In most recent large studies over the past decade, involving average patients with a history of penicillin intolerance, less than 5 % are penicillin skin test positive, specifically when excluding testing with high-dose amoxicillin or using less than 5 mm of wheal as the criteria for a positive skin test result [35–37]. In the most recent report from our group on 500 sequential individuals undergoing a penicillin allergy evaluation between 8 June 2010 and 29 March 2012, only 1.6 % was penicillin skin test or oral amoxicillin challenge positive [38].

Even properly performed penicillin skin testing may be too sensitive, with more false than true positive results. Only about one third of the individuals with positive penicillin skin test results will have clinically significant positive acute oral challenge reactions [6, 7, 39]. Oral challenges have not been widely adopted as a primary test modality, mainly out of fear of causing an anaphylactic reaction, though we know that acute anaphylaxis with oral penicillin use is extremely rare. Though fairly rare, true IgE-mediated allergy to beta-lactams is still significantly more common than clinically significant IgG or T cell mediated anti-beta-lactam reactions.

The sloppy use of the word allergy to define the section of the medical record where adverse drug-associated reactions and drug intolerances are recorded may distort the true risks associated with re-exposures. Because the word allergy is used, many patients and physicians assume the only significant potential risk is anaphylaxis. This may result in an overestimate or underestimate of the true risk of re-exposure.

A clinically significant IgE-mediated anti-beta-lactam allergy will result in at least hives within 1 h of a therapeutic exposure and possibly anaphylaxis. An individual who has a clinically significant drug-associated IgG and complement-mediated hypersensitivity will develop arthralgias, myalgias,

and probably a fever within hours to days of exposure. They could also potentially experience hemolytic anemia or interstitial nephritis. An individual with a clinically significant T cell-mediated drug-associated hypersensitivity will typically have a diffuse rash, non-urticarial, within 2 to 5 days of exposure, and the rash will potentially last weeks. T cell-mediated rashes would typically improve with systemic steroid use.

More severe drug-associated systemic and cutaneous reactions such as drug reaction with eosinophilia and systemic symptoms, toxic epidermal necrolysis, or Stevens–Johnson syndrome probably have underlying immunologic cofactors, but their exact pathologic mechanisms are only partially determined, and their reproducibility upon re-exposure, though presumed to be high, is unknown.

Because toxic epidermal necrolysis, Stevens–Johnson syndrome, severe hepatitis, drug reaction with eosinophilia and systemic symptoms syndrome, interstitial nephritis, and hemolytic anemia are not mediated through IgE, immediate type hypersensitivity testing, challenging, or attempting desensitization in individuals with a history of these conditions associated with use of any drug is not recommended [32].

A recent report by Caubet and co-workers is a breakthrough in the evaluation of children with beta-lactam, mainly amoxicillin-associated, associated adverse drug reactions [7]. It is the first prospective look at a well-characterized population, captured early during the index reaction, and followed with extensive drug allergy and viral testing over a several month period. All patients received oral challenges. Only a minority of penicillin skin test-positive children had oral challenge reactions. Most challenge reactions were delayed onset, which was unexpected for an IgE-mediated event. The oral challenge reactions were not more severe than the index reactions. Many of the challenge reactions were associated with evidence for recent Epstein Barr virus (EBV), or other viral, infection. Having an acute EBV infection 2 months ago may be enough to significantly increase the risk of having a rash associated with amoxicillin use today. This population was selected to exclude individuals with a history of anaphylaxis, but such patients only account for a minority of reactions.

The Safe Use of Cephalosporins in Individuals with a History of Penicillin Intolerance

Cephalosporins are generally grouped into generations. First-generation cephalosporins include cephalexin and cephalothin, and cephaloridine. Second-generation cephalosporins include cefaclor, cefuroxime, cefotetan, cefamandole, and cefoxitin. Third and higher generation cephalosporins include cefdinir, cefixime, cefpiramide, cefoperazone, cefotaxime, ceftriaxone, ceftazidime, moxalactam, and cefepime. A

meta-analysis by Pichichero and Casey in 2007 showed negligible cross-reactivity between penicillin and second or greater generation cephalosporins [40]. The entire meta-analysis included less than 50,000 individuals, with and without a history of penicillin allergy, who received cephalosporins. They were unable to control for gender and other drug intolerance history because this information was not available in the primary references. They showed a possible increased risk of an adverse reaction with the use of cephalothin, cephaloridine, and cephalexin in penicillin intolerance history positive individuals. There were only 1,831 individuals in this meta-analysis, pooled from four trials, who underwent penicillin skin testing to confirm penicillin allergy, with 451 penicillin skin test positive. There was no statistically significant increased risk of new reactions associated with therapeutic cephalosporin use in the penicillin skin test-positive group for any generation of cephalosporins.

The Pichichero and Casey meta-analysis neglected to include the 83 penicillin skin test-positive individuals and 166 age and gender-matched skin test-negative individuals exposed to 1,655 total oral antibiotic courses over about 3 years of follow-up, reported by Macy and Burchette in 2002 [39]. In this study, there were 42 penicillin skin test-positive individuals exposed to 129 courses of oral cephalosporins and 80 control subjects exposed to 221 courses of oral cephalosporins. There were seven (5.4 %) reactions in the penicillin skin test-positive group. There were seven (3.2 %) reactions in the penicillin skin test-negative group, which was not significantly different. In this study, there were also 74 penicillin skin test-positive individuals exposed to 375 courses of non-beta-lactam antibiotics and 116 penicillin skin test-negative individuals exposed to 529 courses of non-beta-lactam antibiotics. There were 16 (4.2 %) reactions in the penicillin skin test-positive group. There were 25 (4.7 %) reactions in the penicillin skin test-negative group, which again was not significantly different. This paper was based primarily on paper record chart review. The threshold for a reaction in this paper was any comment in the medical record of any possible antibiotic-associated side effect, not just a new drug allergy report. The exact reactions were not well described in the medical records.

The largest single study looking at all new antibiotic intolerance reported after penicillin skin testing was published by Macy and Ho in 2011 [41]. The cohort consisted of all patients who had penicillin skin testing at Kaiser Permanente in San Diego County between 1 January 2000 and 31 December 2004. Subjects were followed through 31 December 2009. There were 1,684 study subjects of whom 1,191 (70.7 %) were female. There were 118 (7.0 %) subjects, 85 (72.4 %) females, positive to at least one penicillin skin test reagent and three (0.2 %) were positive only to amoxicillin. The mean follow-up period was 4.5 ± 2.9 years.

Subjects were exposed to a mean of 8.2 ± 10.5 therapeutic antibiotic courses during follow-up. The highest new antibiotic intolerance incidence rates in skin test-negative subjects were noted for penicillins, 2.9 %, and sulfonamides, 2.7 %, $p=0.9097$. Females had higher overall incidences of new antibiotic intolerance, independent of skin test result. Penicillin skin test-negative females treated with penicillin had a nonsignificantly higher new penicillin intolerance incidence, 3.3 % per course versus 1.9 % in males, $p=0.0644$. New intolerance to cephalosporins occurred no more frequently than with non-beta-lactam-antibiotics, independent of skin test result. There were 37 penicillin skin test-positive females exposed to 132 courses of cephalosporins and no new intolerance was reported. There were 17 penicillin skin test-positive males exposed to 37 courses of cephalosporins and one (2.7 %) new intolerance was reported. There were 578 penicillin skin test-negative females exposed to 1,741 courses of cephalosporins and 25 (1.4 %) new intolerances were reported. There were 241 penicillin skin test-negative males exposed to 744 courses of cephalosporins and four (0.5 %) new intolerances were reported. The overall new antibiotic intolerance incidence rate after cephalosporin use was lower than after sulfonamide antibiotic use and not significantly different from the rates seen with tetracyclines, quinolones, macrolides, clindamycin, metronidazole, nitrofurantoin, and other antibiotics. This paper was based on a combination of paper and electronic medical record review. The threshold for a reaction in this paper was any new drug allergy report.

In order to document clinically significant immunologically mediated cross-reactivity between two antibiotics or antibiotic families, the immunologically mediated mechanism responsible for the index reaction first must be confirmed in a group of individuals. Then the adverse reaction rate associated with the use of the second antibiotic in this index group must be significantly higher than the adverse reaction rate for the second antibiotic noted in gender and other drug intolerance history matched control subjects in the population studied. These two important factors have often been ignored because, until the advent of electronic medical records, it was very hard to collect these kinds of data. Finally, the immunologically mediated mechanism for the second reaction needs to be confirmed. This has not been done in large populations for penicillins and any generation of cephalosporins to date. It is also becoming more difficult to even find large groups of penicillin skin test- or oral challenge-positive individuals to determine if there is any clinically significant immunologically mediated cross-reactivity with non-penicillin beta-lactams [38]. It is becoming easier now to look at all antibiotic use and clinical outcomes in individuals with drug intolerances with the advent in 2007 of a completely electronic medical record covering the entire Kaiser Permanente health care program.

Previously Unpublished Data on the Use and Tolerance of Oral Cephalosporins and Sulfonamide Antibiotics in Individuals with and Without a Penicillin Intolerance History

The new intolerance reports associated with oral cephalexin, cefdinir, cefuroxime, and co-trimoxazole use in the electronic medical records of San Diego Kaiser Permanente health plan members, with and without a history of penicillin intolerance, were collected for the time period 8 June 2010 through 29 March 2012 as a part of a study on penicillin skin testing [38]. The data are displayed in Table 2. There were 51,978 health plan members with a history of penicillin allergy and 478,656 health plan members without a history of penicillin intolerance who had at least one health care visit during the study interval. The prevalence of penicillin intolerance rate in females was 11.7 % versus 7.6 % in males. The antibiotics prescribed to these individuals during the 90 days after their clinical visit closest to the middle of the study period were determined along with any new intolerance reports made within 30 days of starting the antibiotic. Cefdinir, cefuroxime, and cephalexin accounted for almost 99 % of all oral cephalosporins used. There were 1,478 individuals exposed to 1,565 courses of cefdinir, 2,647 individuals exposed to 2,747 courses of cefuroxime, 17,476 individuals exposed to 18,721 courses of cephalexin, and 10,533 individuals exposed to 11,364 courses of co-trimoxazole. There was significantly more new cephalosporin intolerance in females: 96/14,029 courses (0.7 %) versus males: 44/9,271 courses (0.5 %), $p=0.0426$. Individuals with a history of penicillin intolerance were significantly more likely to report a new cephalosporin intolerance, 32/2,481 courses (1.3 %) versus 108/20,819 courses (0.5 %), $p<0.0001$. However, individuals with a history of penicillin intolerance were also more likely to report a new intolerance after co-trimoxazole use than after cephalexin use, which had the highest new intolerance rate for the oral cephalosporins evaluated, 65/1,949 courses (3.3 %) versus 27/1,646 courses (1.6 %), $p=0.013$. There were no episodes of antibiotic associated anaphylaxis (ICD-9 code 995.0) reported within 3 days of starting any cephalosporin or co-trimoxazole. Such episodes would result in a medical record entry, emergency room admission, or paramedic treatment, which would have been captured by the electronic health record system. There were no deaths within 3 days of starting any cephalosporin or co-trimoxazole in individuals with a history of penicillin intolerance. There were eight deaths within 3 days of starting a cephalosporin in individuals without a history of penicillin intolerance, four after cephalexin, three after cefuroxime, and one after cefpodoxime. There were two deaths within 3 days of starting co-trimoxazole in individuals without a history of penicillin intolerance. It is also important to keep in mind that only

Table 2 Use and tolerance of oral cephalexin, cefdinir, cefuroxime, and co-trimoxazole in individuals cared for by the Kaiser Permanente health care program in San Diego County between 8 June 2010 through 29 March 2012, with and without a penicillin intolerance history

	Female health plan members with a penicillin intolerance (N=33,457)	Female health plan members without penicillin intolerance (N=252,993)	Male health plan members with a penicillin intolerance (N=18,521)	Male health plan members without penicillin intolerance (N=225,663)
Received at least one cephalosporin	1,456	11,511	783	7,918
% Exposed	4.4 %	4.5 %	4.2 %	3.5 %
Total courses of cephalosporins	1,626	12,403	855	8,416
Courses of cephalexin	1,157	10,476	489	6,599
Courses of cefdinir	212	520	243	588
Courses of cefuroxime	224	1,276	109	1,138
New cephalosporin intolerance reported within 30 days	23	73	9	35
New intolerance rate per cephalexin course	1.9 %	0.6 %	1.0 %	0.4 %
New intolerance rate per cefdinir course	0.5 %	0.6 %	1.6 %	1.0 %
New intolerance rate per cefuroxime course	0.0 %	0.5 %	0.0 %	0.2 %
Received any co-trimoxazole	1,295	5,333	512	3,393
% Exposed	3.9 %	2.1 %	2.8 %	1.5 %
Total courses of co-trimoxazole	1,385	5,710	564	3,705
New sulfonamide intolerance reported within 30 days	55	130	10	50
New intolerance rate per co-trimoxazole course	4.0 %	2.3 %	1.8 %	1.3 %

about 2 % of the penicillin intolerance history positive individuals evaluated for penicillin allergy in the overall population were penicillin skin test or oral amoxicillin challenge positive. Factors other than immunological cross-reactivity between penicillins and cephalosporins are necessary to explain these results.

The Evaluation and Management of Penicillin Intolerance

A positive, even properly performed, immediate type hypersensitivity skin test does not define clinically significant IgE-mediated allergy. It is necessary to have reproducible IgE-mediated symptoms with re-exposure. This holds for IgE-mediated allergy to foods, venoms, pollens, and antibiotics. By using penicillin allergy tests, in vivo or in vitro, with high rates of false positive results, allergists unfortunately can promote needless avoidance and more morbidity.

An acute onset, within 1 h of challenge, urticarial or anaphylactic reaction, is currently considered the gold standard test to verify clinically significant IgE-mediated penicillin

allergy. Observation for 1 h after an oral rechallenge will be adequate to rule in or rule out a clinically significant IgE-mediated reaction. Up to 5 days of follow-up may be needed to rule out a clinically significant IgG or T cell-mediated reaction.

In vitro tests, specifically the commercially available FEIAs for anti-penicillin and anti-amoxicillin IgE, are not useful in diagnosing clinically significant penicillin allergy because they do not correlate to challenge results [42]. Thus, their current clinical use is not recommended.

There has been a gradual and unfortunate trend in some of the world's literature on penicillin allergy testing toward calling smaller and smaller skin test results "positive" and toward using higher and higher concentrations of skin test reagents, particularly amoxicillin [43–45]. This inflates the number of penicillin skin test-"positive" individuals and skews the penicillin skin test-positive population highly toward women [46]. If the criterion for a positive immediate type hypersensitivity penicillin skin test is set too low, for example 3 mm of wheal instead of 5 mm of wheal, then many more females will have false positive skin test results [47]. When this study, performed at the Mayo Clinic, was

re-evaluated using 5 mm as the positive cutoff, the female skin test-positive result predominance disappeared [42, 48]. In the seminal paper from 1992 looking at skin testing with both penicillin major and minor determinants, but without amoxicillin, in hospitalized adults, a 1+ reaction was a 4–6-mm wheal with flare greater than the wheal, 2+ was 7 to 9 mm, 3+ was 10–12 mm, and 4+ was greater than 13 mm [6]. The FDA-approved package insert for Pre-Pen® notes, a positive test result is a wheal of 5 to 15 mm or greater.

Most penicillin allergy testing done in the USA in the past 39 years has only effectively used the major determinant penicilloyl-poly-lysine and native penicillin G. There has been some use of native amoxicillin as a minor determinant skin test reagent, both in Europe and in the USA [37, 45, 49]. There has been a significant disagreement between European and North American clinicians regarding the concentration of amoxicillin that should be used for skin testing, but, interestingly, not the concentration of penicillin, penicilloate, or penilloate, all of which are used at about 0.01 M [50, 51]. Some rare individuals may produce IgE that binds to the unique side chain of amoxicillin but not to any of the core penicillin epitopes [34]. The clinical significance of this amoxicillin-specific IgE is still in question. Oral challenges still need to be part of the penicillin allergy workup to identify false negative skin test results and clinically significant delayed onset T cell-mediated reactions. Amoxicillin is the ideal oral challenge material because, in addition to being the most widely used penicillin class antibiotic, it will identify those penicillin skin test-negative individuals at risk for future clinically significant immunologically mediated reactions, whether directed against the penicillin core structures or the extra hydroxyl group on the amoxicillin side chain [30].

The other significant minor determinants, penicilloate and penilloate, have never been commercially available in North America [49]. Penicilloate and penilloate are unstable in aqueous solution and must either be stored lyophilized or, if in aqueous solution, at -70°C and thawed only once just prior to use. Our group has performed penicillin skin testing on over 3,000 individuals using a panel of reagents including penicilloyl-poly-lysine, native penicillin G, native amoxicillin, penicilloate, and penilloate [34]. Using this panel, we identified about 10 to 20 % more skin test-positive individuals than we would have seen using only penicilloyl-poly-lysine and native penicillin G. Given the low rates of positive skin test results currently being obtained, less than 2 %, the low value added using these difficult to produce and store minor determinants, and the safety of oral amoxicillin challenges, our group abandoned using amoxicillin, penicilloate, and penilloate as skin test reagents in 2010. We estimate that our current practice will result in one additional positive amoxicillin oral challenge result for every 3,375 individuals evaluated for penicillin intolerance in our population [38].

Our group currently uses penicilloyl-poly-lysine, at 5×10^{-5} M, and native penicillin G, at 0.01 M, for penicillin skin testing [38, 48]. A commercial version of the major determinant, penicilloyl-poly-lysine (Pre-Pen®, ALK-Abello, Round Rock, TX), has been sold in the USA since 1974, with intermittent unavailability over the last decade. Since its reintroduction in 2010, there have only been about 28,000 doses of Pre-Pen® sold annually. Pre-Pen® is not currently available in Europe or Canada. In Europe, Diater Laboratorios, S.A., Madrid, Spain, sells a kit which contains penicilloyl-poly-lysine and a minor determinant mixture. We use Pre-Pen® per the directions on its package insert. We obtain the penicillin G from our pharmacy and dilute it to 0.01 M in buffered normal saline. Stock solutions of penicillin G can be stored at 4°C for up to 1 week. Working dilutions either are made daily, or the final concentration, 0.01 M, can be stored frozen at -70°C and thawed once just prior to use.

A positive histamine and a negative normal saline control are used for both puncture and intradermal testing. If dermographism is present, the skin test cannot be accurately performed. Puncture testing is completed prior to starting intradermal testing. A positive test result is a wheal 5 mm or larger at 15 min, with a flare greater than the wheal, for both puncture and intradermal testing. All individuals with negative skin test results are given an oral amoxicillin challenge, 250 mg for an adult or an equivalent weight adjusted dose for young children, and observed for 1 h. Delayed, potential IgG or T cell-mediated reactions are reported over the phone and then observed and treated if needed. We have not had any serious acute or delayed onset reactions with more than 600 oral amoxicillin challenges performed over the past 2 years. Our current combined skin test and acute oral challenge positive result rate is under 2 %. Our clinically significant delayed onset oral challenge positive result rate is much less than 1 %. There will be a low rate of resensitization after all penicillin class antibiotic use in penicillin skin test-negative individuals [52].

The Management of Cephalosporin, Carbapenem, and Monobactam Intolerance

Because there has been no clinically significant IgE-mediated cross-reactivity demonstrated to date between penicillins and cephalosporins, carbapenems, or monobactams, penicillin skin testing in the workup of isolated non-penicillin beta-lactam intolerance is not useful or indicated. Native cephalosporin skin testing may have some utility in the workup of specific cephalosporin intolerance but only if that exact cephalosporin is needed for a life-threatening infection. Cephalosporins are typically used at about 2 mg/mL or 0.005 M for immediate type hypersensitivity skin testing [8]. This concentration is

well under the irritant concentrations for cephalosporins. If skin test positive, it is prudent to avoid that specific cephalosporin and possibly similar cephalosporins that share side chains. If skin test negative, an oral challenge may be performed if an oral version of the cephalosporin is available. During any parenteral rechallenge or treatment, be ready to treat a systemic allergic reaction. Desensitization is always an option if the specific cephalosporin implicated is needed for a life-threatening infection. Oral desensitization should always be performed when possible prior to parenteral antibiotic use.

Compared to the penicillin allergy diagnosis literature, there is a very sparse cephalosporin allergy diagnosis literature [32]. Clinically significant major and minor determinates, if they even exist, have not been well characterized or validated in clinical trials. Our group, even with direct access to all drug intolerance patients in a population of about half a million in San Diego county, finds it difficult to recruit even 100 individuals with histories of adverse reactions associated with any specific non-penicillin beta-lactam for comprehensive evaluations. Since there has been very little clinically significant IgE-mediated cross-reactivity noted between cephalosporins that do not share side chains to date, selecting a different cephalosporin for use in individuals with a history of a specific cephalosporin intolerance is widely done in our group and appears to be safe. We do not recommend skin testing for cephalosporin allergy outside of a research setting.

Skin testing with native carbapenems or monobactams is also of no documented clinical utility at this time and is not recommended outside of a research setting. If an individual has an intolerance to a specific carbapenem or monobactam, either avoid that chemical entity or perform a desensitization

if there is a life-threatening infection that requires treatment with that particular antibiotic. Patriarca and coworkers have shown that aztreonam is tolerated in individuals allergic to other beta-lactams [53]. Buonoma and coworkers have shown that aztreonam is tolerated in individuals with T cell-mediated reactions to other beta-lactams [54].

Conclusions

Beta-lactam intolerance can be safely managed with the following steps, as noted in Table 3. The section of the medical record where drug allergy reports are currently tabulated should be renamed drug intolerances. Drug intolerance reports for beta-lactams ideally should note the exact chemical entity implicated. The reports should also clearly delineate the clinical characteristics and time to onset of the adverse reaction after exposure. It should be clearly noted if toxic epidermal necrolysis, Stevens–Johnson syndrome, erythema multiforme, drug reaction with eosinophilia and systemic symptoms syndrome, blistering eruptions, severe hepatitis, serum sickness, nephritis, and/or hemolytic anemia occurred.

Avoid unnecessary antibiotic use, especially in the setting of possible viral respiratory infections. Expect new intolerances to be reported after 0.5 to 4 % of all antibiotic utilizations, dependent on gender and the specific antibiotic used. Expect individuals with three or more drug intolerances to have higher incidence rates of new drug intolerances reported for all antibiotic usages.

Screen out individuals with a history of beta-lactam associated toxic epidermal necrolysis, Stevens–Johnson syndrome,

Table 3 Seven steps for beta-lactam intolerance management

Step	Recommendations
1	Avoid testing, re-challenging, or desensitizing individuals with histories of beta-lactam-associated toxic epidermal necrolysis, Stevens–Johnson syndrome, drug reaction with eosinophilia and systemic symptoms syndrome, severe hepatitis, interstitial nephritis, or hemolytic anemia.
2	Avoid unnecessary antibiotic use, especially in the setting of viral infections.
3	Expect new intolerances to be reported after 0.5 to 4 % of all antibiotic utilizations, dependent on gender and the specific antibiotic used.
4	Expect a higher incidence of new intolerances in individuals with 3 or more medication intolerances already noted in their medical records.
5	For individuals with an appropriate penicillin class antibiotic intolerance based on a history of anaphylaxis, urticaria, macular papular rashes, unknown symptoms, or symptoms not excluded in step one, proceed with penicillin skin testing. Skin test with penicilloyl-poly-lysine and native penicillin. If skin test negative, proceed with an oral amoxicillin challenge. If skin test and oral challenge negative, penicillin class antibiotics may be used. If skin test or oral challenge positive, avoid penicillin class antibiotics. If skin test or oral challenge positive, non-penicillin-beta-lactams may be used, unless there is a history of intolerance to a specific non-penicillin-beta-lactam, then avoid that specific non-penicillin-beta-lactam. If there is life-threatening infection that can only be treated with a penicillin class antibiotic, proceed with oral penicillin desensitization prior to any oral or parenteral penicillin use.
6	For individuals with an appropriate non-penicillin-beta-lactam intolerance, avoid re-exposure to the beta-lactam implicated. An alternative beta-lactam may be used, ideally with different side chains. Penicillin allergy testing is not useful in the management of non-penicillin-beta-lactam intolerance. Non-penicillin-beta-lactam skin testing is not clinically useful and should not be done outside of a research setting. If the non-penicillin-beta-lactam implicated is needed to treat a life-threatening infection, proceed with desensitization.
7	Be ready to treat anaphylaxis with all parenteral beta-lactam use.

erythema multiforme, drug reaction with eosinophilia and systemic symptoms syndrome, blistering eruptions, severe hepatitis, serum sickness, nephritis, and/or hemolytic anemia. Avoid future exposure to the specific beta-lactam implicated and probably that family of beta-lactams. Do not test, rechallenge, or attempt to desensitize these individuals outside of a research setting.

Individuals with a history of beta-lactam-associated anaphylaxis, shortness of breath, hives, macular papular rashes, other mild rashes, unknown history, and other conditions not excluded above may undergo skin testing, rechallenge, desensitization, or use of alternative beta-lactams as noted below.

Individuals with a history of penicillin class antibiotic intolerance may undergo penicillin skin testing using only penicilloyl-poly-lysine and native penicillin G [38]. Puncture testing is always done prior to intradermal testing. The same reagent concentrations are used for both puncture and intradermal testing. Use 5 mm of wheal, with flare greater than wheal, as the threshold for a positive penicillin skin test result. If the penicillin skin test results are negative, proceed with an oral amoxicillin challenge. Be ready to treat systemic allergic reactions with all oral challenges. If the skin test or oral challenge is positive, continue to avoid all penicillin class antibiotics. If the skin test or oral challenge is positive, other non-penicillin-beta-lactams may be used, unless there is also an intolerance to that specific non-penicillin-beta-lactam. If a penicillin class antibiotic is needed for a life-threatening infection, proceed with an oral penicillin desensitization prior to any parenteral penicillin use. Children with a history of urticaria or macular papular rashes may also go directly to an oral amoxicillin challenge without skin testing [7].

Individuals with a history of a specific cephalosporin, carbapenem, or monobactam intolerance should continue to avoid the specific non-penicillin beta-lactam implicated. If clinically necessary, an alternative beta-lactam, ideally that has different side chains, may be used. If the index non-penicillin beta-lactam is needed for a life-threatening infection, proceed with an oral desensitization, if possible, or a parenteral desensitization, if necessary. Penicillin skin testing is of no utility in the management of isolated non-penicillin beta-lactam intolerance. Non-penicillin beta-lactam skin testing is not recommended outside of a research setting at this time.

Allergists and clinical immunologists should actively address the large and growing problem of beta-lactam intolerance. This will help preserve the utility of most beta-lactam antibiotics for a significant fraction of the population that experience beta-lactam adverse drug reactions.

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