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ANAPHYLAXIS AND DRUG ALLERGY (DA KHAN AND M CASTELLS, SECTION EDITORS)

Penicillin and Beta-Lactam Allergy: Epidemiology and Diagnosis

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Abstract Penicillin is the most common beta-lactam antibiotic *allergy* and the most common drug class *allergy*, reported in about 8 % of individuals using health care in the USA. Only about 1 % of individuals using health care in the USA have a cephalosporin *allergy* noted in their medical record, and other specific non-penicillin, non-cephalosporin beta-lactam *allergies* are even rarer. Most reported penicillin *allergy* is not associated with clinically significant IgE-mediated reactions after penicillin rechallenge. Un-verified penicillin *allergy* is a significant and growing public health problem. Clinically significant IgE-mediated penicillin allergy can be safely confirmed or refuted using skin testing with penicilloyl-poly-lysine and native penicillin G and, if skin test is negative, an oral amoxicillin challenge. Acute tolerance of an oral therapeutic dose of a penicillin class antibiotic is the current gold standard test for a lack of clinically significant IgE-mediated penicillin allergy. Cephalosporins and other non-penicillin beta-lactams are widely, safely, and appropriately used in individuals, even with confirmed penicillin allergy. There is little, if any, clinically significant immunologic cross-reactivity between penicillins and other beta-lactams. Routine cephalosporin skin testing should be restricted to research settings. It is rarely needed clinically to safely manage patients and has unclear predictive value at this time. The use of alternative cephalosporins, with different side chains, is acceptable in the setting of a specific cephalosporin *allergy*. Carbapenems and monobactams are also safely used in individuals with confirmed penicillin allergy. A certain predictable, but low, rate of adverse reactions will occur with all beta-lactam antibiotic use both pre- and post-beta-lactam allergy evaluations.

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Abbreviations

ADR(s)	Adverse drug reaction(s)
EHR	Electronic health record
KPSC	Kaiser Permanente in Southern California

Introduction

Large comprehensive electronic health record (EHR) databases, which link all outpatient, inpatient, and pharmacy interactions, have revolutionized the understanding of penicillin and other beta-lactam-associated adverse drug reactions (ADRs), including allergies. Much of the world's beta-lactam allergy literature has been produced by specialized centers that only evaluate highly selected individuals with extreme sensitivities. Unverified penicillin *allergy*, noted in the EHR, is being increasingly recognized as a significant public health problem [1•]. Avoidance of penicillins and first-generation cephalosporins in patients with a history of penicillin *allergy*, without evaluation, is associated with more hospital utilization along with increased rates of *Clostridium difficile*, vancomycin-resistant *Enterococcus*, and methicillin-resistant *Staphylococcus aureus*. The Choosing Wisely® program of the American Board of Internal Medicine recommended in 2014 that physicians do not overuse non-beta-lactam antibiotics in patients with a history of penicillin allergy, without an appropriate evaluation http://www.choosingwisely.org/doctor-patient-lists/american-academy-of-allergy-asthma-immunology/ .

Our group has published extensively on beta-lactam-associated ADRs occurring in individuals receiving health care from Kaiser Permanente in Southern California (KPSC).

KPSC currently provides health care to about 3.5 million members, essentially a 1 % sample of the US population. Our EHR has been actively linking the outpatient and inpatient arenas with the pharmacy since 2009. This review will concentrate primarily on our epidemiology and testing data. We will use the word *allergy* in this review to define a listing in the EHR drug allergy field.

In studies of specific testing protocols used to determine clinically significant IgE-mediated beta-lactam allergy or acute tolerance in individuals with a history of beta-lactam *allergy*, it is important to know the demographics of the tested population compared to all individuals in the population with the same beta-lactam *allergy*. It is also important to know the underlying population prevalence of beta-lactam *allergy* and the incidence rate of new beta-lactam *allergy* after therapeutic beta-lactam exposures. After the testing is done, it is important to determine what therapeutic antibiotics are subsequently used, the incidence rate of new antibiotic-associated ADRs, and other antibiotic-associated morbidities. Our health plan is unique, to date, in that it has been able to provide the above data electronically over the past 5 years. Much of the world's beta-lactam drug *allergy* evaluation literature is produced by specialized centers that are referred and investigate highly selected cases. They are typically unable to provide data on how these individuals compared to average beta-lactam-*allergic* individuals and what happens with future antibiotic use.

We have noted that the rate of skin test positivity seen with properly performed penicillin skin testing has been falling in our group over the past 20 years, perhaps because of lower rates of outpatient parenteral penicillin use [2•]. We have shown that current commercially available penicillin skin test materials are adequate for the safe and effective determination of active, clinically significant, IgE-mediated penicillin allergy, when used in conjunction with an oral amoxicillin challenge, if skin test is negative [3]. We have recently shown, in a retrospective population-based analysis of about 1.4 million cephalosporin courses, that cephalosporins are widely, safely, and appropriately used in individuals with a history of penicillin allergy and alternative cephalosporins are safely used in individuals with a history of a specific cephalosporin allergy [4•].

Epidemiology

Penicillins are one of the most widely used antibiotic families in the USA with amoxicillin or amoxicillin combination products accounting for the vast majority of the courses. Based on data from www.cddep.org , in 2010, there were 248 penicillin and 114 cephalosporin prescriptions given to outpatients for every 1,000 individuals in the USA [5]. There is no good comprehensive nationwide data on inpatient beta-lactam use.

About 8 % of the US population carries a history of penicillin *allergy*, yet less than one in 20 will have an acute reaction to the gold standard test used to confirm a clinically significant IgE-mediated penicillin allergy, an oral challenge with a therapeutic dose [3]. Only about 1 % of the US population carries a history of cephalosporin *allergy*. There is no comparable data on direct specific cephalosporin skin testing followed, if skin test is negative, by specific rechallenge in large, >500 person, specific cephalosporin-*allergic* cohorts.

There is a certain, predictable rate of new drug *allergy* reports made in the year after any antibiotic use that varies significantly by both gender and antibiotic class [6]. Females report a new penicillin *allergy* in the year after about 2 % of all therapeutic penicillin class antibiotic exposures versus about 1 % for males. Females report a new cephalosporin *allergy* in the year after about 1 % of all therapeutic cephalosporin class antibiotic exposures versus about 0.5 % for males.

From our recently published data reviewing 1,389,538 total courses of cephalosporins administered to 820,124 unique individuals between 1 January 2010 and 31 December 2012, individuals with a history of penicillin *allergy* were more likely to have a new cephalosporin *allergy* report within 30 days of a cephalosporin course, 1.13 % (95 % confidence interval (CI) 1.07 to 1.19 %) compared to individuals with no drug *allergy*, 0.39 % (95 % CI 0.37 to 0.40 %); cephalosporin *allergy*, 0.70 % (95 % CI 0.50 to 0.91 %); or other non-beta-lactam *allergy*, 0.50 % (95 % CI 0.48 to 0.52 %). There would be about one more new cephalosporin *allergy* noted for every 135 individuals given a cephalosporin who have a penicillin *allergy* compared to individuals with no drug *allergy* [4•].

Oral cephalosporins were less commonly associated with physician-documented anaphylaxis, five out of 901,908 courses (95 % CI, one in 1,428,571 to one in 96,154) compared to eight out of 487,630 courses (95 % CI, one in 200,000 to one in 35,971) for parenteral cephalosporins [4•]. This difference did not quite reach statistical significance (p= 0.0761). Physician-documented anaphylaxis was 2.2 times more common in females [10 out of 844,007 courses (95 % CI, one in 222,222 to one in 52,110)], compared to males [3 out of 545,531 courses (95 % CI, zero to one in 85,324)], but this difference also did not reach statistical significance (p= 0.2709). There were 65,915 individuals with a history of a penicillin *allergy* who received a total of 127,125 courses of cephalosporins. There were three cases of cephalosporin-associated anaphylaxis in this group. Though physician-documented cephalosporin-associated anaphylaxis was about 2.9 times more common in individuals with a penicillin *allergy* history compared to individuals with no drug *allergy* history, three in 127,125 courses (95 % CI, zero to one in 19,880) compared to seven in 845,923 courses (95 % CI, one

in 467,290 to one in 69,396), this difference also did not reach statistical significance (p=0.1322). There were 3,313 individuals with a history of a cephalosporin *allergy* who received a total of 6,404 courses of cephalosporin antibiotics, with no cases of cephalosporin-associated anaphylaxis. Data on penicillin-associated anaphylaxis is currently being collected.

There is clinically significant immunologic cross-reactivity between penicillins, and much less, or possibly no, clinically significant immunologic cross-reactivity between specific penicillins, cephalosporins, and other non-penicillin beta-lactams, with the possible exception of those specific beta-lactams that share exact side chains [7, 8]. Unfortunately, IgE immunochemistry vastly overcalls beta-lactam cross-reactivity, which is not observed clinically [9, 10]. The presence of measurable anti-beta-lactam IgE does not mean that therapeutic exposure will cause any clinically significant symptoms [11].

Uniquely cephalosporin-associated toxic epidermal necrolysis, Stevens Johnson syndrome, drug reaction with eosinophilia and systemic symptoms syndrome, severe hepatitis, interstitial nephritis, or hemolytic anemia are extremely rare [4•]. Large comprehensive population-based data has not been published for penicillins to date, though we are currently working on this issue. There are often other medications used at the same time as a cephalosporin, or the underlying infections, that are much more likely to be inciting causes of these very serious reactions. Nephropathy after the use of cephalosporins has recently been noted to be possibly more common than previously appreciated [4•]. *C. difficile*, particularly after third or higher generation, cephalosporins use is very common, occurring in about 3 % per course within 90 days, and is a major public health concern [4•].

Since our report on 500 individuals tested using only penicilloyl-poly-lysine and native penicillin G, followed by an oral 250 mg amoxicillin challenge, if skin test is negative [3], we have tested an additional 799 individuals through 2 July 2014. Among these additional individuals, 763 (95.5 %) were skin tested and oral challenge negative, 18 (2.3 %) were skin test positive, 11 (1.4 %) were acute oral challenge positive, and 4 (0.5 %) were delayed oral challenge positive. It is important to remember that there were also 30 (3.9 %) individuals with subjective oral challenge reactions, such as itching, anxiety, or headaches, during the 1-h observation period that did not require treatment and were not considered clinically significant. Thus to date, only 2.8 % of 1,299 individuals evaluated by this protocol have had IgE-mediated penicillin allergy confirmed, despite these individuals having demographic characteristics that would be expected to result in higher rates of positivity than average health plan members with a history of penicillin *allergy*.

Diagnosis

Beta-lactam testing protocols need to be simple and safe and use materials that are commercially available, because millions of individuals need to be evaluated.

History is an essential component of the beta-lactam allergy evaluation. 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 should not undergo beta-lactam allergy testing, rechallenge, or desensitization. Individuals with a history of penicillin class antibiotic-associated anaphylaxis, shortness of breath, hives, other non-hive rashes, local swelling, gastrointestinal upset, headaches, or unknown or with no known exposure, but just fear of *allergy*, can all safely undergo a penicillin allergy evaluation.

The gold standard test at this time used to confirm a clinically significant IgE-mediated penicillin allergy, or conversely to document acute tolerance, is an oral challenge with a typical therapeutic dose followed by 1 h of observation [12]. We recommend using amoxicillin 250 mg in the setting of penicillin *allergy* because it has the essential immunologically significant penicillin core structure, and there are rare individuals uniquely allergic to the amoxicillin side chain [3]. An oral challenge will also identify significant reproducible delayed onset reactions. A small number of individuals, <1 %, will have a delayed onset, typically after 2–5 days, diffuse macular papular rash, which is thought to be T cell mediated.

Direct oral challenges can be safely done where there is a good clinical history of an adverse reaction that is mild and clearly not potentially IgE-mediated, such as gastrointestinal upset or headaches. Direct oral challenges can also be used where there is no known history of exposure, but fear of possible penicillin *allergy*. This may occur in certain families where a parent will tell a child not to use penicillins because another family member had a problem associated with penicillin use.

Skin testing is essentially used to reduce the number of oral challenge reactions. The definition of an ideal penicillin allergy skin test protocol is a rapid, easy-to-perform, protocol that uses commercially available materials which maximizes the number of negative results and minimizes the number of objective oral challenge reactions and acute systemic skin testing reactions. The current commercially available materials, the major determinant, penicilloyl-poly-lysine (PrePen®, as supplied by ALK), and one minor determinant, native penicillin G (0.01 M or 3.725 mg/ml for potassium penicillin G), are adequate to safely penicillin skin test. These two reagents used for both puncture and intradermal testing, at the same concentrations, perform very close to the ideal

Table 1 Dilution and storage of potassium penicillin G for skin testing

1. For a 5,000,000-unit anhydrous potassium penicillin G bottle, add 3.2 ml of diluent. This results in a stock solution containing 628.8 mg/ml or 1,000,000 units/ml. Potassium penicillin G may be initially dissolved in small amounts of sterile water or sterile isotonic sodium chloride solution also known as normal saline. Try to use the diluent recommended by the manufacturer for the initial dilution. Only sterile normal saline should be used for the serial dilutions, and the same sterile normal saline is used as the negative skin test control. The more concentrated solutions, ≥100,000 units/ml, may be stored in a refrigerator, at 4 °C, for 7 days without significant loss of potency
2. Take 1 ml out of the stock bottle and add it to 9 ml of sterile normal saline diluent. Label this bottle 1. Bottle 1 contains 62.68 mg/ml or 100,000 units/ml of penicillin G
3. Take 1 ml out of bottle 1 and add it to 9 ml of sterile normal saline diluent. Label this is bottle 2. Bottle 2 contains 6.268 mg/ml or 10,000 units/ml of penicillin G
4. Take 5.94 ml out of bottle 2 and add it to 4.06 ml of sterile normal saline diluent. Label this is bottle 3. This is the concentration used for both puncture and intradermal skin testing. Bottle 3 contains 0.01 M, 3.72 mg/ml, or 5,940 units/ml of penicillin G
5. Penicillin G is stable in dilute form for only several hours. Bottles 2 and 3 will need to be made fresh daily for skin testing use. If dilute material is to be stored, generally in 0.2-ml unit dose vials of the 0.01 M working dilution from bottle 3, it must be stored at −70 °C and thawed only once just before use.

penicillin allergy skin test protocol. The method for penicillin G preparation for use as a skin test reagent is displayed in Table 1.

The other widely used minor determinants, penilloate (0.01 M), penicilloate (0.01 M), and amoxicillin (0.01 M), were more useful when the rate of positive skin test results was >10 % and are not needed at this time [2•, 3]. After we calculated that, we have about 10 % fewer positive skin test results and about one additional positive oral challenge reaction for every 3,000 individuals tested for penicillin allergy by not using these three additional reagents in our penicillin allergy skin test panel. We discontinued their clinical use in our program in 2012. Penicillin allergy skin testing is associated with a significant number of false positive results. Among the small number of penicillin skin test-positive individuals who have been given an oral challenge or a therapeutic course of penicillin reported on over the past 20 years, only about one third to one half have had any clinically significant reaction [13, 14]. In our study of 83 penicillin skin test-positive individuals compared to 166 matched penicillin skin test-negative individuals, the ADR rate with future therapeutic cephalosporins or even non-beta-lactam antibiotics was not significantly different [13]. In our more recent study of 118 penicillin skin test-positive individuals exposed to 169 courses of cephalosporins compared to 1,566 penicillin skin test-negative individuals exposed to 2,485 courses of cephalosporins over a 4.5±2.9-year follow-up period, there was no significant difference in the rate of new cephalosporin allergy reports between the two groups [14].

A penicillin allergy evaluation data collection template is displayed in Table 2. Penicillin skin testing is typically done using the outer surface of the upper arm. Drops of penicilloyl-poly-lysine, penicillin, saline, and histamine are pricked using an individual Duotip-Test® device for each drop. Following a 15-min waiting period, skin reactions are read and recorded in millimeters as the mean diameter of wheal over the mean diameter of flare. Positive responses consist of a wheal of 5 mm or more in diameter with surrounding flare greater than the wheal, a negative response to the control saline solution and a positive response to histamine. If the puncture tests are negative, intradermal testing follows. Using the same test materials, 0.02 ml is administered intradermally through individual 27 gauge tuberculin syringes. Tests are read and recorded after 15 min, using the same parameters as above [15]. Puncture testing is necessary prior to intradermal testing to optimize safety. There are rare, but exquisitely sensitive, individuals who can have systemic reactions with intradermal penicillin allergy testing [16]. Adverse reactions associated with skin testing protocols are in general very low, but a higher rate of systemic reactions is seen in protocols which use high dose, >0.01 M, intradermal amoxicillin or other beta-lactam reagents [17, 18]. The skin testing protocol outlined above can be done in about 45 to 60 min.

It is essential to use 5 mm of wheal, or greater, with flare greater than wheal as the criteria for a positive test result, as noted in the Pre-Pen package insert and in the definitive trial by Sogn et al. [19]. If 3 or 4 mm of wheal is used as a positive test result, there will be many more false positive skin test results, particularly among females, and individuals will needlessly continue to avoid penicillin class antibiotics and suffer greater morbidity [20, 21].

If the rate of positive skin test results seen in our group in individuals with a history of hives as the index reaction is normalized to 1, then the rate seen in individuals with a history of anaphylaxis or shortness of breath associated with previous penicillin use is about 1.5, the rate in individuals with a history of non-hive rashes, local swelling, gastrointestinal symptoms, or unknown reactions is 0.5, and with unknown reactions, the rate is about 0.25 [2•]. The rate of positive skin test results is also higher the sooner the skin testing is done to the date of the index reaction.

A single 250 mg oral amoxicillin challenge is adequate to confirm acute tolerance after a negative skin test result. If there is a desire to use a graded challenge, it is important to use at least a 10-fold dose increase in the

Table 2 Penicillin skin testing and oral amoxicillin challenge data collection template

Test performed by: _____ Test ordered by: _____

Last Name: _____ First Name: _____

Medical Record Number: _____

Date of test: __/__/____ Date of birth: __/__/____ Gender: (M / F)

Date of index penicillin-associated adverse reaction: __/__/____

Route of administration: (oral / parenteral)

Time to onset: (< 1 hour / 1-24 hours / 25 – 72 hours / > 73 hours)

Type of index reaction: (anaphylaxis / shortness of breath / hives / angioedema / non-hive rash / GI / other)

Treatment of index reaction: (stopped penicillin only / antihistamine / epinephrine / systemic steroid / other)

Puncture		**Intradermal**	
Time placed:_____ Time read:_____		Time placed:_____ Time read:_____	
1) Penicilloyl-poly-lysine	____/____	5) Penicilloyl-poly-lysine	____/____
2) Penicillin G (0.01M)	____/____	6) Penicillin G (0.01M)	____/____
3) Saline Control	____/____	7) Saline Buffer Control	____/____
4) Histamine	____/____	8) Histamine	____/____

(Report results as mm wheal / mm flare)

Skin test reaction: (None / hives / hypotension)

Treatment given: (None / antihistamine / epinephrine)

Oral amoxicillin 250 mg challenge time given: _____

Objective acute oral challenge reaction: (None / hives / hypotension / other)

Time of onset: _____

Acute challenge reaction treatment given: (None / antihistamine / epinephrine)

Delayed challenge reaction reported: (None / rash / other)

Time to delayed onset reaction: _____

Delayed challenge reaction treatment given: (None / antihistamine / systemic steroids)

Table 3 Seven steps for beta-lactam intolerance management

	Beta-lactam intolerance management
1	Avoid testing, rechallenging, or attempting 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-poly-lysine and native penicillin. If skin test is negative, proceed with an oral amoxicillin challenge. If skin test or oral challenge is 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 reexposure 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 at this time. If the non-penicillin beta-lactam implication is needed to treat a life-threatening infection, proceed with desensitization
7	Expect adverse reactions with all beta-lactam allergy use and be ready to treat anaphylaxis, particularly with parenteral exposures

Modified from Macy and Ngor [29]

graded challenge, for example 25 mg followed by 250 mg of amoxicillin. If a twofold dose increase is used, it could potentially be desensitizing. One hour is an adequate time period for direct observation after an oral challenge for acute severe reactions. Oral challenge-associated reactions should be aggressively treated, just as one would with an oral food challenge. If there is hypotension or shortness of breath, intramuscular epinephrine should be administered immediately. If there are hives, then diphenhydramine, typically 50 mg for an adult, should be administered. Diphenhydramine can be given orally or parenterally, depending on the particular clinical situation. Subjective reactions, such as itching without any hives, anxiety, or headaches, should be expected and can just be closely observed. If any objective symptoms occur, then they should be appropriately treated. Subjective reactions are more frequent in individuals with underlying multiple drug intolerance syndrome [3, 22].

Penicillin allergy evaluations can be safely done in advance of need and are not associated with resensitization [23]. Adverse drug reactions, and even IgE-mediated resensitization, will occur in a small fraction of individuals with future therapeutic courses [24]. In a group of 568 penicillin allergy history-positive but penicillin skin test-negative individuals followed for 4.26±1.64 years and exposed to 3.94±3.91 therapeutic courses of penicillin class antibiotics, there were only 71 (3.2 %) total new ADRs noted in 2,236 total courses. Only 0.38 % (95 % CI 0.09 to 1.71 %) converted to penicillin skin test positive [25].

Commercially available serologic tests used to diagnose penicillin allergy are not clinically useful at this time [11].

Conclusions

Reducing beta-lactam overuse will be critical to reducing the epidemic of beta-lactam allergy and associated ADRs. The rate of penicillin allergy evaluation needs to be dramatically increased, starting with hospitalized patients, who tend to be older, report penicillin allergy about 11 % of the time, and are very likely to receive antibiotics. Additional efforts will also need to be directed at reducing unnecessary or inappropriate third- or greater-generation cephalosporin use, where a narrow spectrum penicillin or first-generation cephalosporin would suffice, if we are to further reduce *C. difficile* rates.

Direct oral challenges can be used for evaluation of delayed onset beta-lactam-associated rashes in children, most of whom also have evidence for viral infections at the time of their beta-lactam-associated ADRs [26•]. Penicillin allergy testing can safely be done in hospitalized patients and even in pregnant women with group B streptococcal colonization [27, 28].

In summary, beta-lactam allergy can be safely managed at this time using the seven steps, slightly modified from our previous recommendations [29], displayed in Table 3.

Compliance with Ethics Guidelines

Conflict of Interest Eric Macy reports grants from ALK during the conduct of the study.

Human and Animal Rights and Informed Consent All of the studies in this article performed by the author were reviewed and approved by the Kaiser Permanente Southern California Institutional Review Board.

References

Papers of particular interest, published recently, have been highlighted as:
- Of importance

1.• Macy E, Contreras R. Healthcare utilization and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: a cohort study. J Allergy Clin Immunol. 2014;133:790–6. *Largest study to date showing potential penicillin "allergy" associated morbidity.*
2.• Macy E, Schatz M, Lin C, Poon KWT. The falling rate of positive penicillin skin tests from 1995 to 2007. Perm J. 2009;13:12–8. *Largest study to date showing changes in positive test result frequency over time.*
3. Macy E, Ngor EW. Safely diagnosing clinically significant penicillin allergy using only penicilloyl-poly-lysine, penicillin, and oral amoxicillin. J Allergy Clin Immunol Pract. 2013;1:258–63.
4.• Macy E, Contreras R. Adverse reactions associated with oral and parenteral cephalosporin use: a retrospective population-based analysis. J Allergy Clin Immunol (in press). (Largest study to date showing relative safety of cephalosporin use in the setting of penicillin "allergy")
5. Suda KJ, Hicks LA, Roberts RM, Hunkler RJ, Taylor TH. Trends and seasonal variation in outpatient prescription rates in the United States, 2006 to 2010. Antimicrob Agents Chemother. 2014;58:2763–6.
6. Macy E, Poon KWT. Self-reported antibiotic allergy incidence and prevalence: age and sex effects. Am J Med. 2009;122:778e1–e7.
7. Pichichero ME, Zagursky R. Penicillin and cephalosporin allergy. Ann Allergy Asthma Immunol. 2014;112:404–12.
8. Zhao Z, Baldo BA, Rimmer J. Beta-lactam allergenic determinants: fine structural recognition of a cross-reacting determinant on benzylpenicillin and cephalothin. Clin Exp Allergy. 2002;32:1644–50.
9. Liu XD, Gao N, Qiao HL. Cephalosporin and penicillin cross-reactivity in patients allergic to penicillins. Int J Clin Pharm Ther. 2011;49:206–16.
10. Pipet A, Veyrac G, Wessel F, Jolliet P, Magnan A, Demoly P, et al. A statement on cefazolin immediate hypersensitivity: data from a large database, and focus on the cross-reactivities. Clin Exp Allergy. 2011;41:1602–8.
11. Macy E, Goldberg B, Poon KWT. Use of commercial anti-penicillin-IgE FEIAs to diagnose penicillin allergy. Ann Allergy Asthma Immunol. 2010;105:136–41.
12. Bousquet PJ, Pipet A, Bousquet-Rouanet L, Demoly P. Oral challenges are needed in the diagnosis of β-lactam hypersensitivity. Clin Exp Allergy. 2008;38:185–90.
13. Macy E, Burchette RJ. Oral antibiotic adverse reactions after penicillin testing: multi-year follow-up. Allergy. 2002;57:1151–8.
14. Macy E, Ho NJ. Adverse reactions associated with therapeutic antibiotic use after penicillin skin testing. Perm J. 2011;15:31–7.
15. Macy E, Richter PK, Falkoff R, Zeiger RS. Skin testing with penicilloate and penilloate prepared by an improved method: amoxicillin oral challenge in patients with negative skin test responses to penicillin reagents. J Allergy Clin Immunol. 1997;100:586–91.
16. Macy E. Risks of penicillin skin testing. Ann Allergy Asthma Immunol. 2000;85:330–1.
17. Minh HBC, Bousquet PJ, Fontaine C, Kvedariene V, Demoly P. Systemic reactions during skin tests with beta-lactams: a risk factor analysis. J Allergy Clin Immunol. 2006;117:466–7.
18. Antico A, Pagani M, Compalati E, Vescovi P, Passalacqua G. Risk assessment of immediate systemic reactions from skin tests with β-lactam antibiotics. Int Arch Allergy Immunol. 2011;156:427–33.
19. Sogn DD, Evans III R, Shepherd GM, Casale TB, Condemi J, Greenberger PA, et al. Results of the National Institute of Allergy and Infectious Diseases collaborative clinical trial to test the predictive value of skin testing with major and minor penicillin derivatives in hospitalized adults. Arch Intern Med. 1992;152:1025–32.
20. Lin E, Saxon A, Riedl M. Penicillin allergy: value of including amoxicillin as a determinant in penicillin skin testing. Int Arch Allergy Immunol. 2010;152:313–8.
21. Park MA, Matesic D, Markus PJ, Li JTC. Female sex as a risk factor for penicillin allergy. Ann Allergy Asthma Immunol. 2007;99:54–8.
22. Macy E, Ho NJ. Multiple drug intolerance syndrome: prevalence, clinical characteristics and management. Ann Allergy Asthma Immunol. 2012;108:88–93.
23. Bittner A, Greenberger PA. Incidence of resensitization after tolerating penicillin treatment in penicillin-allergic patients. Allergy Asthma Proc. 2004;25:161–4.
24. Hershkovich J, Broides A, Kirjner L, Smith H, Gorodischer R. Beta lactam allergy and resensitization in children with suspected beta lactam allergy. Clin Exp Allergy. 2009;39:726–30.
25. Macy E, Mangat R, Burchette RJ. Penicillin skin testing in advance of need: multiyear follow-up in 568 test result-negative subjects exposed to oral penicillins. J Allergy Clin Immunol. 2003;111:1111–5.
26.• Caubet JC, Kaiser L, Lemaitre B, Fellay B, Gervaix A, Eigenmann PA. The role of penicillin in benign skin rashes in childhood: a prospective study based on drug rechallenge. J Allergy Clin Immunol. 2011;127:218–22. *Demonstrates the safety of direct oral challenges*.
27. Macy E, Roppe L, Schatz M. Routine penicillin skin testing in hospitalized patients with a history of penicillin allergy. Perm J. 2004;8:20–4.
28. Macy E. Penicillin skin testing in pregnant women with a history of penicillin allergy and group B streptococcus colonization. Ann Allergy Asthma Immunol. 2006;97:164–8.
29. Macy E, Ngor E. Recommendations for the management of beta-lactam intolerance. Clin Rev Allergy Immunol. 2014;47:46–55.