

Proactive management of penicillin and other antibiotic allergies

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ABSTRACT

Background: Antibiotic allergies, especially penicillin, are the most frequent drug allergy listed in the medical record. Proactive evaluations of antibiotic allergies, particularly penicillin allergies, have been recommended by various specialty societies.

Objective: To review the history of the discovery of penicillin, implications of the penicillin allergy label, various delabeling strategies as well as a brief overview of the approach to cephalosporin, fluoroquinolone, and macrolide allergy.

Methods: Recent studies on penicillin allergy delabeling and on cephalosporin and fluoroquinolone allergies were reviewed.

Results: Although Alexander Fleming is often solely credited with the discovery of penicillin, other scientists were critical to the development of penicillin as a life-saving antibiotic. The vast majority of patients with a penicillin allergy label are not allergic; however, this label results in increased morbidities and mortality. A variety of penicillin delabeling strategies can be used in both the outpatient and the inpatient settings. The role of direct penicillin challenge in patients at low risk is emerging and is the method of choice for children. Patients with an unconfirmed penicillin allergy have a low risk of reacting to cephalosporins. The R1 side chain largely dictates cephalosporin allergy and cross-reactivity. Drug challenge is the preferred method for evaluation of both fluoroquinolone and macrolide allergy.

Conclusion: Multiple effective methods are available to delabel patients of common antibiotic allergies. Delabeling patients in a proactive manner can reduce patient morbidity.

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HISTORY OF THE DISCOVERY OF PENICILLIN

Before reviewing penicillin allergy, it is worthwhile to discuss the fascinating story behind the discovery of penicillin. Alexander Fleming was born on August 6, 1881, in Scotland (Fig. 1). Eventually he moved to London and initially worked in a shipping office for several years, and, after inheriting money from his uncle, pursued a medical education. He was a graduate of St. Mary's Medical School at London University in 1906. He served in World War I and observed that many soldiers died from infections, not wounds inflicted in battle. Fleming eventually became a bacteriologist and continued to work at St. Mary's Hospital in London.

In 1928, Fleming began experiments that involved staphylococcal bacteria. During one of these experiments, an uncovered petri dish became contaminated with mold spores. He later commented "It was noticed for some distance around the mould colony the staphylococcal colonies had become translucent and

evidently lysis was going on. This was an extraordinary appearance and seemed to demand an investigation, so the mould was isolated in pure culture and some of its properties were determined."¹ The mold was identified as *Penicillium notatum*. He then streaked different microbes across the plate and found that some were inhibited and others were not.

He noted that the antibacterial properties were not due to the mold itself but rather some "juice" of the *Penicillium*.² In his acceptance speech for the Nobel Prize, Fleming indicated how he coined the term penicillin, "I have been frequently asked why I invented the name penicillin. I simply followed perfectly orthodox lines and coined the word which explained that the substance penicillin was derived from the plant of the genus *Penicillium* just as many years ago the word 'Digitalin' was invented for a substance derived from the plant *Digitalis*."¹ Although his work was published in 1929, it received little attention.³ It was very difficult to concentrate penicillin, and he and his colleagues were never able to produce enough penicillin to perform any additional experiments.

In the 1930s, with the introduction of sulfonamide antibiotics, there was renewed interest in penicillin, and Sir Howard Florey led an Oxford team in 1939 to begin a systematic investigation of antibacterial substances reduced by microorganisms. One of his team members, the biochemist Ernst Chain, found Fleming's 1929 article on penicillin and proposed to his supervisor Florey that he try to isolate the compound.^{3,4}

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Figure 1. Sir Alexander Fleming, who discovered penicillin.

Florey assembled a team that worked on growing large amounts of *Penicillium*. Norman Heatley designed a “counter current” apparatus to extract penicillin as well as special rectangular culture vessels used to grow the mold in large quantities. Chain was able to successfully purify penicillin from an extract of the mold. Although the *in vitro* activity of penicillin was known, its activity *in vivo* had not been studied. On May 25, 1939, the group injected eight mice with a virulent strain of *Streptococcus*; four were injected with penicillin and all lived; all four control mice died. Florey called the results “a miracle.” They published their findings in the *Lancet* in August 1940, which described the production, purification, and experimental use of penicillin to protect animals infected with several bacteria.⁵ On February 12, 1941, Albert Alexander an Oxford constable with numerous facial abscesses was the first person to receive penicillin. Within 24 hours his fever improved but, unfortunately, further penicillin therapy was not continued due to a lack of supply, and he died 1 month later.

In June 1941, Florey and Heatley traveled to the United States to convince the government and manufacturers to produce penicillin to start clinical trials.⁴ In a short period, there was unprecedented cooperation between the United States and Great Britain for penicillin production. In 1942, at Yale, Anne Miller was the

first patient saved by penicillin therapy, and the treatment nearly exhausted the entire U.S. supply of penicillin.⁶ By D-Day, 21 U.S. companies had produced 2.3 million doses of penicillin. The availability of penicillin during World War II led to a dramatic reduction in mortality from bacterial infections. Penicillin has continued to be an important antibiotic ever since. In 1945, Fleming, Chain, and Florey were awarded the Nobel prize in physiology or medicine for their work on the discovery of penicillin. Norman Heatley, who was key to the discovery of penicillin, was largely ignored until 1990 when he received an honorary Doctorate of Medicine from Oxford.

EPIDEMIOLOGY OF PENICILLIN ALLERGY

By 1945, shortly after penicillin was used as a therapeutic agent, the first descriptions of penicillin allergy, including anaphylaxis, were reported, and, by 1946, the first death attributed to penicillin anaphylaxis was published.^{7,8} Penicillin remains the most common drug listed as an allergy in medical records. Recent studies of large populations in the United States showed that 11-12% of patients have a label of penicillin allergy in their health record.^{9,10} Penicillin is also a leading cause of drug-induced anaphylaxis. A recent U.S. study of a large electronic health record data base of >1.7 million patients determined that 1.1% reported drug-induced anaphylaxis (not verified by a medical record review), with the most common culprit being penicillin.¹¹ Penicillin is also the most commonly identified drug that caused fatal drug-induced anaphylaxis. Nevertheless, the actual incidence of anaphylaxis to penicillin is low, with a recent study of audit-confirmed anaphylaxis showing an incidence of 1 in 207,191 with oral exposures and 1 in 95,298 with parenteral penicillin exposure.¹²

LOW PREVALENCE OF CONFIRMED PENICILLIN ALLERGY IN PATIENTS LABELED AS PENICILLIN ALLERGIC

Although penicillin allergy is a very commonly listed drug allergy in the medical record, confirmed penicillin allergy is much lower and seems to have declined over time. Some studies from the early 1970s found that >60% of patients with a history of penicillin allergy were positive on penicillin skin testing results.¹³ Longitudinal studies from Kaiser Permanente in Southern California found the rate of positive penicillin skin test results to have decreased, from 15% in 1995 to 3% in 2007,¹⁴ and to <1% in 2013 (Fig. 2).¹⁵ The largest amount of data on penicillin skin testing (without confirmatory challenges) comes from the Mayo Clinic, with a total of 30,883 patients with a history of penicillin allergy who have undergone penicillin skin testing and only 1% were found to be positive (M. Park, personal communication).

This rate of positive penicillin skin test results is lower than the 8% rate reported by the Mayo group from patients studied in 2004, which is in keeping with the trend observed at Kaiser Permanente.¹⁶ In addition, although a positive penicillin skin test result is often considered the reference standard for penicillin allergy, some patients may be sensitized (*i.e.*, positive skin test result) but not clinically allergic, as shown by a negative oral penicillin challenge.¹⁷

WHY DO WE CARE ABOUT A PENICILLIN ALLERGY LABEL?

Although numerous antibiotics are available, penicillin remains the drug of choice for several infections. Patients with methicillin-sensitive *Staphylococcus aureus* (MSSA) bacteremia have a lower 90-day mortality when receiving beta-lactam therapy compared with vancomycin. There is also a higher rate of clinical failure for blood stream infections with Gram-negative bacilli when using non-beta-lactam antibiotics.¹⁸ Decision analysis models have determined that patients with MSSA bacteremia have worse outcomes (including higher mortality) if treated with vancomycin instead of being evaluated for penicillin allergy.¹⁹ Benzathine penicillin remains the treatment of choice for patients with syphilis.

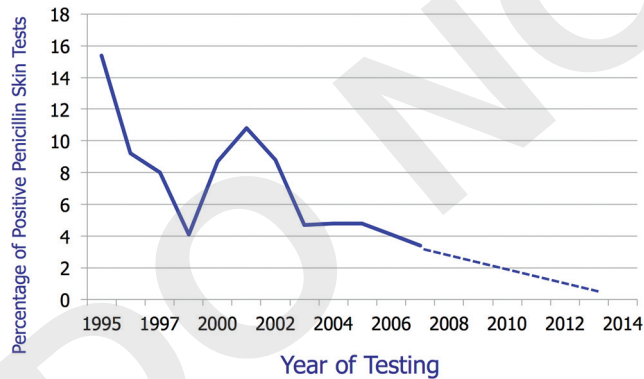


Figure 2. The decline in positive penicillin skin test results based on data from Kaiser Permanente studies.

Recently, several studies demonstrated that having a label of penicillin allergy (which in most cases is false) is associated with morbidity. Large case-control studies both in the United States and United Kingdom that involved >50,000 patients labeled as penicillin allergic, found higher rates of infections with MSSA, vancomycin-resistant enterococcus (VRE), and *Clostridium difficile*.^{9,20} In addition, prolonged hospitalizations, higher readmissions, and higher surgical-site infections have been found in patients labeled penicillin allergic. A recent study demonstrated that a label of penicillin allergy was associated with a higher risk of all-cause mortality.²¹ Studies from the United States and other countries have also shown that a label of penicillin allergy results in higher cost medical care.²² Several studies have also demonstrated that removing this penicillin allergy label can result in cost savings, with the largest study demonstrating a reduction of \$1915 per patient per year.²³

METHODS FOR DELABELING PENICILLIN ALLERGY

There are multiple methods that can be used to delabel patients of a penicillin allergy (Table 1). This process can occur both in outpatient and inpatient settings, including the intensive care unit. Although, historically, this has been the purview of allergy and immunology specialists only, many other health-care specialists are becoming involved in the delabeling process. The reagents of penicillin skin testing vary for different studies. In addition, delabeling may not always require penicillin skin testing.

Penicillin Skin Tests

Penicillin is metabolized to different metabolites, including the minor determinants penicilloate and penil- loate. Because penicillin is a hapten, it can be conjugated to a larger molecule (polylysine) to make it more immu- nogenic. Penicilloyl-polylysine is known as the major de- terminant of penicillin and is commercially available as Pre-Pen (AllerQuest LLC, Plainville, CT). The minor

Table 1 Methods to delabel penicillin allergy

Setting	Method	Comment
Outpatient	Referral based skin test and challenge	With or without minor determinant mixture
	Direct challenge	Low-risk history
	Protocol driven	Allergy clinic; other clinics
Inpatient	Allergy consultation	Least efficient
	Proactive testing protocol	Pharmacists or other health-care providers
	Intensive care unit testing	Skin testing
	Emergency department	Skin testing or challenge by nonallergy spe- cialists or other healthcare providers

determinants of benzylpenicillin that are considered most important are benzylpenicillin, benzylpenilloate, and benzylpenicilloate. Collectively, these are referred to as the minor determinant mixture (MDM). It is important to note that the only minor determinant that currently is commercially available in the United States is benzylpenicillin. Early large studies of penicillin skin testing by using the major determinant and MDM evaluated patients with a history of penicillin allergy, including patients with anaphylaxis, and found the negative predictive value to be 98%.^{24,25} Anaphylactic reactions after negative penicillin testing results to the full complement of determinants is rare.

In Europe and Australia, a high percentage of patients who are penicillin allergic are selectively sensitized to aminopenicillins not benzylpenicillin and are detected through skin testing with high concentrations of amoxicillin. Such aminopenicillin selective reactors are rare in the United States. Given the lack of a commercially available MDM, most U.S. allergists skin test with the major determinant and benzylpenicillin, followed by an amoxicillin challenge to exclude any aminopenicillin sensitivities. Similarly, high negative predictive values (98%) have been shown with this testing strategy, with the caveat being a very low prevalence of true penicillin allergy and a very low enrichment of patients who are anaphylactic.¹⁵ Recently, a multicenter U.S. study of a penicillin skin test kit that contained both major and minor determinants as well as amoxicillin evaluated 455 patients with a “convincing” history of penicillin allergy.²⁶ A higher rate of positive skin test results were seen in this group (13.8%), but the negative predictive value was 97.9%, similar to older studies. Furthermore, 6.3% had positive test results to amoxicillin alone. Because oral challenges were not performed in patients with positive skin test result results, it is unknown how many of these were false positives. This penicillin skin test kit has been submitted to the U.S. Food and Drug Administration for approval.

Direct Penicillin Challenge without Penicillin Skin Testing

Drug challenges are considered the reference standard for determining tolerance to a drug. A single full-dose penicillin challenge can be performed in patients with an extremely low likelihood of reacting and is recommended for those patients labeled with penicillin allergy but whose history was not consistent with a drug allergy (*e.g.*, headache, nausea, family history of penicillin allergy) or after negative penicillin skin testing results.¹⁹ Given the low prevalence of penicillin allergy, particularly in children, several studies have now looked at a diagnostic approach, starting with a graded penicillin challenge without preceding penicillin skin testing. Mill *et al.*²⁷ performed graded amoxicillin

challenges in 818 consecutive children with reactions to amoxicillin (excluding anaphylaxis or severe cutaneous adverse reactions). Only 2.1% had immediate reactions, and 3.8% had delayed reactions, and most all reactions were mild, with no need for epinephrine.²⁷

Several other direct penicillin challenge studies have been performed, predominately in children, and demonstrated similar levels of efficacy and safety in delabeling.²⁸ Direct penicillin challenge has also been shown to be an efficient way to delabel patients during routine office visits to an allergy clinic for other indications.²⁹ A recent randomized controlled trial evaluated 159 patients and children at low risk to either penicillin skin test and challenge or direct penicillin challenge.³⁰ More patients were delabeled (96.2%) after direct challenge than after skin tests (87.5%), and reactions to direct challenge were mild. Nearly all of these studies were performed by allergy specialists. Although some studies have used this approach in adults, larger studies are needed before this approach can be widely recommended.

PROACTIVE PENICILLIN ALLERGY DELABELING

Many national organizations have recommended evaluating unconfirmed penicillin allergy as part of antimicrobial stewardship efforts, including the American Academy of Allergy, Asthma & Immunology, the Infectious Diseases Society of America, and the Society for Healthcare Epidemiology of America. Approximately 10% of the U.S. population (approximately 30 million patients) are labeled as being allergic to penicillin. Yet, there are <5000 board certified allergists in the United States. Thus, there are clearly not enough allergy specialists to evaluate all patients with penicillin allergy. Due to these unmet needs, many innovative strategies have been developed.

Inpatient Penicillin Allergy Testing

Performing penicillin allergy evaluations on inpatients is most commonly achieved by consulting an allergy service. However, many hospitals do not have access to allergists willing to perform penicillin testing. A recent systematic review identified 24 studies, including 6 in which testing was performed exclusively in the intensive care unit.³¹ The population weighted mean of a negative penicillin skin test result in the inpatient setting was 95%, similar to outpatient testing. Changes in use of beta-lactams also increased in these studies with higher percentage changes in the intensive care unit cohort.

At Parkland Hospital in Dallas, a penicillin allergy testing service was developed in November 2014. The Parkland Pharmacy Department received funding from a Medicaid 1115 waiver and with close collaboration

with the University of Texas Southwestern Division of Allergy and Immunology, protocols were developed, and a dedicated allergy pharmacist was trained in history taking and penicillin skin testing. Filters were developed within the electronic medical record to identify inpatients labeled as allergic to penicillin and patients were screened with a number of factors, including current use of antibiotics, use of carbapenems or monobactams, and comorbid diseases, to identify those patients who would benefit most from a penicillin allergy evaluation. The initial results of this proactive inpatient penicillin allergy testing program were published in 2017 and resulted in delabeling of 228 patients.³²

Since then, an additional allergy trained pharmacist as well as backup trained pharmacists have continued this program and, to date, >800 patients have been tested, and 98% have had their penicillin allergy label removed. Refinements to this protocol have included the targeting of aztreonam usage, which is predominantly in patients labeled penicillin allergic. A study at Parkland Hospital found that adding a penicillin allergy consult to the aztreonam order set resulted in reduction in use of aztreonam, increased use of penicillin and cephalosporins, and decreased average antibiotic costs from \$1265 to \$592, a 53% savings.³³ Advantages of an inpatient testing program include ready access to patients who may not be available for outpatient evaluations, immediate changes in antibiotics, and potential antibiotic cost savings.

Outpatient Penicillin Allergy Testing Service Lines

Beta-lactam antibiotics are frequently administered before surgery for surgical prophylaxis, including orthopedic surgeries. Patients with a history of penicillin allergy typically receive vancomycin instead. Programs to identify patients who are penicillin allergic before surgery have been successful in delabeling patients and reducing the need for broad-spectrum antibiotics, *e.g.*, vancomycin. The largest experience with preoperative testing for penicillin allergy comes from the Mayo Clinic, where a preoperative evaluation clinic has been in place since 2001.³⁴ As mentioned previously, this program evaluated >30,000 patients and was able to delabel 99% of them. Other recent programs used electronic best practice alerts to identify patients scheduled for orthopedic surgery and facilitate referral to specialized penicillin allergy clinics.³⁵ Dedicated penicillin allergy testing clinics have been developed as an efficient method for delabeling patients, with some clinics able to evaluate six patients in a half day without the need for increased staff or additional costs.³⁶ Penicillin allergy testing in outpatient clinics has been shown to be quite cost-effective, with a recent study showing that the base

cost of an evaluation that used time-driven activity-based costing was \$227.³⁷

Penicillin Allergy Pathways

Another approach to improve antimicrobial stewardship is the development of algorithms to be used in patients with a history of penicillin allergy. Blumenthal *et al.*³⁸ developed and evaluated a clinical pathway geared toward inpatient practitioners to guide in decision-making and to promote drug challenges when appropriate. Utilization of this pathway did reduce exposure to vancomycin, fluoroquinolones, and aztreonam. Unfortunately this pathway does little to delabel patients of their penicillin allergy but is a useful interim measure. Due to its simplicity, these pathways and other similar ones have been adopted in different countries.³⁹

RISK OF REACQUIRING PENICILLIN ALLERGY AFTER DELABELING

Once a patient has been delabeled of his or her penicillin allergy, this is often not a permanent change. The most common reason that patients reacquire a penicillin allergy label after a negative penicillin allergy testing result is due to inappropriately adding back the allergy to the medical record. In many cases (>20%), even after negative testing results, the medical record is not modified to reflect this.¹⁹ At Parkland, we have been evaluating multiple interventions to prevent the penicillin allergy label from returning, including counseling at the time of testing, post-hospital discharge counseling, best practice advisory pop-up alerts, wallet cards, and chart review and contact of patients, which all led to a <2% rate of penicillin allergy relabeling.⁴⁰

In addition to false relabeling of a penicillin allergy, some patients may reacquire their allergy. Studies that evaluated the risk of resensitization after oral courses of penicillin revealed a very low risk of reacquiring a penicillin allergy.⁴¹ With regard to the risk of reacquiring a penicillin allergy after parenteral courses of penicillin, the data are somewhat mixed. A recent study evaluated 32 inpatients with a history of a penicillin allergy and who had negative penicillin allergy testing results.⁴¹ After their negative test results, they received a total of 111 courses of penicillins and none experienced an immediate reaction. Based on these data, the risk of resensitization even after parenteral penicillin therapy is very low.

EVALUATION OF CEPHALOSPORIN, MACROLIDE, AND QUINOLONE ALLERGY

Cephalosporins

While results of early studies indicate that cross-reactivity with other beta-lactams ranged from 10 to 50%, more recent studies indicate that the risk of cross-

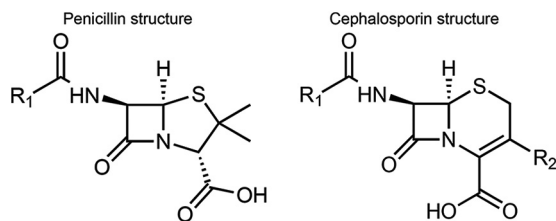


Figure 3. Beta-lactam rings in penicillin and cephalosporins.

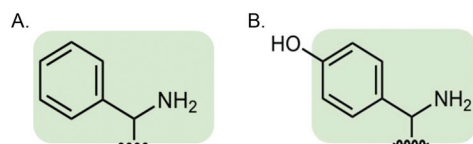


Figure 4. (A) An identical R1 side chain in ampicillin, cefaclor, and cephalexin. (B) an identical R1 side chain in amoxicillin, cefadroxil, and cefprozil.

reactivity is much lower.⁴³ As the name implies, all beta-lactams share a common beta-lactam ring structure (Fig. 3). Although the beta-lactam ring is important for penicillin allergy, it seems to be much less critical for allergic reactions to other beta-lactams. For patients with a benign history of penicillin allergy, the risk of reacting to cephalosporins, including first-generation cephalosporins, is <1%.^{43,44} Data from Kaiser Permanente show similar, very low rates of reactions in patients with an unconfirmed penicillin allergy history and who are administered cephalosporins.⁴⁵ The researchers concluded that *C. difficile* infection was a much greater risk from cephalosporins than allergic reactions in these patients.

In patients with confirmed penicillin allergy, the risk of reacting to cephalosporins seems to be higher. Romano *et al.*⁴⁶ evaluated 128 patients with positive penicillin skin test results and performed cephalosporin skin testing, and, when negative, they challenged to cephalosporins. Of the initial group, 10.9% had positive skin test results to cephalosporins. Of those with negative cephalosporin skin test results, 101 patients (60% with penicillin anaphylaxis) were challenged to cefuroxime and ceftazidime, and all were negative. There is no increased risk of cephalosporin use in patients with negative penicillin allergy skin test results. In contrast, in patients who are confirmed allergic to cephalosporins, there seems to be a higher risk (25%) of being sensitized to penicillins. Whether there is clinical reactivity is not known. Some of this risk can be explained through shared R1 side chains between aminopenicillins and cephalosporins, including cefaclor, cephalexin, cefadroxil, and cefprozil (Fig. 4). However, most patients with confirmed cephalosporin allergy who demonstrate sensitization to penicillin *via* skin or *in vitro* tests, the

positive test results are not related to shared R1 side chains.

In patients with primary cephalosporin allergy, 90% of reactions seem to be related to the R1 group. Skin testing to cephalosporins with disparate R1 groups has a high negative predictive value.⁴⁷ In a study of 19 patients with severe anaphylaxis to cefazolin, 100% had negative skin test results to cefalotin (which has a different R1 side chain) and all tolerated the challenge.⁴⁸ Challenges in subjects with positive skin test results to cephalosporins with identical side chains have not been performed. The subject of cephalosporin allergy has recently been comprehensively reviewed.⁴²

Fluoroquinolones

Immunoglobulin E mediated reactions to fluoroquinolones are being reported more frequently. However, immediate reactions in some cases may be due to pseudoallergic reactions caused by activation of the Mas-related G protein-coupled receptor X2 (MRGPRX2) receptor on mast cells.⁵⁰ Skin testing is not reliable due to the high irritant potential for fluoroquinolones, and, thus, drug challenges are recommended for diagnosis.⁵¹ Reactions may not be due to a class effect; however, cross-reactivity patterns among fluoroquinolones are not clear and must be tested on an individual basis.

Macrolides

True macrolide allergy is rare. After evaluation, the vast majority of patients are found to be tolerant. Skin testing has not been shown to be reliable, and drug challenges are recommended.⁵² Patterns of cross-reactivity are variable, but cases of anaphylaxis with cross-reactivity to both azithromycin and clarithromycin have been reported.⁵³

REFERENCES

1. Fleming A. Nobel Lecture Ceremony. 1945.
2. Tan SY, Tatsumura Y. Alexander Fleming (1881–1955): discoverer of penicillin. *Singapore Med J.* 2015; 56:366–367.
3. Fleming A. On the antibacterial action of cultures of a *Penicillium* with special reference to their use in the isolation of *B. influenza*. *Br J Exp Pathol.* 1929; 10:226–236.
4. Gaynes R. The discovery of penicillin—new insights after more than 75 years of clinical use. *Emerg Infect Dis.* 2017; 23:849–853.
5. Chain E, Florey HW, Gardner NG, Heatley NG, Jennings MA, Orr-Ewing J. Penicillin as a chemotherapeutic agent. *Lancet.* 1940; 236:226–228.
6. The Mould in Dr Florey's Coat: Eric Lax. *Abacus.* 2005; 389 pp. ISBN 0-3491-1768-3.
7. Cormia FE, Jacobsen LY, Smith EL. Reactions to penicillin. *Bull U S Army Med Dep.* 1945; 4:694–702.
8. Wilensky AO. Fatal delayed anaphylactic shock after penicillin. *JAMA.* 1946; 131:1384.
9. Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin “allergy” in hospitalized patients: a cohort study. *J Allergy Clin Immunol.* 2014; 133:790–796.

10. Zhou L, Dhopeswarkar N, Blumenthal KG, Goss F, Topaz M, Slight SP, et al. Drug allergies documented in electronic health records of a large healthcare system. *Allergy*. 2016; 71:1305–1313.
11. Dhopeswarkar N, Sheikh A, Doan R, Topaz M, Bates DW, Blumenthal KG. Drug-induced anaphylaxis documented in electronic health records. *J Allergy Clin Immunol Pract*. 2019; 7:103–111.
12. Chiriac AM, Macy E. Large health system databases and drug hypersensitivity. *J Allergy Clin Immunol Pract*. 2019; 7:2125–2131.
13. Sullivan TJ, Wedner HJ, Shatz GS, Yecies LD, Parker CW. Skin testing to detect penicillin allergy. *J Allergy Clin Immunol*. 1981; 68:171–180.
14. Macy E, Schatz M, Lin C, Poon KY. The falling rate of positive penicillin skin tests from 1995 to 2007. *Perm J*. 2009; 13:12–18.
15. 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; 1:258–263.
16. Frigas E, Park MA, Narr BJ, Volcheck GW, Danielson DR, Markus PJ, et al. Preoperative evaluation of patients with history of allergy to penicillin: comparison of 2 models of practice. *Mayo Clin Proc*. 2008; 83:651–662.
17. Tannert LK, Mortz CG, Skov PS, Bindslev-Jensen C. Positive skin test or specific IgE to penicillin does not reliably predict penicillin allergy. *J Allergy Clin Immunol Pract*. 2017; 5:676–683.
18. Chen JR, Khan DA. Evaluation of penicillin allergy in the hospitalized patient: opportunities for antimicrobial stewardship. *Curr Allergy Asthma Rep*. 2017; 17:40.
19. Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and management of penicillin allergy: a review. *JAMA*. 2019; 321:188–199.
20. Blumenthal KG, Lu N, Zhang Y, Li Y, Walensky RP, Choi HK. Risk of methicillin resistant *Staphylococcus aureus* and *Clostridium difficile* in patients with a documented penicillin allergy: population based matched cohort study. *BMJ*. 2018; 361:k2400.
21. Blumenthal KG, Lu N, Zhang Y, Walensky RP, Choi HK. Recorded penicillin allergy and risk of mortality: a population-based matched cohort study. *J Gen Intern Med*. 2019; 34:1685–1687.
22. Mattingly TJ, 2nd, Fulton A, Lumish RA, Williams AMC, Yoon S, Yuen M, et al. The Cost of self-reported Penicillin allergy: A systematic review. *J Allergy Clin Immunol Pract*. 2018; 6:1649–54.e4.
23. Macy E, Shu YH. The effect of penicillin allergy testing on future health care utilization: a matched cohort study. *J Allergy Clin Immunol Pract*. 2017; 5:705–710.
24. Sogn DD, Evans R III, Shepherd GM, Casale TB, Condeemi 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; 152:1025–1032.
25. Gadde J, Spence M, Wheeler B, Adkinson NF Jr. Clinical experience with penicillin skin testing in a large inner-city STD clinic. *JAMA*. 1993; 270:2456–2463.
26. Solensky R, Jacobs J, Lester M, Lieberman P, McCafferty F, Nilsson T, et al. Penicillin allergy evaluation: a prospective, multicenter, open-label evaluation of a comprehensive penicillin skin test kit. *J Allergy Clin Immunol Pract*. 2019; 7:1876–1885.e3.
27. Mill C, Primeau MN, Medoff E, Lejtenyi C, O'Keefe A, Netchiporouk E, et al. Assessing the diagnostic properties of a graded oral provocation challenge for the diagnosis of immediate and nonimmediate reactions to amoxicillin in children. *JAMA Pediatr*. 2016; 170:e160033.
28. Macy E, Vyles D. Who needs penicillin allergy testing?. *Ann Allergy Asthma Immunol*. 2018; 121:523–529.
29. Kuruvilla M, Shih J, Patel K, Scanlon N. Direct oral amoxicillin challenge without preliminary skin testing in adult patients with allergy and at low risk with reported penicillin allergy. *Allergy Asthma Proc*. 2019; 40:57–61.
30. Mustafa SS, Conn K, Ramsey A. Comparing direct challenge to penicillin skin testing for the outpatient evaluation of penicillin allergy: a randomized controlled trial. *J Allergy Clin Immunol Pract*. 2019; 7:2163–2170.
31. Sacco KA, Bates A, Brigham TJ, Imam JS, Burton MC. Clinical outcomes following inpatient penicillin allergy testing: a systematic review and meta-analysis. *Allergy*. 2017; 72:1288–1296.
32. Chen JR, Tarver SA, Alvarez KS, Tran T, Khan DA. A proactive approach to penicillin allergy testing in hospitalized patients. *J Allergy Clin Immunol Pract*. 2017; 5:686–693.
33. Chen JR, Tarver SA, Alvarez KS, Wei W, Khan DA. Improving aztreonam stewardship and cost through a penicillin allergy testing clinical guideline. *Open Forum Infect Dis*. 2018; 5:oky106.
34. Park M, Markus P, Matesic D, Li JT. Safety and effectiveness of a preoperative allergy clinic in decreasing vancomycin use in patients with a history of penicillin allergy. *Ann Allergy Asthma Immunol*. 2006; 97:681–687.
35. McDanel DL, Azar AE, Dowden AM, Murray-Bainer S, Noiseux NO, Willenborg M, et al. Screening for beta-lactam allergy in joint arthroplasty patients to improve surgical prophylaxis practice. *J Arthroplasty*. 2017; 32:S101–S108.
36. Kleris R, Tang M, Radojicic C, Lugar PL. Pricking away at penicillin allergy with a dedicated outpatient clinic. *J Allergy Clin Immunol Pract*. 2019; 7:1358–1359.e1.
37. Blumenthal KG, Li Y, Banerji A, Yun BJ, Long AA, Walensky RP. The cost of penicillin allergy evaluation. *J Allergy Clin Immunol Pract*. 2018; 6:1019–1027.e2.
38. Blumenthal KG, Shenoy ES, Varughese CA, Hurwitz S, Hooper DC, Banerji A. Impact of a clinical guideline for prescribing antibiotics to inpatients reporting penicillin or cephalosporin allergy. *Ann Allergy Asthma Immunol*. 2015; 115:294–300.e2.
39. Chiriac AM, Banerji A, Gruchalla RS, Thong BYH, Wickner P, Mertes PM, et al. Controversies in drug allergy: drug allergy pathways. *J Allergy Clin Immunol Pract*. 2019; 7:46–60.e4.
40. Lutfeali S, Kasra F, Patel S, Joshi S, Tarver SA, Alvarez K, et al. Multiple interventions can reduce rates of false penicillin "allergy" relabeling after negative testing. *J Allergy Clin Immunol*. 2019; 143:AB194.
41. Solensky R, Earl HS, Gruchalla RS. Lack of penicillin resensitization in patients with a history of penicillin allergy after receiving repeated penicillin courses. *Arch Intern Med*. 2002; 162:822–826.
42. Dorman SM, Seth S, Khan DA. Risk of allergic reactions to recurrent intravenous penicillin administration in penicillin skin test negative patients. *J Allergy Clin Immunol Pract*. 2018; 6:196–200.
43. Khan DA, Banerji A, Bernstein JA, Bilgicir B, Blumenthal K, Castells M, et al. Cephalosporin allergy: current understanding and future challenges. *J Allergy Clin Immunol Pract*. 2019; 7:2105–2114.
44. Daulat S, Solensky R, Earl HS, Casey W, Gruchalla RS. Safety of cephalosporin administration to patients with histories of penicillin allergy. *J Allergy Clin Immunol*. 2004; 113:1220–1222.
45. Goodman EJ, Morgan MJ, Johnson PA, Nichols BA, Denk N, Gold BB. Cephalosporins can be given to penicillin-allergic patients who do not exhibit an anaphylactic response. *J Clin Anesth*. 2001; 13:561–564.

46. Macy E, Contreras R. Adverse reactions associated with oral and parenteral use of cephalosporins: a retrospective population-based analysis. *J Allergy Clin Immunol*. 2015; 135:745–752.e5.
47. Romano A, Guéant-Rodriguez RM, Viola M, Pettinato R, Guéant JL. Cross-reactivity and tolerability of cephalosporins in patients with immediate hypersensitivity to penicillins. *Ann Intern Med*. 2004; 141:16–22.
48. Romano A, Gaeta F, Valluzzi RL, Maggioletti M, Zaffiro A, Caruso C, et al. IgE-mediated hypersensitivity to cephalosporins: cross-reactivity and tolerability of alternative cephalosporins. *J Allergy Clin Immunol*. 2015; 136:685–691.e3.
49. Sadleir PH, Clarke RC, Platt PR. Cefalotin as antimicrobial prophylaxis in patients with known intraoperative anaphylaxis to cefazolin. *Br J Anaesth*. 2016; 117:464–469.
50. McNeil BD, Pundir P, Meeker S, Han L, Undem BJ, Kulka M, et al. Identification of a mast-cell-specific receptor crucial for pseudo-allergic drug reactions. *Nature*. 2015; 519:237–241.
51. Doña I, Moreno E, Pérez-Sánchez N, Andreu I, Hernández Fernandez de Rojas D, Torres MJ. Update on quinolone allergy. *Curr Allergy Asthma Rep*. 2017; 17:56.
52. Kuruvilla M. Macrolide allergy. In: Khan DA, Banerji A, editors. *Drug allergy testing*. St Louis, MO: Elsevier, 2017; p. 129–136.
53. Swamy N, Laurie SA, Ruiz-Huidobro E, Khan DA. Successful clarithromycin desensitization in a multiple macrolide-allergic patient. *Ann Allergy Asthma Immunol*. 2010; 105:489–490. □

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