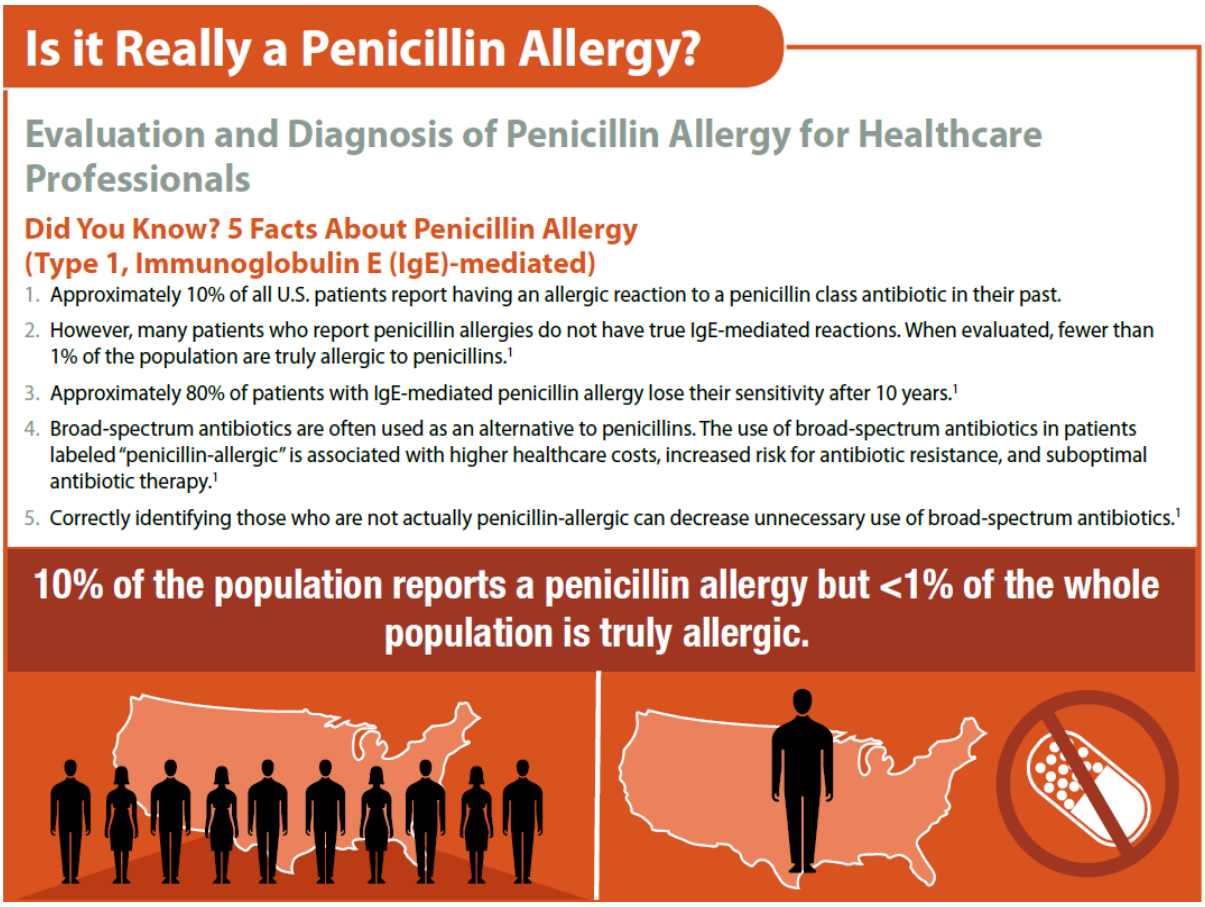
TACKLING THE EPIDEMIC OF THE PENICILLIN ALLERGY LABEL



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This is to acknowledge that David Khan, M.D. has disclosed that he does not have any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Khan will not be discussing off-label uses in his presentation.

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Dr. Khan has been the Program Director for the Allergy & Immunology fellowship program for over 20 years. He has been involved with writing practice guidelines for the specialty of Allergy & Immunology for 15 years. His research interests include, drug allergy, therapies for refractory chronic urticaria, and the interaction of depression and asthma.

Purpose and Overview: The purpose of this lecture will be to review the epidemiology, immunopathology, and associated morbidity of penicillin allergy. Current diagnostic testing strategies as well as recommendations for risk stratification of patients with penicillin allergy will be discussed.

Educational Objectives:

1. Be able to discuss the morbidity associated with a label of penicillin allergy.
2. Be able to discuss the key elements in taking a history of a patient with a penicillin allergy.
3. Gain an understanding of the diagnostic approaches and their success in de-labeling patients with penicillin allergy.
4. Be able to discuss the indications and limitations of penicillin desensitization.

History of the Discovery of Penicillin

The story behind the discovery of penicillin is a fascinating one and worth discussing in some detail. Alexander Fleming was born on August 6, 1881 in Scotland (Figure 1). Eventually he moved to London and worked initially 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 1922, while infected with a cold, he transferred some of his nasal mucus to a Petri dish. He left it on his laboratory desk for several weeks during which time numerous colonies of bacteria proliferated. He later found the dish and observed that the area where the mucus had been inoculated remained clear. Through further studies he was able to identify a substance in the mucus that inhibited bacterial growth and he named it lysozyme. He discovered lysozyme in tears, saliva, skin, hair, fingernails and egg white. In his Nobel acceptance speech he noted that "A thick milky suspension of bacteria could be completely cleared in a few seconds by a fraction of a drop of human tears or egg white."[1]

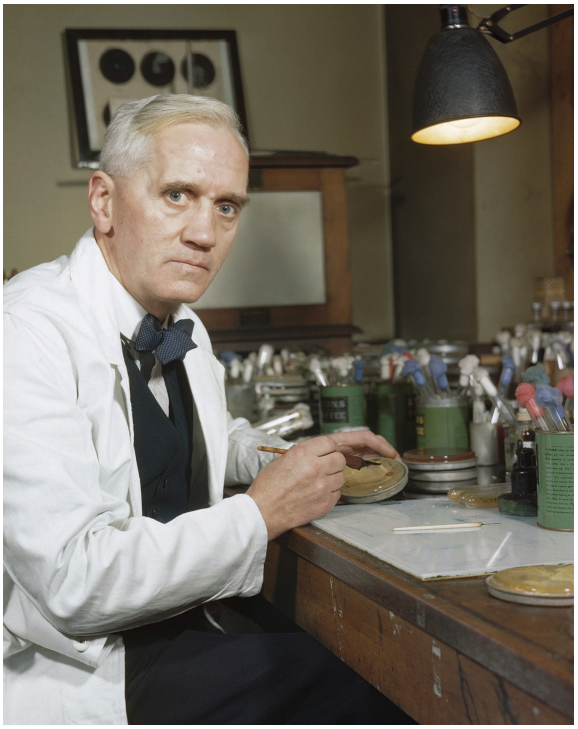


Figure 1. Sir Alexander Fleming who discovered penicillin.

In 1928 Fleming began experiments involving staphylococcal bacteria. During one of these experiments an uncovered petri dish was left next to an open window and 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." 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. (Figure 2).

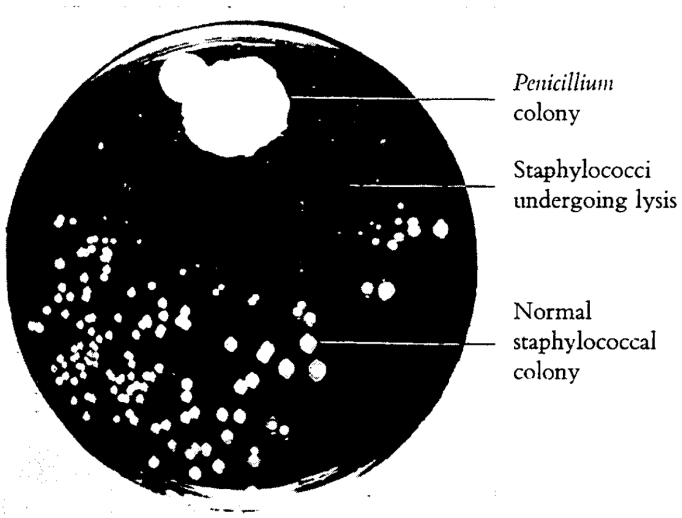


Fig. 1. Photograph of a culture-plate showing the dissolution of staphylococcal colonies in the neighbourhood of a *Penicillium* colony.

Figure 2. Photograph of one of Fleming's culture plates showing lysis of staphylococcal colonies around a *Penicillium* colony. From Alexander Fleming's Nobel Speech.

He noted that the antibacterial properties were not due 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*." While his work was published in 1929 it received little attention.[3] Fleming noted it was very difficult to concentrate penicillin.

In the 1930s with the introduction of sulfonamide antibiotics, there was renewed interest in penicillin and Dr. Chain and Sir Howard Florey in 1939 began a systematic investigation of antibacterial substances reduced by microorganisms. Chain found Flemings 1929 article on penicillin and proposed to his supervisor Florey that he try to isolate the compound.[4] They initially studied lysozyme but later, worked on penicillin. Florey assembled a team who worked on growing large amounts of *Penicillium* (led by Norman Heatley a fungal expert) and Chain successfully purified penicillin from an extract of the mold. On May 25, 1939 the group injected eight mice with a virulent strain of *Streptococcus*; 4 were injected with penicillin and all lived, and 4 control mice all died. Chain called the results "a miracle". They published their findings in the Lancet in August 1940 describing the production, purification, and experimental use of penicillin to protect animals infected with several bacteria.[5] On February 12th 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 one month later.

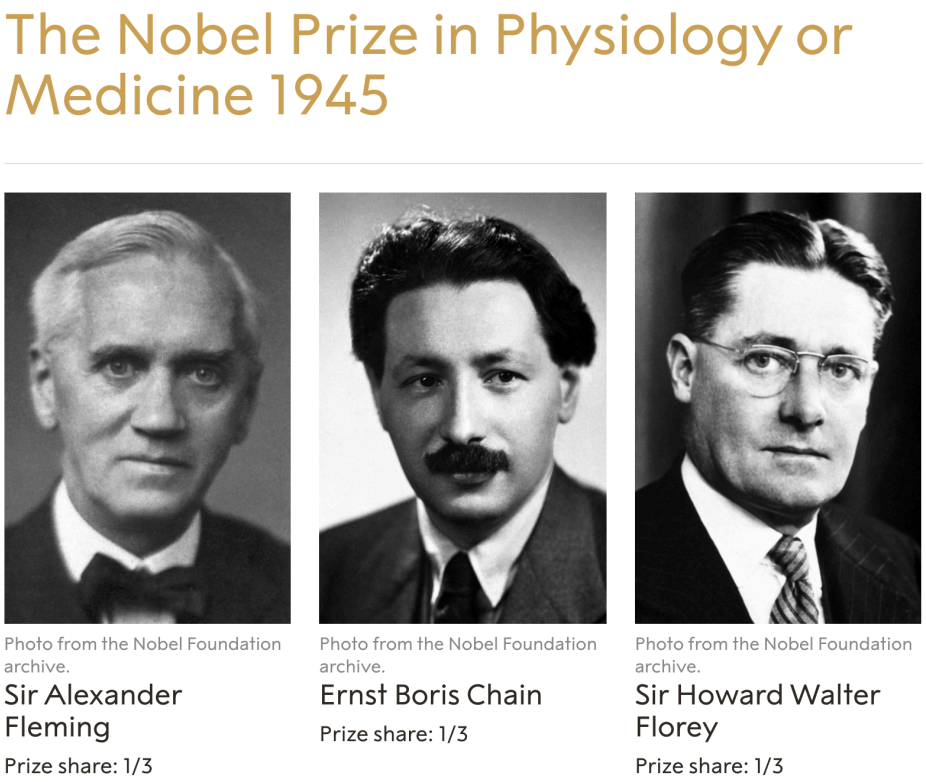


Figure 3: Nobel winners “for the discovery of penicillin and its curative effect in various infectious diseases”.

In June 1941, Florey and Heatley travelled to the US smearing their coats with the *Penicillium* strain for safety, rather than taking a precious vial that could have been stolen. In a short period of time there was unprecedented cooperation between the US and Great Britain for penicillin production. In 1941 the US did not have enough stock of penicillin to treat a single patient but by 1943 had enough to satisfy the demands of the Allied Armed Forces. 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 (Figure 3).

Epidemiology of Penicillin Allergy

Shortly after penicillin was used as a therapeutic agent, allergic reactions were noted and the first fatality from anaphylaxis was reported in 1945. Penicillin remains the most common drug listed as an allergy in medical records (Figure 4). Recent studies of large populations in the US have shown that 11 to 12% of patients have a label of penicillin allergy in their health record.[6, 7] Penicillin is also a leading cause of drug-induced anaphylaxis. A recent U.S. study of a large

electronic health record database of over 1.7 million patients determined that 1.1% reported drug-induced anaphylaxis, with the most common culprit being penicillin.[8] Penicillin is also the most commonly identified drug causing fatal drug induced anaphylaxis.

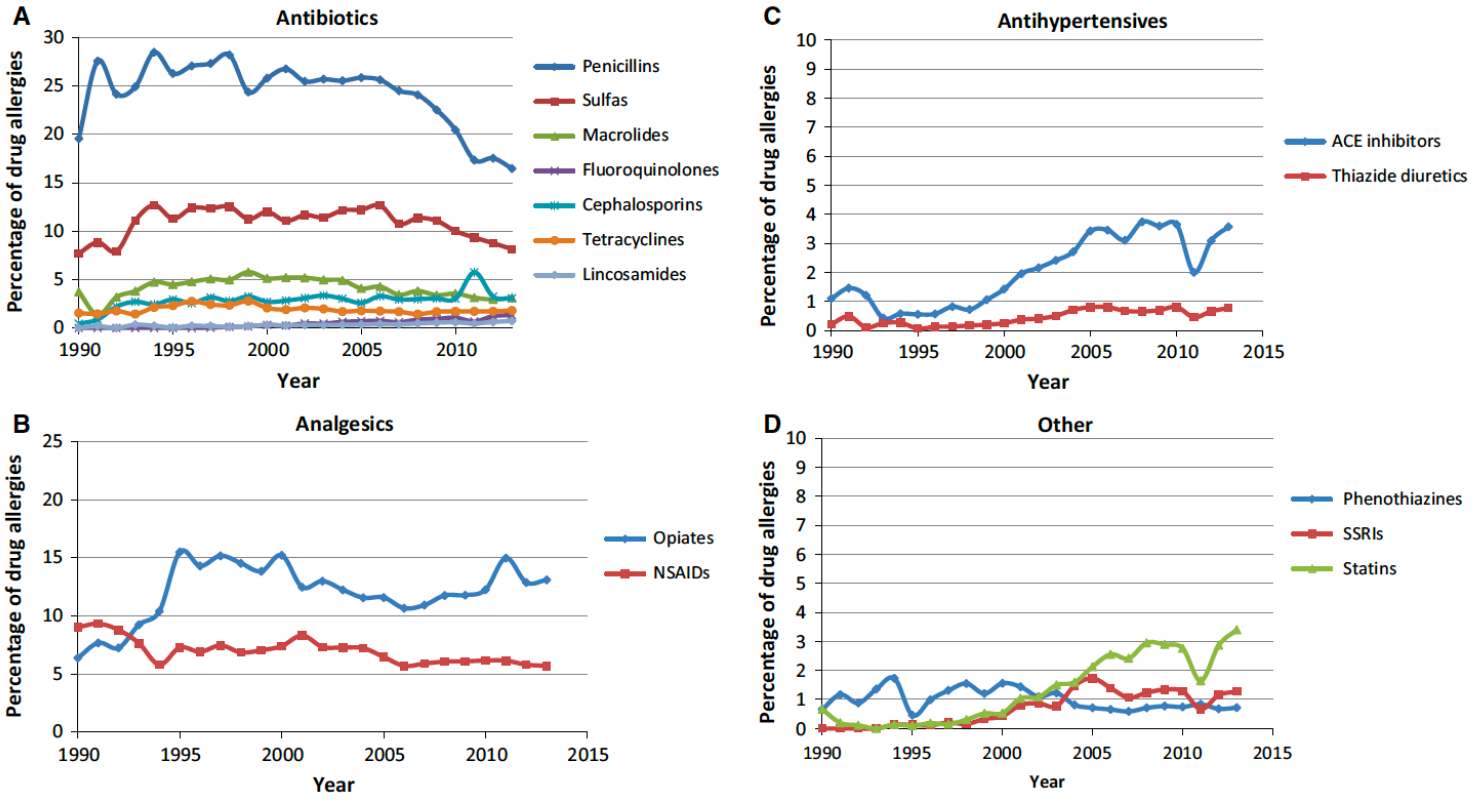


Figure 4. Frequency of reported drug allergies in a large U.S. health database.[7]

Low Prevalence of Confirmed Penicillin Allergy in Patients Labeled as Penicillin Allergic

While penicillin allergy is a very commonly listed drug allergy in the medical record, confirmed penicillin allergy is much lower and appears to have declined over time. Some studies from the early 1970's found that more than 50% of patients with histories of penicillin allergy were positive on penicillin skin testing. Longitudinal studies from Kaiser Permanente in Southern California found the rate of positive penicillin skin tests to have decreased from 15% in 1995, to 3% in 2007, and <1% in 2013. The largest data on penicillin skin testing comes from Mayo Clinic with a total of 30,883 patients with histories of penicillin allergy who have undergone penicillin skin testing and only 1% have been found to be positive (personal communication with Miguel Park).

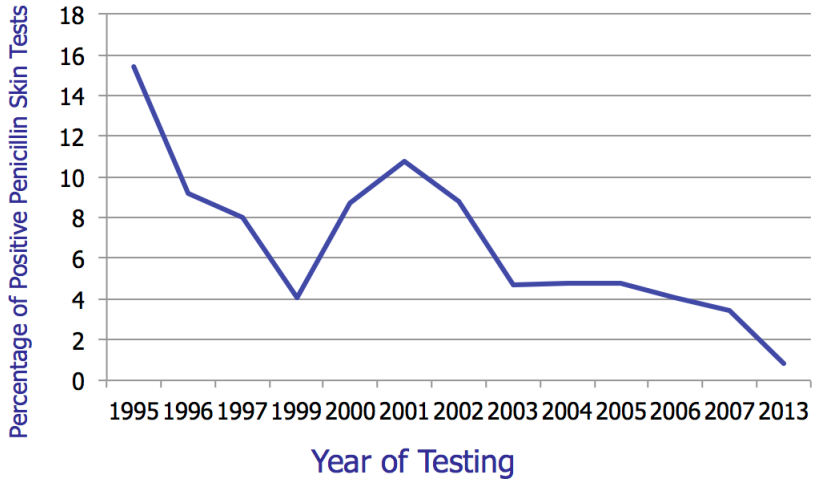


Figure 5. Decline in positive penicillin skin tests based on data from Kaiser Permanente studies.

Why are so many patients labeled with "penicillin allergy" not really allergic?

While there are multiple reasons for the false label of penicillin allergy, there are likely two key issues. One is that patients were falsely labeled with penicillin allergy in the first place. The second reason is that patients may lose their allergy overtime.

The most common manifestation for drug allergies is rashes. Whenever a patient develops a rash on a medication, especially an antibiotic, it is quite common for them to be labeled with an allergy. However not all rashes in the setting of antibiotic use are due to a drug allergy. This is especially true in children who frequently get exanthema from viral infections. The best evidence for this comes from a study from Switzerland that prospectively evaluated children who developed rashes in association with beta-lactam therapy.[9] At the time of their rashes, serologies for viruses were performed as well as throat swabs for PCR testing for common respiratory viruses. Eight-eight children were evaluated two months later for beta-lactam allergy through skin testing and drug challenge. More than 93% of children had no evidence for a confirmed drug allergy when tested two months after their rash. However, more than 50% had a positive viral PCR test. In the few children who had confirmed positive penicillin challenges, infection with EBV was common. The results of this study confirm that most acute rashes attributed to penicillin in children are not drug related.

The natural history of documented penicillin allergy is that it wanes overtime. An often-quoted study from the early 1980s found that 78% of patients who were tested more than 10 years after their reaction to penicillin were negative. However these patients were never initially tested to confirm their penicillin allergy.[10] Prospective studies in patients confirmed to be allergic to penicillins by skin testing have shown a decline in positivity with approximately 50% becoming skin test negative after five years (Figure 6).[11] Similar studies have shown a decline in skin test positivity in patients allergic to cephalosporins. Therefore over time, it is expected that patients will lose penicillin specific IgE in those who truly were allergic in the first place.

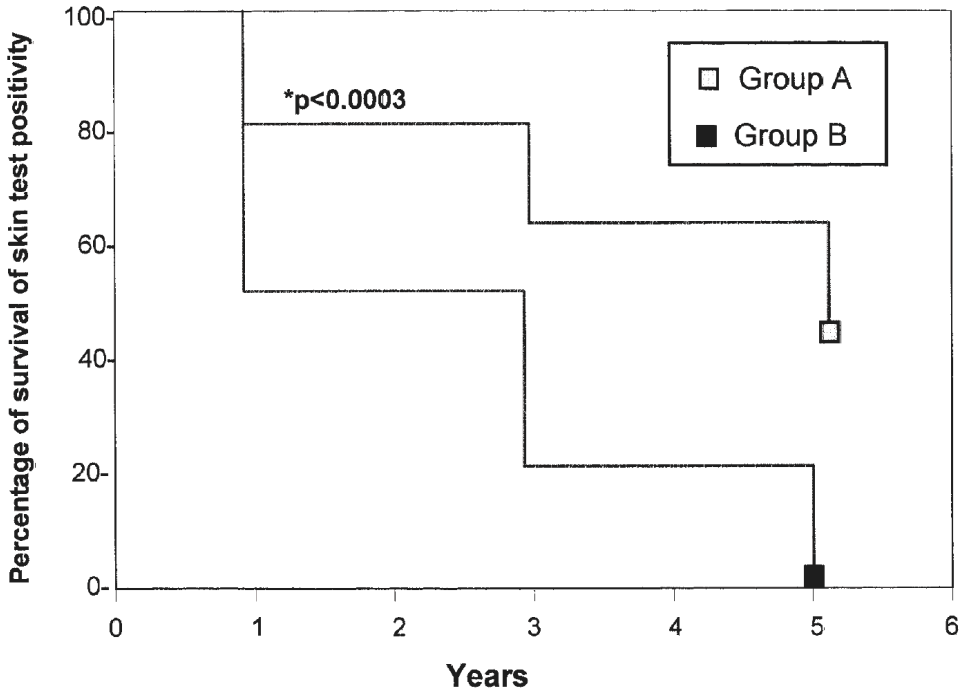


Figure 6. Natural decline over time in positive penicillin skin tests (Group A) or positive aminopenicillin skin tests (Group B).

Why do we care about a penicillin allergy label?

While numerous antibiotics are available, penicillin remains the drug of choice for several infections (Figure 7). Patients with MSSA bacteremia have a lower 30-day mortality when receiving beta-lactam therapy compared to vancomycin. There is also a higher rate of clinical failure for blood stream infections with gram-negative bacilli when using non-beta-lactam antibiotics. Decision analysis models have determined that patients with MSSA bacteremia have worse outcomes if treated with vancomycin instead of being evaluated for penicillin allergy.[12] Benzathine penicillin remains the treatment of choice for patients with syphilis.

Recently, several studies have 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 involving more than 50,000 patients labeled as penicillin allergic, have found higher rates of infections with MSSA, VRE, and C. difficile.[6, 13] In addition, prolonged hospitalizations, higher readmissions, and higher surgical site infections have been found in patients labeled penicillin allergic. Studies from the United States and other countries have also shown that a label of penicillin allergy results in higher cost medical care. 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.[14]

Table 1. Pathogens and Common Syndromes for Which β-Lactams Are Considered the Treatment of Choice

Organism	Examples
Group A *Streptococcus*	Pharyngitis, skin and soft tissue infections (cellulitis, erysipelas, pyoderma), necrotizing fasciitis, myositis, acute rheumatic fever, acute glomerulonephritis, pneumonia, postpartum endometritis, toxic shock syndrome, bacteremia
Group B *Streptococcus*	Meningitis, puerperal sepsis
Viridans group streptococci and *Streptococcus gallolyticus* (bovis)	Endocarditis
Listeria monocytogenes	Meningitis
Actinomyces spp	Cervicofacial, pelvic, and respiratory infections
Cutibacterium acnes (formerly *Propionobacterium acnes*)	Bone and joint and central nervous system shunt infections
Staphylococcus aureus	Skin and soft tissue, bone and joint, and respiratory tract infections[a]
Pasteurella multocida	Skin and soft tissue infections, bacteremia, and respiratory tract infections
Neisseria gonorrhoeae	Urethritis, epididymitis, pharyngitis, conjunctivitis, cervicitis, proctitis, disseminated disease (septic arthritis, endocarditis)
Neisseria meningitidis	Meningitis
Treponema pallidum (syphilis)	Primary syphilis (chancre), secondary syphilis (rash, condylomata lata), tertiary syphilis (aortitis), meningitis

Figure 7. Pathogens and infectious illnesses where beta-lactams or penicillin are the drug of choice.[12]

Given that the label of penicillin allergy is associated with higher morbidity and higher cost and that the majority of patients are falsely labeled, this is certainly an area for needed interventions. In 2017, the CDC released a fact sheet (shown on the cover) with a subtitle “Is It Really a Penicillin Allergy?” This fact sheet reinforced the low frequency of true penicillin allergy, the associated morbidity, and recommended penicillin allergy evaluations.

Immunopathology of Penicillin Allergy

Penicillins, like most drugs, are small molecules that act as haptens and need to bind to proteins in plasma to form immunogenic hapten-protein complexes. Penicillin hypersensitivity can manifest in several ways with different underlying immunologic mechanisms (Figure 8). Type I IgE-mediated reactions are one of the more common types of penicillin hypersensitivity. These reactions typically occur within minutes to a few hours after exposure to penicillin. They manifest as a spectrum of signs and symptoms with the most common being urticaria and/or angioedema and the least common but most severe, anaphylaxis. Type II antibody-mediated cytotoxic reactions may result in hemolytic anemia or thrombocytopenia. Type III immune complex reactions result in serum sickness like reactions (SSLR). These reactions are characterized by

rashes, fever, and arthralgia. As opposed to true serum sickness reactions, renal dysfunction, vasculitis, and hypocomplementemia are rare and SSLR generally have a benign course.

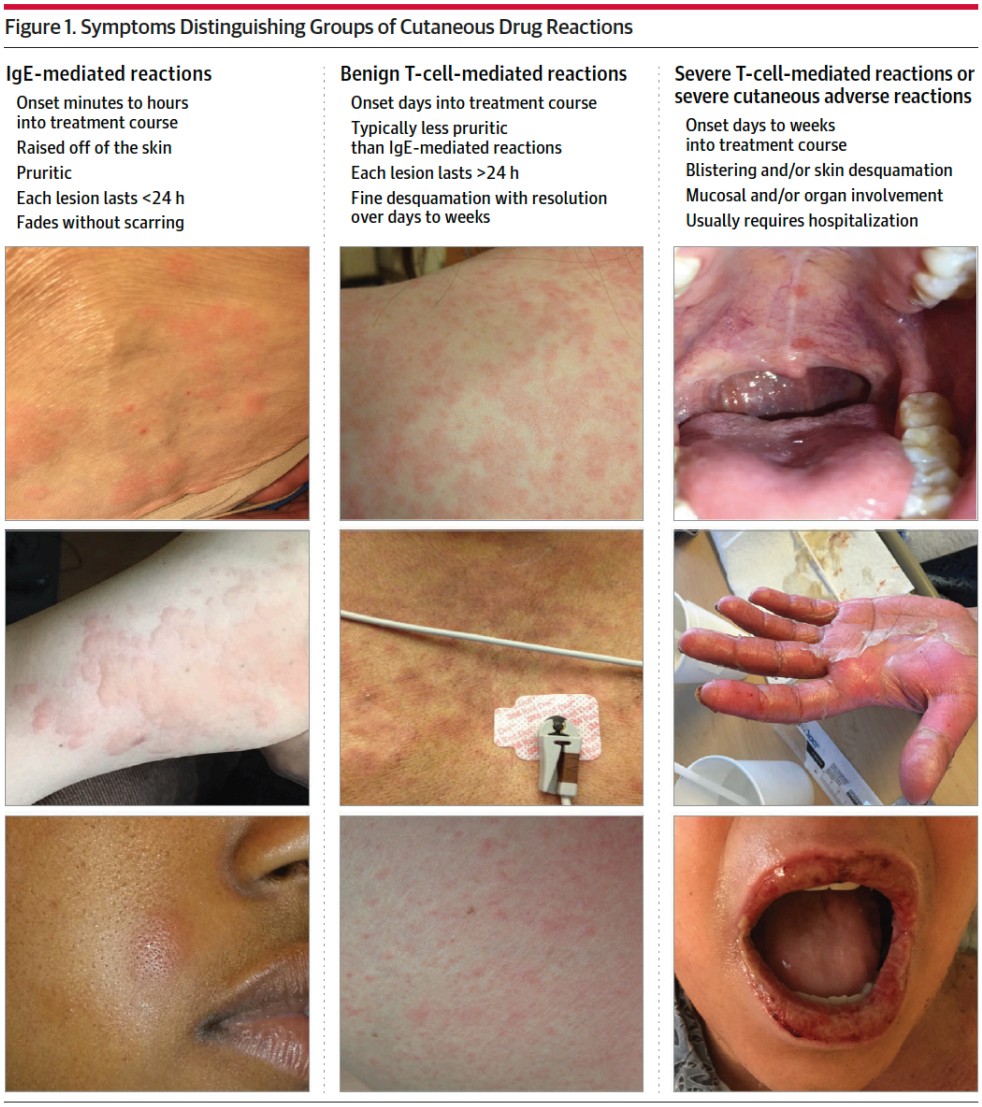


Figure 8. Clinical features of benign and severe penicillin hypersensitivities.[12]

Delayed hypersensitivity reactions to penicillin generally evolve over a period of days and are likely due to penicillin specific T cell-mediated reactions. The most common delayed hypersensitivity reaction is a benign exanthema (maculopapular rash). These rashes generally begin on the trunk and spread in a symmetric fashion to the extremities and are pruritic. With resolution, exanthema may cause some skin scaling analogous to a sunburn. Other delayed cutaneous reactions include fixed drug eruptions, leukocytoclastic vasculitis, and bullous reactions. Severe cutaneous adverse reactions (SCAR) are relatively infrequent with penicillins with the exception of acute generalized exanthematous pustulosis (AGEP) of which aminopenicillins are a relatively common cause. Since penicillins are such a commonly used antibiotic, they are frequently implicated as causes of SCAR reactions but whether they are truly the culprit or merely an innocent bystander is often less clear.

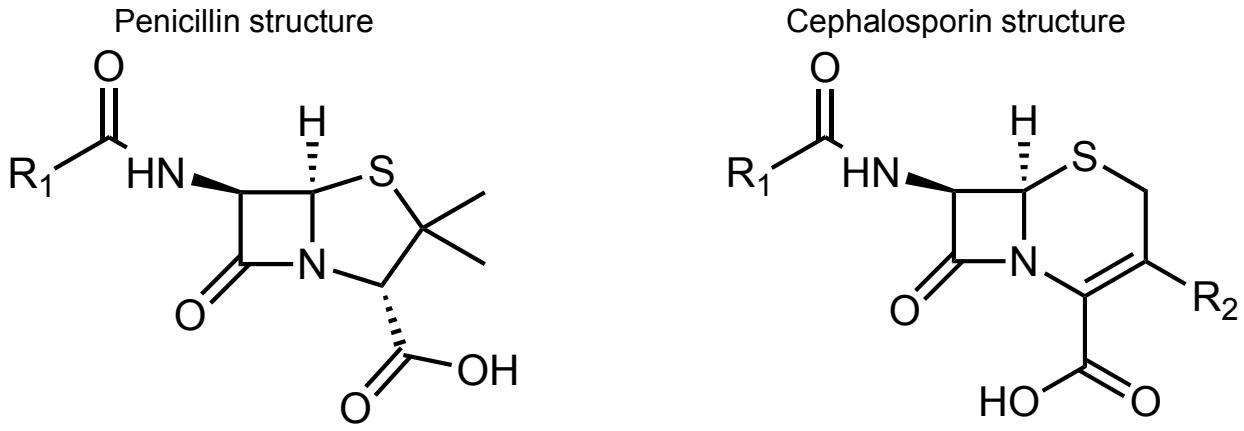
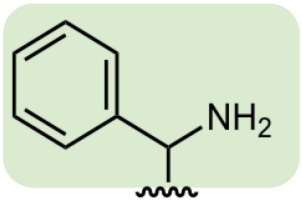


Figure 9. Beta-lactam rings in penicillin and cephalosporins.

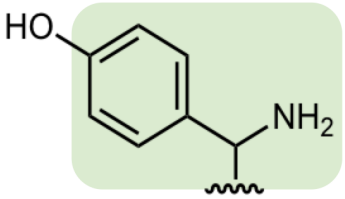
Cross-Reactivity with other Beta-Lactams

While early studies suggested that cross reactivity with other beta lactams ranged from 10 to 50%, more recent studies have indicated that the risk of cross-reactivity is much lower. As the name implies, all beta-lactams share a common beta-lactam ring structure (Figure 9). While the beta-lactam ring is important for penicillin allergy, it appears to be much less critical for allergic reactions to other beta-lactams. For patients with benign histories of penicillin allergy, the risk of reacting to cephalosporins, including first-generation cephalosporins, is less than 1%. A retrospective study conducted at Parkland analyzed data for 606 inpatients who were prescribed 685 courses of cephalosporins.[15] Only one patient was noted to have a mild worsening of underlying eczema after cefazolin therapy. However it was noted that Parkland pharmacists would deny use of cephalosporin in patients with more severe allergic histories (e.g. anaphylaxis). Studies from Kaiser have shown similar, very low rates of reactions in patients with unconfirmed penicillin allergy histories who are administered cephalosporins.[16] The authors concluded that *C. difficile* infection was a much greater risk from cephalosporins then allergic reactions in these patients.

In patients with confirmed penicillin allergy, the risk of reacting to cephalosporins appears to be higher. Romano et al. evaluated 128 patients with positive penicillin skin tests and performed cephalosporin skin testing and when negative, they challenged to cephalosporins. Of the initial group, 10.9% had positive skin tests to cephalosporins. Of those with negative cephalosporin skin tests, 101 patients (60% with penicillin anaphylaxis) were challenged to cefuroxime and ceftazidime and all were negative. Overall this data suggests that in patients with unconfirmed and benign penicillin allergies, the risk of reacting to any generation cephalosporin is quite low and likely similar to the general population (1-3%). There is no increased risk of cephalosporin use in patients with negative penicillin allergy skin tests.



R1 side chain in ampicillin, cefaclor and cephalexin



R1 side chain in amoxicillin, cefadroxil and cefprozil

Figure 10. Shared R1 side chains of aminopenicillins and specific cephalosporins. While not identical, there is likely clinical cross-reactivity amongst these beta-lactams.

In contrast, in patients who are confirmed allergic to cephalosporins, there appears to be a higher risk (25%) of being sensitized to penicillins.[17] 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 (Figure 10). However most patients with confirmed cephalosporin allergy who demonstrate sensitization to penicillin via skin or *in vitro* tests, the positive tests are not related to shared R1 side chains.

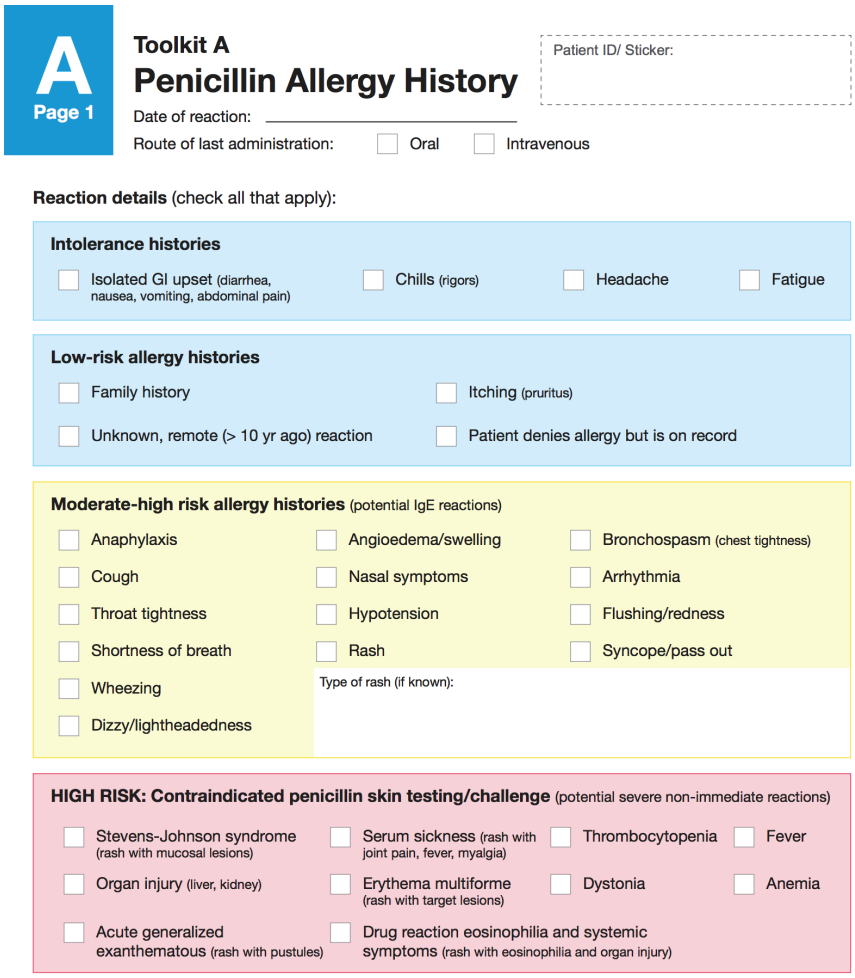
In regards to cross-reactivity between penicillin allergic subjects and carbapenems, the risk is exceedingly low. Romano and colleagues have prospectively studied over 600 patients with documented penicillin allergy (the majority with anaphylaxis) and less than 1% had a positive skin test to carbapenems.[18] All patients with negative skin tests tolerated the carbapenem. Most patients with unconfirmed penicillin allergy can receive carbapenems via a graded dose challenge beginning with 1/10th of the dose followed 30 minutes later by the rest of the therapeutic dose. Lastly there is no increased risk of administering aztreonam in patients who are confirmed allergic to penicillin.

Diagnosis of Penicillin Allergy

History Taking

Diagnostic strategies for penicillin allergy like most drug allergies begin with a careful history. The history will guide the choice of testing and other procedures. There are several important aspects to a good drug allergy history (Figure 11). A description of the signs and symptoms associated with penicillin therapy is essential. One of the first steps is to determine whether the history is even consistent with a drug allergic reaction versus an intolerance. Symptoms of headache, isolated gastrointestinal symptoms, or subjective chills are not consistent with an allergy history. A family history of a penicillin allergy is not a risk factor. Drug rashes are the most common presentation for penicillin allergy but unfortunately most patients and many

providers cannot accurately distinguish urticaria from other benign exanthema. Most drug hypersensitivity rashes should be pruritic. In my opinion, showing different pictures of rashes to patients is usually not particularly helpful either. Knowing when the reaction occurred in association with drug exposure can be helpful but this information is usually lacking. Objective findings such as rash, angioedema, hypotension, hypoxia are all much more convincing of a true allergy rather than isolated itching or throat tightness. Patients with isolated throat tightness without documented orofacial angioedema are much more likely to have drug associated vocal cord dysfunction (not a true allergy) then laryngeal edema.



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Toolkit A

Penicillin Allergy History

Patient ID/ Sticker:

Date of reaction: _____

Route of last administration: ☐ Oral ☐ Intravenous

Reaction details (check all that apply):

Intolerance histories

☐ Isolated GI upset (diarrhea, nausea, vomiting, abdominal pain) ☐ Chills (rigors) ☐ Headache ☐ Fatigue

Low-risk allergy histories

☐ Family history ☐ Itching (pruritus)

☐ Unknown, remote (> 10 yr ago) reaction ☐ Patient denies allergy but is on record

Moderate-high risk allergy histories (potential IgE reactions)

☐ Anaphylaxis ☐ Angioedema/swelling ☐ Bronchospasm (chest tightness)

☐ Cough ☐ Nasal symptoms ☐ Arrhythmia

☐ Throat tightness ☐ Hypotension ☐ Flushing/redness

☐ Shortness of breath ☐ Rash ☐ Syncope/pass out

☐ Wheezing Type of rash (if known):

☐ Dizzy/lightheadedness

HIGH RISK: Contraindicated penicillin skin testing/challenge (potential severe non-immediate reactions)

☐ Stevens-Johnson syndrome (rash with mucosal lesions) ☐ Serum sickness (rash with joint pain, fever, myalgia) ☐ Thrombocytopenia ☐ Fever

☐ Organ injury (liver, kidney) ☐ Erythema multiforme (rash with target lesions) ☐ Dystonia ☐ Anemia

☐ Acute generalized exanthematous (rash with pustules) ☐ Drug reaction eosinophilia and systemic symptoms (rash with eosinophilia and organ injury)

Figure 11. Sample penicillin allergy history tool to aid in decision-making.[12]

The history is also important in determining which patients cannot be evaluated through allergy testing of any kind. Drug hypersensitivity reactions that are single organ based such as drug induced liver injury, cytopenias or pneumonitis are not amenable to penicillin allergy evaluation. SCAR such as SJS/TEN, DRESS, and AGEP currently do not have accurate tests with reliable negative predictive value and therefore penicillin allergy evaluation cannot be performed. While in general, serum sickness like reactions are often not evaluated, many children who have had SSLR to penicillins can be challenged, and many will be found to tolerate penicillins.

Penicillin Skin Tests

Penicillin skin testing has been in use since the 1960s. Penicillin is metabolized to different metabolites including the minor determinants penicilloate and penilloate. Since penicillin is a hapten, it can be conjugated to a larger molecule (polylysine) to make it more immunogenic. Penicilloyl-polylysine is known as the major determinant of penicillin and is commercially available as PREPEN®. The minor 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 is commercially available is benzylpenicillin. Early large studies of penicillin skin testing using the major determininant and MDM evaluated patients with histories of penicillin allergy, including patients with anaphylaxis, and found the negative predictive value to be 98%. Anaphylactic reactions following negative penicillin testing to the full complement of determinants is rare. In Europe and Australia, a high percentage of penicillin allergic patients 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 US. Given the lack of a commercially available MDM, most US 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 anaphylactic patients. An example of a positive penicillin skin test with wheal and flare response is shown below (Figure 12).

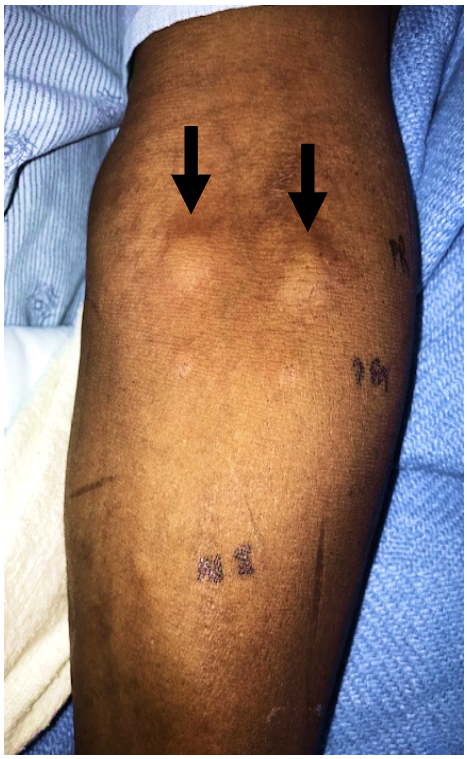

Figure 12. Positive penicillin skin test to major determinant (arrows). Photo courtesy of Felicia DiLoreto, Pharm.D.

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 histories are not consistent with a drug allergy (e.g. headache, nausea, family history of penicillin allergy) or after negative penicillin skin testing. A graded penicillin challenge is performed starting with a lower dose such as 1/10th of a therapeutic dose followed 30-60 minutes by a full therapeutic dose. Compared to penicillin skin testing, graded penicillin challenges are simple to perform and do not require expertise and proficiency in penicillin allergy skin testing. 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. performed graded amoxicillin challenges in 818 consecutive children with reactions to amoxicillin (excluding anaphylaxis or SCAR). Only 2.1% had a immediate reactions and 3.8% had delayed reactions and most all were mild with no need for epinephrine (Figure 13).[19] Several other direct penicillin challenge studies have been performed, predominately in children demonstrating similar levels of efficacy and safety in de-labeling. Nearly all of these studies have been performed by allergy specialists. While some studies have used this approach in adults, larger studies are needed before this approach can be widely implemented.

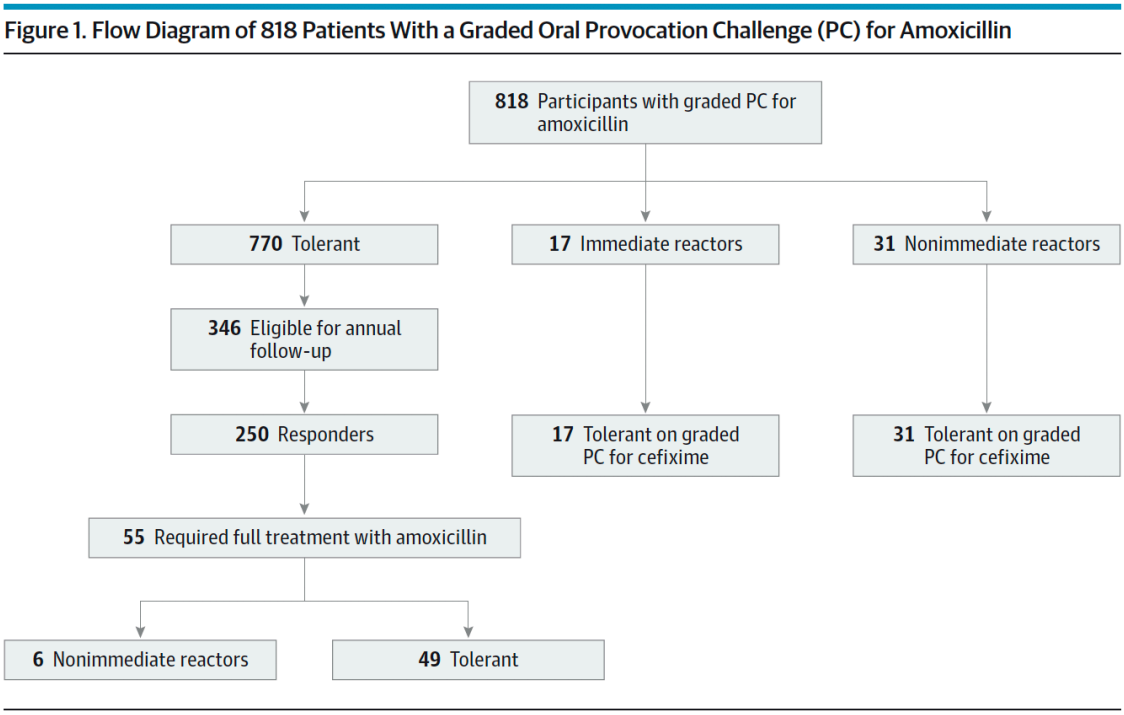

Figure 13. Outcomes of direct graded amoxicillin challenges in children with non-anaphylactic reactions to amoxicillin. Overall 94% tolerated the challenge.[19]

Approaches to De-labeling Penicillin Allergy

Many national organizations have recommended evaluating unconfirmed penicillin allergy as part of antimicrobial stewardship efforts including the American Academy of Allergy, Asthma, and Immunology (AAAAI), the Infectious Diseases Society of America (IDSA), and the Society for Healthcare Epidemiology of America (SHEA). Approximately 10% of the US population, (30 million patients) are labeled as being allergic to penicillin. Yet there are less then 5000 board certified allergists in the US. 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 six where testing was performed exclusively in the intensive care unit.[20] The population weighted mean of a negative penicillin skin test in the inpatient setting was 95%, similar to outpatient testing. Changes in use of beta lactams also increased in these studies with higher percent changes in the ICU cohort.

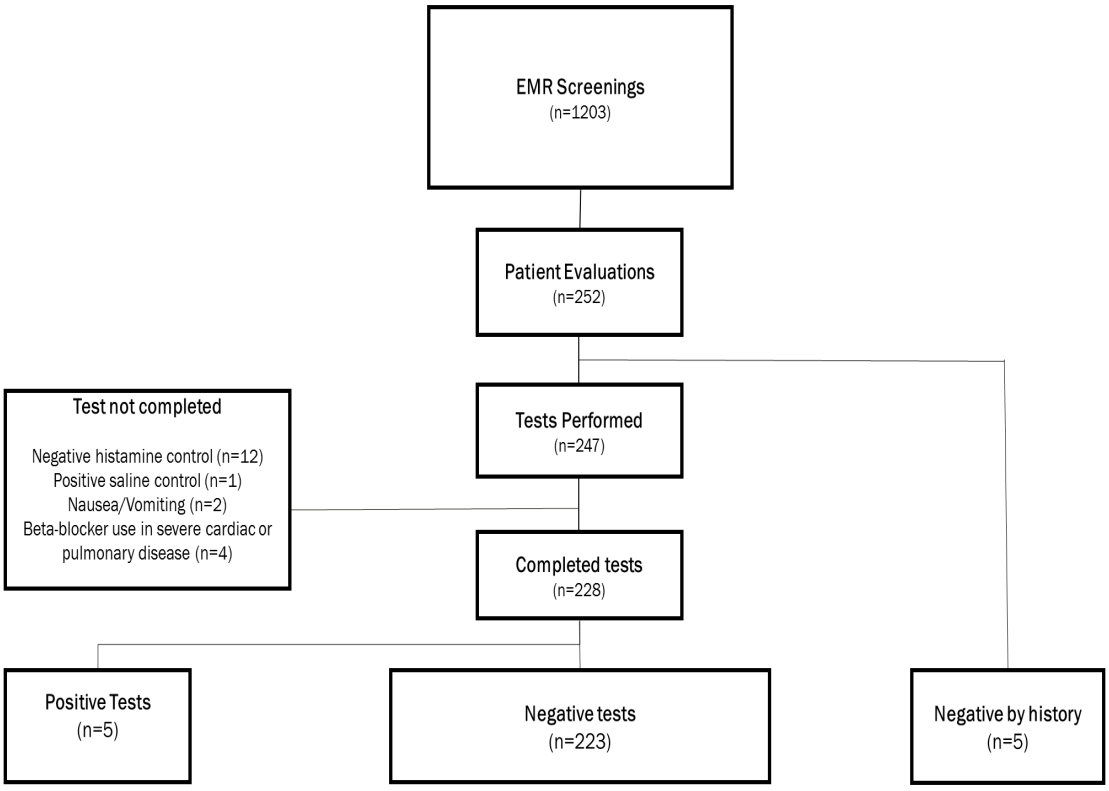

Figure 14. Early results from a program of proactive penicillin allergy testing at Parkland using dedicated allergy-trained pharmacists. Of tested individuals, 98% were de-labeled. Note 5 patients were de-labeled just by chart review.[21]

At Parkland Hospital 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 UT 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 EPIC 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 (Figure 14). Since then an additional allergy trained pharmacist, as well as back-up trained pharmacists have continued this program and to date more than 700 patients have been tested, and 98% have had their penicillin allergy label removed. Several other US centers have developed similar programs based on our success at Parkland. 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 projected direct cost savings of 82 to 92%.[22] 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 preoperatively for surgical prophylaxis including orthopedic surgeries. Patients with a history of penicillin allergy typically receive vancomycin instead. Programs to identify penicillin allergic patients preoperatively have been successful in de-labeling patients and reducing the need for broad-spectrum antibiotics such as 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.[23] As mentioned previously, this program has evaluated over 30,000 patients and has been able to de-label 99% of them. Other recent programs have utilized electronic best practice alerts to identify patients scheduled for orthopedic surgery and facilitate referral to specialized penicillin allergy clinics.[24] Dedicated penicillin allergy testing clinics have been developed as an efficient method for de-labeling patients with some clinics able to evaluate six patients in a half day without need for increased staff or additional costs.[25] 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 using time-driven activity-based costing was $227.[26]

Penicillin Allergy Pathways

Another approach to improve antimicrobial stewardship is the development of algorithms to be used in patients with histories of penicillin allergy. Blumenthal and colleagues have developed and evaluated a clinical pathway geared towards inpatient practitioners to guide in decision-making and promote drug challenges when appropriate (Figure 15).[27] Utilization of this pathway did reduce exposure to vancomycin, fluoroquinolones, and aztreonam. Unfortunately this pathway does little to de-label 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.[28]

Figure 15. Clinical guideline for antibiotics in penicillin allergic inpatients.[27]

Risk of Reacquiring Penicillin Allergy after De-labeling

Once a patient has been de-labeled of their penicillin allergy this is often not a permanent change. The most common reason patients reacquire a penicillin allergy label after negative penicillin allergy testing is due to inappropriately adding back the allergy to the medical record. In many cases (> 20%) even after negative testing the medical record is not modified to reflect this.[12] 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, all leading to a <2% rate of penicillin allergy relabeling.[29]

In addition to false relabeling of penicillin allergy, some patients may reacquire their allergy. Studies evaluating the risk of resensitization following oral courses of penicillin have revealed a very low risk of re-acquiring a penicillin allergy.[30] Regarding the risk of re-acquiring penicillin allergy following parenteral courses of penicillin the data is somewhat mixed. A recent study evaluated 32 Parkland inpatients with histories of penicillin allergy that had negative penicillin allergy testing.[31] Following their negative tests they received a total of 111 courses of penicillins and none experienced an immediate reaction (Figure 16). Based on this data, we feel the risk of resensitization even after parenteral penicillin therapy is very low.

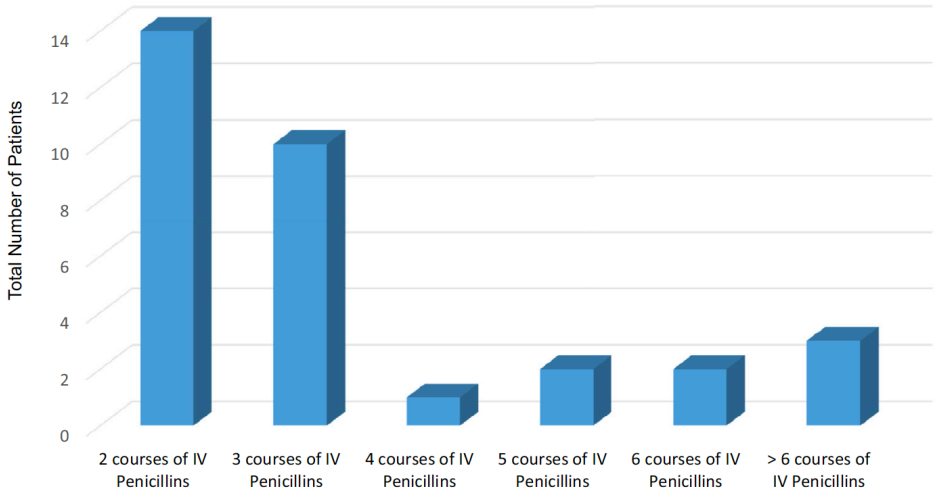

Figure 16: Individual courses of penicillins following negative penicillin allergy tests. No immediate reactions occurred after 111 courses.[31]

Penicillin Desensitization

For patients proven to be penicillin allergic or in patients with a high risk of penicillin allergy (e.g. recent anaphylaxis) who require penicillin therapy, rapid penicillin desensitization can be performed. Drug desensitizations are procedures that induce a temporary state of tolerance so that a patient may safely receive penicillin therapy. Penicillin desensitizations may be performed orally or intravenously. The initial dose is typically 1/10,000th of the final dose and is administering in doubling doses every 15 minutes (Figure 17). Immediate reactions during penicillin desensitizations occur in ~10% of patients and are typically mild, and ~ 30% of patients may have immunologic reactions during therapy most commonly urticaria.[32] However, after penicillin therapy is discontinued, the patient will lose their state of tolerance. Thus these procedures do not “cure” patients of their penicillin allergy and if penicillin is required again, another desensitization procedure would be needed. For patients in need of benzathine penicillin for syphilis, these long acting injections may be safely administered up to 3 weeks following desensitization.[33] We generally avoid “empiric” penicillin desensitizations as it may lead to unnecessary desensitizations and it is best to prove or disprove a penicillin allergy.

Table 1. Schedule for oral penicillin desensitization: administer penicillin V elixir orally every 15 minutes

Dose	Penicillin V, *units/mL*	Dose volume, *mL*	Dose, *units*	Cumulative dose	Record vitals/reaction
1	1000*	0.1	100	100	
2	1000	0.2	200	300	
3	1000	0.4	400	700	
4	1000†	0.8	800	1500	
5	1000	1.6	1600	3100	
6	1000	3.2	3200	6300	
7	1000	6.4	6400	12,700	
8	10000‡	1.2	12,000	24,700	
9	10,000	2.4	24,000	48,700	
10	10,000	4.8	48,000	96,700	
11	80,000§	1.0	80,000	176,000	
12	80,000	2.0	160,000	336,700	
13	80,000	4.0	320,000	656,700	
14	80,000	8.0	640,000	1,296,700	

Total time: 3 hours, 45 minutes; total dose: 1.3 million units; total volume: 36.1 mL.
*One (1)—1-cc syringe filled with 1000 units/mL penicillin V elixir
†Two (2)—10-cc syringe filled with 1000 units/mL penicillin V elixir
‡One (1)—10-cc syringe filled with 10,000 units/mL penicillin V elixir
§One (1)—20-cc syringe filled with 80,000 units/mL penicillin V elixir
Use penicillin V elixir 250 mg/mL = 80,000 units/mL (1 mg = 1600 units).
To make 10,000 units/mL penicillin V solution: add 2 mL of 80,000 units/mL to 14 mL of normal saline.
To make 1000 units/mL penicillin V solution: add 2 mL of 10,000 units/mL to 18 mL of normal saline.

Figure 17. Oral penicillin desensitization protocol.[34]

What Can You Do to Address Penicillin Allergy?

As mentioned previously, allergy specialists alone (including at UTSW) are not capable of de-labeling all false penicillin allergy labels. However, there are several steps that all healthcare providers can take to assist in this endeavor. When entering a penicillin allergy into the medical record, make sure it actually is an allergy. For intolerances to penicillin it's important to note this in the allergy field. In patients who already carry a label of penicillin allergy, the first step in the de-labeling process is to take a history of the reaction. Typically in less than a minute, one can risk stratify a patient for appropriate next steps. If you can document the patient has taken any form of penicillin since their label of penicillin allergy (e.g. amoxicillin, ticarcillin, etc) one can simply delete the allergy label from the medical record. This does not require an allergist! In patients deemed to be of low risk (family history of penicillin allergy, symptoms of an intolerance, remote and unknown reactions) a direct challenge with amoxicillin can be performed. For higher risk patients, referral for penicillin allergy testing may be appropriate. However, some type of stratification based on benefit should be considered. Patients who are likely in need of penicillin therapies, those with significant comorbid diseases, potential transplant recipients and other considerations should prioritize which patients should be referred. Ultimately, establishment of various service lines for outpatients and inpatients is needed to effectively tackle this epidemic. Hospital administrators need to be aware of the importance of de-labeling penicillin allergic patients so that appropriate resources can be leveraged. Ongoing research will help determine what is the safest, cost-effective and most efficient method to de-label penicillin allergic patients.

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