The Evolution of Our Understanding of Penicillin Allergy: 1942-2022

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This article reviews our evolving understanding of penicillin hypersensitivity at the 80th anniversary of penicillin's clinical introduction. Penicillin breakdown products covalently bond to serum proteins, leading to classic drug hypersensitivity. Penicillin remains the most frequently reported drug "allergy." Adverse reactions were presumed, in retrospect incorrectly, to implicate a risk for anaphylaxis, and therefore skin testing for IgE became the focus. Skin test positivity may wane over time. This insight has led to the radical conclusion that penicillin hypersensitivity may not be "forever." Atopic background, other drug allergies, family history, gender, and race are apparently not risk factors for penicillin hypersensitivity. Confirmed penicillin hypersensitivity has declined since the 1960s, potentially due to "cleaner" penicillin products and lower dose oral, instead of parenteral, use. Avoiding penicillins, without evaluation, caused unanticipated problems that have been appreciated only recently including longer hospital stays, increased cost of care, suboptimal outcomes from serious infections, and greater toxicities and costs with alternative antibiotics. There are personal and public health advantages with broadly implemented penicillin allergy delabeling based on a reaction history—based risk assessment. Limited skin testing followed by an oral challenge, if negative, for higher-risk histories, and direct oral challenges in lower-risk individuals are currently the reference standard tests to confirm current tolerance. © 2022 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2023;11:405-13)

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Currently, approximately 10% of individuals using health care in the United States report a penicillin allergy, yet more than 95% would tolerate an oral challenge with a therapeutic dose.[1] A reported penicillin allergy is more likely in hospitalized or a high utilizing patients, those with more life-time exposures to penicillins, particularly parenteral, those with other drug intolerances, the elderly, and in females.[2] A reported penicillin allergy makes a new allergy with every other related or unrelated antibiotic exposure more likely.[3]

There is a predictable population-based rate of new penicillin "allergy" reports per course.[4] In average patients, a new penicillin allergy is reported within 30 days after approximately 0.5% of all penicillin-class antibiotic courses.[5] Only approximately 1%-2% of individuals reporting a penicillin allergy currently will be confirmed to have an active clinically significant IgE-mediated allergy, and an additional 1%-2% will have a, typically benign, delayed-onset rash most consistent with T-cell—mediated hypersensitivity.[6] Removing a penicillin allergy label, "delabeling," can be done by the review of clinical history and if needed appropriate testing.[6] Penicillin allergy delabeled individuals, based on a negative oral challenge, are still at least twice as likely to report a new allergy with any future penicillin use. But avoiding penicillins, when they are the treatment of choice, is associated with vastly greater morbidity.[7-9] Penicillin-associated anaphylaxis is currently extremely rare, occurring in only approximately 1 in 255,000 oral and 1 in 124,000 parenteral exposures.[5] Penicillin-associated serious cutaneous adverse reactions (SCARs) are even rarer. There were no deaths from penicillin-associated anaphylaxis identified in a greater than 37-million patient-year cohort reviewed from Kaiser Permanente Southern California between 2009 and 2017.[5]

SETTING THE STAGE: 1940-1950

Though penicillin was initially discovered by Alexander Fleming in 1928 at Saint Mary's Hospital in London, his student Cecil George Paine first used penicillin clinically.[10,11] Penicillin spontaneously hydrolyzes in aqueous phase and is very susceptible to destruction by a variety of penicillinases if there are contaminating bacteria present during production.[12] This made production of clinically useful quantities initially very difficult. Penicillin was first produced and concentrated in clinically useful quantities by a large research team led by Howard Florey and Ernst Boris Chain at the University of Oxford in 1940.[13] Fleming first personally used penicillin to treat a case of Streptococcal meningitis in 1942.[14] Fleming, Florey, and Chain received the Nobel Prize in Physiology or Medicine in 1945 "for the discovery of penicillin and its curative effect in various infectious diseases."[15]

Grossman[16] reminisced on his involvement with one of the first uses of penicillin, in a civilian in the United States, when his group treated a patient with β-hemolytic Streptococcus sepsis on March 12, 1942. "We discussed what to do with the pungent, brown-red powder. We decided to dissolve it in saline and pass it through an E.K. Seitz [asbestos] filter pad to sterilize it," wrote his co-worker Tager in 1976.[16] In England, at the same time, the

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Abbreviations used
CI- Confidence interval
CVID- Common variable immunodeficiency
FDA- Food and Drug Administration
MDM- Minor determinate mixture
OR- Odds ratio
PPL- Penicilloyl-polylysine
SCAR- Serious cutaneous adverse reaction
SSLR- Serum sickness–like reaction

semipurified penicillin was often yellowish.[13] Crystalline penicillin is colorless, and the contaminating materials present in early penicillin preparations are suspected to have contributed to many of the early, immunologically, and nonimmunologically mediated side effects.[13]

Keefer et al's[17] writing for the Committee on Chemotherapeutic and Other Agents of the National Research Council in 1943 reported on the outcomes of 500 of the first individuals treated with penicillin. Overall, they noted what they felt was relatively low toxicity and a low incidence of systemic adverse reactions. Penicillin preparations in the early 1940s contained 10%-15% penicillin. Urticarial eruptions occurred in 14 (2.8%). Urticaria could occur immediately or up to several days after treatment. It did not always recur with repeat exposures. There were other rarer cases of potential hypersensitivity, transient throbbing head pain, facial flushing, testicular tingling, muscular pain, and chest constriction. These complaints typically lasted for minutes and disappeared spontaneously. They postulated that impurities carried over from the extraction process were responsible for these reactions, including urticaria. Passing penicillin through an asbestos filter reduced the reaction rate, and newer lots of penicillin did not cause as many reactions. Aside from the patients who developed urticaria, they concluded that there were none who developed any signs of a more severe hypersensitivity to penicillin, despite up to 3 courses of treatment.[17]

McClosky and Smith[18] at the National Institutes of Health reported in 1944 the anaphylactic sensitization to penicillin in guinea pigs. Criep[19] at the University of Pittsburg in 1944 was one of the first to document positive penicillin skin-test results in a 23-year-old man with recurrent episodes of acute urticaria after repetitive injections of penicillin.

Suchecki[20] reported in 1946 that there appeared to be higher rates of adverse reactions with subsequent exposures to penicillin. There had been 2 cases of anaphylaxis associated with systemic penicillin administration noted in individuals with multiple exposures, but no deaths up to 1946. Delayed-onset contact dermatitis occurred after 5% to 25% of topical exposures, but this was "less" than with topical sulfonamide antibiotics commonly used during this era.

Gordon[21] noted that by 1946, penicillin use was associated with serum sickness–like reactions (SSLR) in approximately 1 in 1750 exposures. The onset was typically 2 to 7 days after stopping penicillin therapy and generally approximately 10 to 15 days after the start of the course. The clinical symptoms included joint pain, malaise, fever, and occasionally exfoliative dermatitis of the hands. This exfoliative dermatitis would be more likely to be classified now as a SCAR rather than as an SSLR.

In 1946, O'Donovan and Klorfajn[22] reported on oral "desensitization." The patient had been initially exposed to topical penicillin in June 1944. He was re-exposed to topical penicillin in October 1944 and had a rash approximately 2 weeks later. He was re-exposed to topical penicillin again in December 1944 and had a more severe rash that started sooner. Extensive testing with topical penicillin preparations was performed in early 1945, which confirmed what is now known as T-cell–mediated delayed-onset hypersensitivity. He was then given a test dose of 15,000 units of penicillin intramuscularly and had anaphylaxis. Patch testing after the anaphylaxis event confirmed continued delayed-onset hypersensitivity. Small, repeated-dose oral exposures allowed the subject to survive subsequent penicillin exposures, without further anaphylaxis, but still induced severe cutaneous reactions. Peck et al[23] in 1947 described a case of a benign cutaneous delayed-onset, probably T-cell–mediated, reaction to penicillin, which was essentially treated through over a period of several weeks by administering subcutaneous injections of penicillin 3 times a week. Garai[24] reported a similar case in 1949 where that patient was given doses several times daily. None reflect what we now consider to be desensitization to an IgE-mediated allergy.[24]

Lepper et al[25] reported in 1949 that penicillin use had been associated with 2 reported deaths from anaphylaxis and 1 reported death from a SCAR, exfoliative dermatitis. They reported on the adverse reactions noted in 1310 sequential penicillin exposures at a single center, noting in 8 of 29 (27.5%) with previous exposures, but only in 12 of 388 (3.1%) without previous exposures.

William Frankland[26] went to work with Fleming at Saint Mary's in 1946 after being released from a prisoner of war camp. He was reminiscing in 2003 as part of the Allergy Archives project.[26]

> Alexander Fleming was my boss for 2 years when working in the Allergy Department, and I was eventually persuaded [in 1948] to write a chapter on penicillin allergy in the second edition of a very popular multiauthor book on penicillin of which he was the editor. Although I was very friendly with Fleming, he would never accept that penicillin caused allergic problems because he considered that penicillin reactions were caused not by penicillin but by impurities in the penicillin preparations then available. When I wrote a chapter in his book, my conclusions were that "with increasing use of penicillin, allergic reactions would become more common." Fleming made me change this to "the more recent penicillin preparations rarely cause local or general reactions." Who was I to argue and disagree with the discoverer of penicillin?

In retrospect, both were right. By 1950, the high rate of immunologically mediated hypersensitivity reactions associated with early, impure, penicillins was well known. The recognition of the importance of managing these reactions would increase as Franklin correctly noted, and eventually the rate of these reactions would fall with purer preparations as Fleming hoped.

THE IMMUNOLOGY OF PENICILLIN HYPERSENSITIVITY: 1950-1970

In 1955, Berger and Eisen[27] concluded that skin testing with native penicillin was not a reliable way to determine penicillin hypersensitivity. The immunochemistry of penicillin breakdown products was first studied in detail by Bernard Levine and Zoltan

Ovary at the New York University School of Medicine in the late 1950s and extended by Charles W. Parker and associates at Washington University in St. Louis, identifying what are now known as the major determinant, penicilloyl, and the minor determinants (MDM), penicilloate and penicilliloate.[28]

In 1962, Reisman et al[29] in Buffalo, New York, reported one of the first well-documented cases of desensitization in a 27-year-old woman with oral penicillin—associated urticaria and hypersensitivity confirmed by positive native penicillin skin testing.

Parker[30] was one of first to prepare penicilloyl-polylysine (PPL) to mimic the haptenation of the major determinant on serum proteins that occurs *in vivo*. The advantage of the polylysine conjugates over the corresponding protein derivatives for human testing was a lower degree of immunogenicity.

Rytel et al[31] at the Great Lakes Naval Training Center reported in 1963 on the use of PPL to skin-test 1022 naval recruits to determine correlation between skin-test reactions and systemic penicillin allergy. Their criteria for a positive test result were negative (no increase in the size of the original bleb or a wheal less than 8 mm in diameter), weakly positive (definite increase in the size of the original bleb with a wheal 8-12 mm in diameter), and strongly positive (marked increase in the size of the original bleb with a wheal over 12 mm in diameter). Individuals with a history of a penicillin allergy had a 35% incidence of positive skin-test results compared with 6.8% in nonallergic recruits. A strongly positive skin-test result carried an almost 9-fold greater risk of occurrence of a systemic reaction after future penicillin treatment than did a negative skin test. The test was reproducible, and PPL in the dosages employed was nonsensitizing. Parker[30] provided 5.3×10^{-5} molar PPL.

Brown et al[32] noted in 1959 that anaphylaxis, requiring hospitalization, after parenteral penicillin exposures was occurring in their population at a rate of 0.32 per 1000. In 1964, they reported using 0.05 mL of 6×10^{-5} molar PPL for intradermal skin testing in 1003 patients with a history of penicillin sensitivity with 396 (39.4%) positive results, using a wheal of >12 mm as the criteria.[32] Levine[33] reported in 1964 on an improved method of producing PPL.

Rolinson and Sutherland[34] in 1965 noted that although a small proportion of penicillins may be irreversibly bound to human serum, most binding was reversible. Cloxacillin had much higher serum binding than did benzylpenicillin.

Idsoe et al[35] representing the World Health Organization in 1968 reviewed penicillin-associated adverse reactions. They noted that available data did not permit conclusions as to the true frequency of allergic reactions to penicillin that varied from 0.7% to 10% in different studies in different countries. Anaphylaxis may have occurred in 0.015% to 0.004%, with a fatality rate from shock of 0.0015% to 0.002% among treated patients. Thus, the low end of their estimate was 15 deaths from penicillin-induced anaphylaxis for every 1,000,000 individuals treated with penicillin before 1968. They reviewed 151 anaphylactic fatalities reported to have followed penicillin administration noting that 70% had received penicillin previously and 33% had a penicillin allergy history. In most fatal cases, the symptoms leading to death occurred within 15 minutes. They concluded that there was no evidence that the rate of reactions had increased after 1958.

THE REFINEMENTS OF SKIN TESTING FOR PENICILLIN ALLERGY: 1970-1990

At the end of the 1960s and beginning of the 1970s, Adkinson et al[36] at Johns Hopkins noted that 24% of inpatients with a history of penicillin allergy undergoing skin testing with PPL and MDM were positive using 3-mm wheal or 5-mm flare as positive criteria for scratch testing and 5-mm wheal for the positive criteria for intradermal testing. Interestingly, 10 of 152 (6.6%) individuals with no history of a penicillin allergy were also skin-test positive. The Food and Drug Administration (FDA) approved the commercial sale of PPL initially on October 30, 1974. This remains the only FDA-approved penicillin skin-test reagent.[37]

Green et al[38] in 1977 reported the seminal results of multicenter cooperative study of almost 3000 patients by members of the Penicillin Study Group of the American Academy of Allergy using skin tests to penicillin G and PPL for the evaluation of penicillin hypersensitivity. A positive result was defined as a mean diameter of the wheal ≥3 times the control wheal. Positive skin-test results were noted in 326 of 1718 (19%) patients with a history of penicillin allergy versus 86 of 1229 (7%) patients with no such history. The 26 (1.5%) patients with a history of anaphylaxis were much more likely, 46%, to be skin-test positive. There were 9 skin-test-positive patients treated with a therapeutic penicillin and 6 (67%) had a recurrent reaction thought to be possibly mediated by IgE compared with only 10 of the 346 (3%) skin-test-negative patients.

Sullivan et al[39] in Dallas, Texas; St. Louis, Mo; and Stony Brook, NY reported in 1981 on a cohort of 740 patients skin-tested with penicillin G, penicilloic acid, and PPL between 1970 and 1979. The criteria for positive intradermal test results were 1+, greater than the control but smaller than 8 mm in diameter; 2+, a wheal 8 to 12 mm in diameter; 3+, a wheal 12 to 20 mm in diameter; and 4+, a wheal larger than 20 mm in diameter. Overall, 93% were skin-test positive 7 to 12 months after reactions, but only 22% were positive after 10 or more years. In the 85 individuals with therapeutic exposures to penicillin after negative testing, there were 2 (2.4%) with recurrent reactions.

Adkinson et al[40] at Johns Hopkins evaluated a total of 5063 consecutive, qualifying outpatients in a Baltimore, Md, sexually transmitted disease clinic for penicillin hypersensitivity between 1979 and 1984. The study group was young (73% between 20 and 40 years old), 66% male, 90% Black, and 25% had a history of atopy. Penicillin skin testing was performed using PPL and MDM (both prepared and standardized by Schwarz Pharma). Only intradermal testing was performed, and the criterion for a positive test was a wheal ≥5 mm at 20 minutes. Erythema was difficult to read in most of the primarily dark-skinned subjects, so this parameter was not measured. Positive skin tests were observed in 7.1% of 776 (15.3%) individuals with a previous history of penicillin allergy and in 1.7% of 4287 subjects with a negative history of penicillin allergy ($P < .001$).

Sullivan et al[41] at Texas Southwestern Medical Center published a model protocol for oral penicillin desensitization in 1982 that remains the basis for current protocols. They noted that mild cutaneous reactions were common after desensitization during the therapeutic administration and highlighted the

importance of treating through these reactions. Brown et al[42] in 1982 noted that long-term ticarcillin desensitization could be maintained by the continuous oral administration of penicillin, highlighting the immunologic importance of the core penicillin structure.

Mendelson et al[43] in 1984 reported on a group of 240 penicillin-allergic children skin-tested with PPL and MDM. The patients were tested when well, in no immediate need for penicillin, and during a routine office visit. There were 21 (8.8%) who were skin-test positive. All of the skin-test-negative children were given a 10-day course of oral penicillin and 3 (1.4%) had a benign delayed onset rash 7 to 10 days after starting the penicillin. All skin-test-negative patients were then skin-tested again 1 to 9 months after completion of the oral challenge. Only 2 (0.5%), both of whom tolerated the challenge, converted to skin-test positive. This was an important confirmation that the testing and challenge protocol was not sensitizing.

Neftel et al[44] in 1986 finally established the relationship between penicillin degradation byproducts, which spontaneously occur when penicillin is in an aqueous phase, and clinically significant hypersensitivity reactions. They noted that in a case cohort of 193 patients treated with intravenous penicillin-G without special precautions (bolus doses stored up to 36 hours at 4°C or continuous infusions), there were 16 (8.3%) definite, 13 (6.7%) probable, and 27 (14.0%) possible adverse reactions. In a control group of 116 patients treated exclusively with freshly dissolved doses only, there were only 1 (0.9%) definite, 2 (1.7%) probable, and 5 (4.3%) possible adverse reactions. They identified 7 (3.6%) individuals with hemolytic anemia and 12 (6.2%) with neutropenia in the first group and none in the second group. They concluded that degradation and transformation products formed *in vitro* were the causative agents rather than the native penicillin molecule itself. This helps explain the higher rates of sensitizations and hypersensitivity reactions that occur with parenteral penicillin exposures compared with oral exposures.

In 1992, the 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 were published.[45] They used octabenzylpenicilloyl-octalysine as the major determinant and potassium benzylpenicillin, benzylpenicilloate, and benzylpenicilloyl-N-propylamine in an MDM and each also administered individually. The skin-test reagents were produced under the direction of the senior study author, Bernard B. Levine, and manufactured by Pentest Inc, New York, NY. The criteria for a positive skin-test result were determined by measuring the 2 largest diameters of the test reaction in millimeters and recording the average. The results were scored as follows: negative, poorly outlined bleb or puckering without erythema; positive, sharply outlined wheals of 4 to 20 mm with surrounding erythema (1+, 4-6 mm and flare; 2+, 7-9 mm and flare; 3+, 10-12 mm and flare; and 4+, 13 mm with pseudopods and flare); and uninterpretable, wheal and no flare, borderline wheal size, negative histamine control, or positive skin-test to MDM but negative to the components of MDM administered by the same route. They tested 1539 patients at 8 clinical centers with 17 affiliated hospitals, 825 with a history of a penicillin allergy and 714 with no known history of a penicillin allergy. In the history-positive cohort, 146 (18%) were positive, 656 (80%) were negative, and 23 (3%) were uninterpretable. In the history-negative cohort, 29 (4%) were positive, 678 (95%) were negative, and 7 (1%) were uninterpretable. There were 566 history-positive skin-test-negative individuals treated with a therapeutic penicillin, and only 7 had an acute-onset hypersensitivity event. There were 661 history-negative skin-test-negative subjects treated with a therapeutic penicillin, and none had an acute-onset hypersensitivity event.

ELABORATION OF THE NATURAL HISTORY OF PENICILLIN ALLERGY: 1990-2010

Because of the lack of commercially available minor determinates for penicillin skin testing, Macy et al[46] developed an improved method of extraction for penicilloate and penilloate in the mid-1990s, which changed the solvents used during recrystallization, and reported on its clinical use in 1997. Nuclear magnetic resonance and mass spectrometry of the newly produced penicilloate and penilloate showed no evidence of organic contamination. Using the newly produced material, as a part of a panel individual reagents that included PPL, sodium benzylpenicillin (0.01 mol/L), sodium amoxicillin (0.01 mol/L), penilloate (0.01 mol/L), and penicilloate (0.01 mol/L), there were 60 positive test results of the first 348 (17.2%) tested, with 20% of the subjects having positive results only to the newly produced minor determinants. Skin-test-negative individuals were offered a confirmatory oral amoxicillin 250 mg challenge. There were mild acute-onset oral challenge reactions in 11 (5.1%) of 215 (75%) challenged, and mild delayed-onset reactions in 2 (0.9%). Thus overall, 21% of the cohort was determined to be hypersensitive and the number would likely have been slightly higher if all were oral challenged.

Solensky et al[47] at the Texas Southwestern Medical center reported in 2002 on a group of 46 individuals with a history of penicillin allergy who were skin-test negative. They were each given 3 courses of penicillin and had repeat penicillin skin testing after each course. No patients had conversion of their skin-test results to positive.

In 2003, Macy et al[48] provided data on the type, severity, and frequency of adverse reactions associated with oral penicillin use in individuals who had histories of penicillin "allergy" yet also had negative results on penicillin skin testing performed in advance of need. Repeat skin testing was offered to those with penicillin-associated adverse reactions with therapeutic use drawn from a group of 1246 penicillin skin-test-negative individuals tested initially between November 16, 1994, and August 13, 2001. The mean length of follow-up was 4.26 $\pm$ 1.64 years (range, 0.39-7.12 years). The mean number of penicillin exposures was 3.94 $\pm$ 3.91 courses (range, 1-22 courses). Only 65 of 568 (11.4%) subjects had any penicillin-associated reactions, and 6 subjects had 2 reactions each. A reaction occurred in 27 subjects (4.8%) with their first penicillin re-exposure. There were 71 (3.2%) reactions with 2236 total penicillin courses. There were no serious reactions. Repeat penicillin skin testing was performed in 33 subjects $\geq$18 years, and only 1 (3.3%) subject was positive.

Macy et al[49] reported a falling rate of positive penicillin skin-test results, again using a panel of individual reagents including penicillin (0.01 molar), PPL in the form of Pre-Pen or self-produced PPL (6×10^{-5} molar), penicilloate (0.01 molar), penilloate (0.01 molar), and amoxicillin (0.01 molar) at Kaiser Permanente in San Diego between 1995 and 2007. The rate fell from >10% to <5% over the 13 years studied using at least 5-mm wheal with flare > wheal as the criteria for a positive result

on both puncture and intradermal testing. The positive result rate could be accounted for by the year of testing without any significant contribution from the patient's age, gender, or the time since reaction.

Using too small of a wheal, <5 mm, as the criteria for a positive result leads to more false-positive results, primarily in females, most who tolerate oral amoxicillin challenges.

Park et al[50] at the Mayo Clinic in 2007 reported on skin testing 1759 presurgical patients, 998 (56.7%) females, with a history of penicillin allergy between June 1, 2002, and June 30, 2004, using PPL, penicillin G, amoxicillin, and a crude alkaline hydrolysis mix as a source for MDM. Their criterion for a positive result was $\geq 3 \times 3$ mm wheal and flare. Only 64 (4%) had a positive result, but 53 (83%) were females (odds ratio [OR], 3.6; 95% confidence interval [CI], 1.9-7.2; $P = .001$). In a multivariate logistic regression analysis adjusted for age, history of multiple drug allergies, and elapsed time from the index reaction to testing, female sex remained a significant risk (OR, 3.2; 95% CI, 1.6-6.7; $P = .001$). When the criterion for a positive result was corrected to $\geq 5 \times 5$ mm wheal and flare, this gender difference disappeared.[51]

Cetinkaya et al[52] reported in 2007 that occult sensitization to penicillin, documented by positive penicillin skin-test results, developed in hospital nurses who had never noted a reaction associated with a therapeutic penicillin exposure. They concluded that these health care workers might be at increased risk of clinically significant hypersensitivity reactions should they be exposed to penicillins, administered for therapeutic purposes in the future.

The development of comprehensive electronic medical records including pharmacy dispensing data, starting in approximately 2007, revolutionized our understanding of the epidemiology of penicillin allergy and the potential morbidity associated with an unconfirmed penicillin allergy.[3-5,7-9]

The use of *in vitro* testing to identify clinically significant antipenicillin IgE has not been shown to date to be reliable in average individuals with a history of a penicillin allergy because it does not correlate to skin testing or oral challenge results.[53,54]

PENICILLIN ALLERGY EVALUATIONS THAT INCLUDED DIRECT ORAL CHALLENGE: 2010-2020S

In 2010, Louis Mendelson, Charlotte Ressler, James Wolfe, and N. Franklin Adkinson Jr brought PPL back to the market in the United States after a 6-year absence. With the renewed availability of commercial PPL and the falling rate of positive skin tests, Macy et al[55] at Kaiser Permanente Southern California discontinued skin testing with penicilloate, penilloate, and amoxicillin in 2010. In 2013, they reported outcomes of the first 500 individuals evaluated with only PPL and benzylpenicillin between June 8, 2010, and March 29, 2012, and all persons with negative skin-test results were given an oral amoxicillin 250 mg challenge and observed for 1 hour. Only 4 persons (0.8%; 95% CI, 0.32%-2.03%) had a positive skin test result. Only 4 persons (0.8%; 95% CI, 0.32%-2.03%) had an acute objective oral amoxicillin challenge reaction. Fifteen persons (3.0%; 95% CI, 1.83%-4.98%) had subjective oral challenge reactions, either acute transient itching or dizziness. All were women, and 11 (73.3%) had multiple drug intolerance syndrome. None had severe reactions or objective signs. These were not considered to be positive challenge reactions. Sixty-eight subjects (13.6%) who were negative on testing were exposed to 88 courses of penicillins during 90 days of follow-up. New reactions were reported after 4 courses (4.5%), and 3 (75%) of these occurred in subjects with multiple drug intolerance syndrome. Kaiser Permanente now skin-tests using only commercial PPL and only in higher risk individuals, with most patients going to direct oral challenge.[2]

Fernández et al[56] with the DAP-Diater group reported in 2013 on a multicenter clinical trial of newly produced PPL (benzylpenicilloyl octa-L-lysine) and benzylpenilloate performed at 18 Spanish centers. Their cohort of 94 patients included 35 (41%) with an index event of anaphylaxis or anaphylactic shock and 51 (58%) with urticaria. There were 57 (61%) patients who were skin-test positive, 46 (52%) to PPL and 33 (38%) to benzylpenilloate. No oral challenges were performed to confirm the skin test results; thus, no positive or negative predictive value to the testing could be determined. This study showed that penicillin skin testing those rare individuals with an index reaction of anaphylaxis can lead to high levels of positive skin-test results, though the predictive value of such results is presumptive.

Mill et al[57] in 2016 reported a breakthrough study that used a direct oral amoxicillin challenge to delabel amoxicillin allergic children. There were 818 children given an oral amoxicillin challenge between 2012 and 2015. There were no exclusions based on their clinical history of the index reactions, but because anaphylaxis is so rare, there were no children with a history of anaphylaxis in this cohort. There were 17 (2.1%) who had mild immediate challenge reactions and 31 (3.8%) with mild delayed reactions. Only 1 of the 17 (5.9%) who were acutely oral challenge positive was skin-test positive when tested with benzylpenicillin and PPL 2 to 3 months later. It is very likely that if all 818 children were initially skin-tested, there would have been more than 1 positive result.

Tannert et al[58] in Denmark noted in 2017 that a positive skin-test or specific IgE to penicillin does not reliably predict penicillin allergy. They concluded that the best predictor for a clinically significant (IgE-mediated) penicillin allergy is a combination of a positive case history with simultaneously positive skin-test and specific-IgE results or a positive challenge result.

Banks et al[59] at the Walter Reed National Military Medical Center, United States Marine Corps Recruit Depot, San Diego, and Kaiser Permanente San Diego reported in 2019 on their experiences using direct oral amoxicillin challenges, primarily in adults without histories of anaphylaxis, between 2014 and 2018. They reported on a total of 1841 individuals challenged, and only 19 had objective acute- or delayed-onset reactions.

In 2019, Solensky et al[60] reported the outcomes of a clinical trial using an extensive panel of newly produced skin-test reagents including PPL, amoxicillin, and an MDM with penicillin G, penicilloate, and penilloate, with the goal of getting FDA approval for commercial use. They recruited 455 patients, and 63 (13.8%) had 1 or more positive skin-test results, with 65% of the positive skin-test results only to the MDM and/or amoxicillin. There were 373 skin-test-negative subjects given an oral amoxicillin 250 mg challenge, and still 8 (2.1%) developed acute-onset reactions. All but 1 of the reactions was mild or moderate, and most subjects who required treatment received only antihistamines. Amoxicillin and MDM may have a place in the evaluation of high-risk individuals, but their widespread use in lower risk individuals may lead to more false-positive skin test results. Overall, even with comprehensive penicillin skin testing,

TABLE I. Penicillin timeline

1928	Fleming—discovered penicillin
1930	Paine—first clinical use
1940	Florey and Chain—production in clinically useful quantities
1942	Fleming—first personal clinical use
1942	Grossman and Tager—first clinical used in the United States
1943	Keefer—outcomes of first 500 individuals treated
1944	Penicillin approved for use in the United States
1944	McClosky and Smith—anaphylactic sensitization in guinea pigs
1944	Criep—acutely positive skin test
1945	Fleming, Florey, and Chain—Nobel Prize
1946	Suchecki—higher rates of adverse reactions with repeat exposures
1946	Gordon—serum sickness−like reactions in approximately 1 in 1750 exposures
1946	O'Donovan and Klorfajn—repeated treatment after hypersensitivity
1947	Peck—treating through benign delayed-onset reactions
1948	Franklin—understanding immunogenicity risk with early preparations
1949	Lepper—deaths from anaphylaxis and SCARs
1955	Berger and Eisen—penicillin G not a reliable skin test reagent
1959	Brown—anaphylaxis in approximately 3 in 10,000 exposures
1960	Levine, Ovary, and Parker—major and minor determinant identification
1962	Reisman—desensitization to acute hypersensitivity
1963	Rytel—9-fold > risk for systemic reaction with positive skin test to PPL
1964	Parker—production of PPL
1964	Brown—66% of previous reactors negative to PPL
1964	Levine—improved method of producing PPL
1965	FDA approval of cloxacillin
1965	Rolinson and Sutherland—binding to serum proteins
1968	Idsoe—15 anaphylaxis deaths per 1 million exposures, peaked 1958
1970	Adkinson—75% of previous reactors negative to PPL and MDM
1974	FDA approved PPL and amoxicillin
1977	Green—80% of previous reactors negative to penicillin G and PPL
1981	Sullivan—>4-fold lower positive skin test rate at >10 years vs <1 year
1982	FDA approved dicloxacillin
1982	Sullivan—oral penicillin desensitization protocol
1982	Brown—ticarcillin desensitization maintained by oral penicillin exposure
1984	Adkinson—93% of previous reactors negative to PPL and MDM
1984	Mendelson—skin testing and oral challenges do not resensitize
1984	FDA approved amoxicillin/clavulanate
1986	Neftel—sensitizing breakdown products in aqueous penicillins
1986	FDA approved ticarcillin/clavulanate
1992	Sogn—NIAID trial on PPL and MDM
1997	Macy—improved methods for production of penilloate and penicilloate
2002	Solensky—repetitive challenges do not result in resensitization
2003	Macy—very few post-delabeling reactions result in resensitization
2004	Commercial PPL not available in the United States
2005	FDA approved piperacillin/tazobactam
2006	Macy—delabeling is safe in pregnancy
2007	Park—women are more likely to have low-level false-positive skin tests
2007	Cetinkaya—topical penicillin exposures lead to sensitization
2009	Macy—falling rate of positive skin tests at a single center over 13 years
2010	Commercial PPL available again in the United States
2013	Macy—testing using PPL and penicillin with oral amoxicillin challenge safe
2013	Fernandez—very high rates of positive skin tests with anaphylaxis history
2014	Macy and Contreras—penicillin allergy associated with worse outcomes
2014	Choosing Wisely recommendation to evaluate all penicillin allergies
2016	Mills—direct oral challenges are safe and effective in children

(continued)

TABLE I. *(Continued)*

2017	Tannert—penicillin skin testing alone does not reliably predict allergy
2017	Macy and Shu—delabeling results in less health care utilization
2018	Blumenthal—penicillin allergy associated with more resistant infections
2018	Blumenthal—penicillin allergy associated with more surgical infections
2019	Banks—direct oral challenges are safe and effective in children and adults
2019	Blumenthal—penicillin allergy associated with earlier death
2019	Solensky—skin testing with amoxicillin, PPL, and MDM in medium-to-high-risk individuals, 14% skin-test-positive and still 2% positive oral challenges in the skin-test-negative
2020	Blumenthal—penicillin allergy associated with increased utilization
2020	Liang—penicillin-associated anaphylaxis is currently extremely rare

FDA, Food and Drug Administration; *MDM*, minor determinate mixture; *NIAID*, National Institute of Allergy and Infectious Diseases; *PPL*, penicilloyl-polylysine; *SCAR*; serious cutaneous adverse reaction.

a large majority (86.2%) of patients with moderate-to-severe prior reactions can be shown to be without current sensitization and thus at low risk for re-treatment. The FDA review of these materials is still ongoing.

Several groups have recently confirmed the initial observations by Macy[61] in 2006 on the safety and effectiveness of penicillin allergy delabeling in pregnant women using both skin testing and oral challenges.[61-63]

THE PUBLIC HEALTH BENEFITS OF PENICILLIN ALLERGY DELABELING

There is now a clearer understanding of the benefits of penicillin allergy delabeling. Improving the evaluation of penicillin allergy was noted in the core elements of hospital antibiotic stewardship programs in 2019 by the Centers for Disease Control and Prevention.[64] Macy and Contreras[9] reported in 2014 that hospitalized individuals with a history of penicillin allergy had greater levels of health care utilization and higher rates of serious drug resistant bacterial infections. This led to the Choosing Wisely recommendation in 2014 to "Don't overuse non-beta lactam antibiotics in patients with a history of penicillin allergy, without an appropriate evaluation."[65] In 2017, Macy and Shu[8] reported that individuals who were delabeled used significantly less health care. Blumenthal et al[66] confirmed in 2018 a clinically meaningful increased risk of new *Clostridioides difficile* and methicillin-resistant *Staphylococcus aureus* infections in a population-based matched-cohort study with a 6-year follow-up. Blumenthal et al[67] reported in 2018 that patients with a reported penicillin allergy had a 50% increased odds of a surgical-site infection, mostly attributable to second-line antibiotic therapy. Blumenthal et al[68] reported in 2019 that patients with a reported penicillin allergy had an increased rate of death. Blumenthal et al[69] reported in 2020 that in high-cost high-need patients, a penicillin allergy was associated with increased health care utilization.

AREAS IN NEED OF FURTHER RESEARCH

Clinically, it remains unclear how important side chain–specific immune responses to penicillin-class antibiotics are with respect to cross-reactivity with other β-lactam antibiotics sharing exact or similar side chains.[70] Higher rates of anaphylaxis have been noted with halogenated penicillins, specifically dicloxacillin, and this deserves additional study, both for confirmation and mechanism.[5] There may also be an important role for side chain–specific responses to flucloxacillin and piperacillin.[71,72]

There was a case report in 1987 of ampicillin-associated anaphylaxis in a penicillin skin-test-negative individual with common variable immunodeficiency (CVID), with reduced ability for IgE responses.[73] Hartman et al[74] in the United States Immunodeficiency Network Consortium in 2017 reported on a multicenter cohort of individuals with CVID. Of 100, 33 had a history of penicillin allergy. Of the 15 who underwent penicillin skin testing, using >3-mm weal as the criteria for a positive result, there were unexpectedly 2 patients who had positive intradermal testing to PPL, but both tolerated a graded oral amoxicillin challenge. Further research is needed to determine whether acute penicillin reactions in patients with CVID are IgE-mediated or are derived from another pathway. It remains essential to evaluate immunocompromised individuals and delabel whenever possible.

It is known that penicillin allergy delabeling prevents infectious disease morbidity and reduces health care utilization, but what remains unknown are the most effective ways to institutionalize systematic penicillin allergy evaluations using nonallergy specialists in most hospitalized and urgent care patients. Penicillin allergy relabeling after delabeling also remains an issue, as does the recording of penicillin allergy status in medical records.[75]

Gao et al[76] reported in 2020 that penicillins are able to activate complement via the contact system, and this reaction can be blocked with icatibant. This may help explain rare cases of apparently nonallergic penicillin–associated anaphylaxis and warrants further investigation.

A clinically useful *in vitro* point-of-care screening test that will accurately predict positive oral challenges is needed. Such a validated predictor could substantially optimize the choice of antibiotics in patients with serious infections and facilitate antimicrobial stewardship.

CONCLUSIONS

Table I reviews the timeline starting with the discover of penicillin through 2022. When penicillin was originally available for clinical use in 1942, it was relatively impure and associated with high levels of immunologically and nonimmunologically mediated side effects. It was most widely used as parenteral preparation, in an aqueous phase, which facilitated reactogenic break-down products. Currently, anaphylaxis from penicillins is extremely rare. The morbidity associated with avoiding the use of a penicillin based on an unconfirmed allergy label, when it is the drug of choice, is now significantly greater than the risk of a

serious, immunologically based, adverse reaction. The rate of history-positive individuals confirmed to have penicillin-specific IgE has fallen significantly over the past several decades. Penicillin allergy evaluation has now evolved to use a risk-based approach based on the clinical history of the index reaction and the time since the reaction to select low-risk patients for delabeling by oral challenge. Skin testing is currently still indicated in higher risk individuals with recent or severe anaphylaxis. The essential clinical conclusions over the past 80 years are that most patients currently labeled as penicillin allergic are not currently at serious risk, and that appropriate penicillin allergy delabeling prevents morbidity and excess health care utilization.[2,6,8]

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