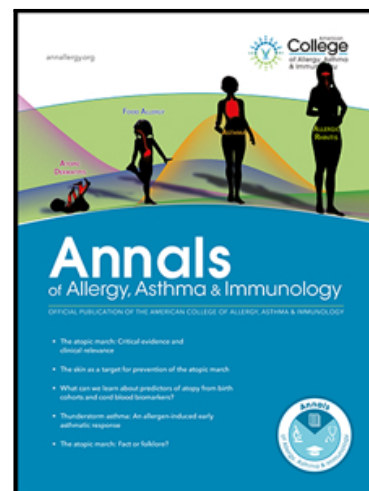


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Review

Penicillin minor determinants: History and relevance for current diagnosis

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Conflict of Interest:

Drs Adkinson, Mendelson and Ressler are founders and officers of AllerQuest which manufactures penicillin skin test reagents. They have equity ownership in the company. John Keogh is professional scientific writer who was paid by AllerQuest to supervise the preparation of this manuscript.

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Abstract: Objective: To review the history of the penicillin minor

determinants and evaluate their relevance for current diagnosis.

Data Sources: Skin testing to detect immunoglobulin E (IgE) sensitivity to penicillins in patients with a history of penicillin allergy has been the subject of more than 55 years of published research involving tens of thousands of patients.

Study Selections: Selection of data was based on its relevance to the objective of this article.

Results: It was established early on that testing with the major penicilloyl determinant using the polyvalent penicilloyl-polylysine (PPL) is negative in a substantial portion (10-64%, including recent increases) of those at risk for immediate hypersensitivity reactions. A variety of minor penicillin determinants are clinically significant in that their use in skin testing is essential to detect all those at risk. In particular, a minor determinant mixture (MDM) of benzylpenicillin, benzylpenicilloate, and benzylpenilloate, used in conjunction with PPL, has been shown in numerous studies to achieve an average negative predictive value (NPV) of 97.9% in history-positive patients.

Benzylpenicillin alone, as the sole minor determinant, leaves many skintest-

positive patients undiscovered. Use of amoxicillin as an additional minor determinant reagent appears to identify another 2-8% of skintestpositive

patients in some populations.

Conclusion: IgE skin testing, using both the major and appropriate minor determinants of penicillin, can identify, with a high degree of reliability (NPV ~ 97%), penicillin-allergy-history-positive patients who can receive beta-lactam antibiotics without concern for serious acute allergy, including anaphylaxis. The few false negative skin tests reported globally are largely confined to minor, self-limited cutaneous reactions.

Keywords: penicillin skin test reagents, penicillin allergy, beta-lactam allergy, penicillin hypersensitivity, IgE-mediated reaction, major determinant, minor determinant, minor determinant mixture, MDM, benzylpenicilloate, benzylpenilloate, amoxicillin

KEY MESSAGES

- Early immunochemical studies of penicillin allergy revealed minor antigenic determinants in addition to the major penicilloyl determinant.
- These minor penicillin determinants are often involved in more severe and serious cases of anaphylaxis to penicillins.
- The use of skin testing with benzylpenicillin alone is insufficient to detect all immunoglobulin E (IgE) with minor determinant specificities.
- A "minor determinant mixture" (MDM) composed of equal quantities of benzylpenicillin and both its alkaline and acid hydrolysate products (penicilloate and penilloate) has been used successfully in multiple large studies over 5 decades to detect clinically significant minor penicillin determinant IgE antibodies by skin testing.
- An MDM is used worldwide for immediate skin-testing detection of penicillin minor determinant IgE, and its use with a major determinant antigen such as penicilloyl-polylysine allows skin-test-negative patients to be safely treated with penicillins regardless of history and may eliminate the need for an oral challenge.

Immunochemistry of Penicillins

The formation of penicillin antigens was first studied in detail by Bernard Levine and Zoltan Ovary at New York University School of Medicine in the late 1950s.¹ The pioneering work of Levine and his colleagues was confirmed and extended by Charles W. Parker and associates at Washington University in St. Louis.^{2,3,4} Their clinical and animal studies in the 1960s made it clear that no single penicillin structure could detect all the antibodies responsible for a variety of types of penicillin allergy. D- α -benzylpenicilloyl was defined as the major antigenic determinant, responsible for a large majority of penicillin-specific immune responses. But the major determinant, even when presented in a multivalent form as penicilloyl-polylysine (PPL) was known early on to be insufficient for accurate diagnosis of immediate-type, immunoglobulin E (IgE)–dependent, hypersensitivity.^{5,6} This has been confirmed over the last 50 years, through a progression of clinical studies with various minor determinant formulations, populations, and historical clinical reactions, as summarized in Table 1.

[Insert Table 1.]

To explore the history and utility of the penicillin minor determinants, we searched the PubMed database for reports of original clinical research conducted with PPL, benzylpenicillin, benzylpenicilloate, benzylpenilloate, or amoxicillin when used for detection of allergy to penicillin or its analogs. Our search extended from at least 1960 to the initial months of 2018.

The Role of Major and Minor Antigenic Determinants in Immediate Penicillin Allergy

We now know that benzylpenicillin (as well as other penicillins) spontaneously breaks down to form a principal protein derivative, referred to as the major allergenic determinant (penicilloyl), and several “minor” allergenic epitopes, the most important of which are benzylpenicillin (penicillin G), benzylpenicilloate, and benzylpenilloate (Figure 1). First

evaluated as individual determinants of reactivity to penicillin in the 1960s, these small derivative compounds were already known in the literature from World War II–related efforts to elucidate the chemistry of penicillin.⁵⁹ Other related compounds tested as minor determinants include penicilloyl-amine, penicillamine, an isoxazolone, and penilloaldehyde.⁶ Each is “minor” only in the sense of having relatively low rates of sensitization.

[Insert Figure 1.]

Levine et al. (1966) were able to associate the various adverse clinical responses of patients sensitive to penicillin with the antibody class that formed.⁵ They used direct skin tests for wheal and flare to detect skin-sensitizing antibodies (SSAs) to PPL, benzylpenicillin, and benzylpenicilloate, and were able to determine hemagglutination titers of IgM and IgG in which these antigenic epitopes were distinguished. The immediate allergic reactors developed marked hypotension and urticaria 3-20 minutes after exposure to penicillin. Analyzed 7-10 days later, these subjects had SSAs with major and minor determinant specificities, in marked contrast to non-reactive controls. In 1966 the SSAs (also known as “reagins”) were identified with a newly described antibody class, IgE. Interestingly, the IgG and IgM titers in the immediate reactors were similar to those of controls.⁵

So-called “accelerated allergic reactors” (those with generalized urticaria between 2 and 36 hours after initial exposure, persisting for 1-5 days) all had PPL-specific IgE, and some had positive skin tests to minor determinants. The late urticarial reactors (those with generalized urticaria 8-21 days after exposure) had essentially the same immune responses as the accelerated reactors. Thus immediate, sometimes severe reactions in penicillin-allergic patients were confined to what we now know as IgE antibody responses to both penicilloyl and minor determinant antigens, and did not appear to be mediated by IgG or IgM antibodies.

Immediate skin reactivity in penicillin-sensitive patients was exhibited to PPL and also to benzylpenicillin, benzylpenicilloate, and benzylpenilloate, either alone or in combination. Specificity of the antibody response to benzylpenicillin and benzylpenicilloate as well as to PPL was shown by solid-phase inhibition studies. This important clinical correlation has been continuously confirmed since these early studies,⁶ based on experience in over 1750 sensitized patients (Table 2). The percentage of patients who test positive to each of these reagents has varied among studies (Table 3). It is likely that the frequency of skin test responses to each of these reagents has been affected over time by the treatment history of the population under study and possibly other factors. The very high rates of positive responses to the amoxicillin reagent in southern Europe, where amoxicillin use is predominant, suggest regional differences in the pattern of sensitivity to the major and minor determinants.^{51,60,61} High rates of response to determinants other than PPL and MDM were also reported in studies in Kuwait and Manitoba, Canada.^{20,50,57}

[Insert Table 2.]

From the early studies of Levine and Parker and associates, the pattern which emerged was an association of positive PPL skin tests with immediate or delayed urticarial reactions, with many if not most positive minor determinant skin tests seen in patients with recent and/or severe immediate, often anaphylactic, reactions.^{5,9,21,30,62,63} Evidence from studies conducted over the past 50 years (see Table 1) is in general agreement with this early observation. For example, Siegel and Levine, analyzing sera from five patients who had recently had immediate systemic (anaphylactic) reactions within 5 to 10 minutes after contact with penicillin, found that four of the five had positive skin-test reactions to benzylpenicillin but not to PPL, extending Siegel's previous observations in a cohort of 18 such patients.^{62,63} Silviu-Dan et al. (1993) noted that

nearly half of patients with a history of immediate reactions to penicillins were skin-test positive for semisynthetic penicillins (ampicillin, amoxicillin, and/or cloxacillin) but negative for PPL and benzylpenicillin.⁵⁰ Later studies have confirmed the value of including minor determinants in identifying patients at higher risk of serious IgE-mediated reactions.^{37,38,60,64} Klaustermeyer and Gowda reported a case in which a patient's skin tests included only PPL and benzylpenicillin because of lack of availability of other minor determinants; despite negative test results, the patient developed life-threatening anaphylaxis within 30 minutes after receiving parenteral ticarcillin-clavulanate.³⁸ While the clinical association of minor determinant IgE with recent and severe anaphylaxis is not a reliable risk factor with clinical utility, the historical association strongly suggests the potential importance of detecting penicillin minor determinant IgE when it is present.

For ease of use, benzylpenicillin, benzylpenicilloate, and benzylpenilloate can be combined as a minor determinant mixture (MDM) in a single solution, as they neither inhibit one another's reactivity nor cause one another to degrade. They will, however, inhibit reactions to PPL, and so PPL must be administered separately.^{6,65}

Testing with PPL and Benzylpenicillin Alone Is Not Sufficient

Levine and Zolov (1969) asserted early on that PPL alone is insufficient to reliably establish the presence or absence of penicillin allergy.³⁰ Several early studies showed rates of response to MDM only in excess of 25%.^{20,25,30,33} The inadequacy of use of PPL alone was first definitively demonstrated in a large US study, reported 25 years ago, that found that PPL alone identified only about 75% of sensitized patients, and that addition of the minor determinants was required for maximum skin-test sensitivity.³⁶ This conclusion has been reinforced by numerous studies since (e.g., Table 3).

Testing with benzylpenicillin alone is insufficient to detect all IgE with minor determinant specificities. Table 3 shows the positive penicillin skin-test patterns among history-positive patients in three well-designed US studies using PPL, benzylpenicillin, benzylpenicilloate, benzylpenilloate, and amoxicillin reagents. Only 36-68% of these patients tested positive to PPL. Of the remaining patients, 23-28% of patients tested positive to only benzylpenicillin, benzylpenicilloate, and/or benzylpenilloate, with no one component dominating across studies. Another 2-8% tested positive only to amoxicillin, suggesting that this most frequently prescribed oral penicillin may in a few patients be a minor determinant itself.

[Insert Table 3.]

Sensitivity and Safety of Penicillin Skin Test Evaluations in History-Positive Patients

When used according to practice guidelines in the United States and Europe,⁶⁶ skin testing is a reliable means of establishing the current absence of major and minor determinant IgE to penicillins. This provides a high degree of confidence that penicillin therapy will not lead to a significant immediate reaction, despite history of such reactions, including anaphylaxis, in the past.

Table 4 lists the results of 17 published clinical studies, all of which involved skin testing with PPL, and the classic “minor determinant mixture”(MDM): benzylpenicillin, benzylpenicilloate, and benzylpenilloate. Some patients were also tested with amoxicillin and/or other reagents. In these studies, 969 (16.6%) of 5,828 history-positive patients had positive skin test results. Of the 969 skin-test-positive patients, 178 (18.4%) responded to only one or more of the constituents of the MDM and, therefore, would not have been identified if only the major determinant had been used.

[Insert Table 4.]

The finding that semisynthetic penicillins could also induce skin-test positivity²¹ was published in reports from Spain and Italy by Blanca et al. and others.^{64,67-69} Vega et al. (1994) also described a group of patients with suspected beta-lactam allergy who demonstrated allergic reactions only to amoxicillin (30.5%) while tolerating penicillin.⁶¹ Of these individuals, 63% were skin-test positive for amoxicillin, and 22% were positive on radioallergosorbent testing. All of these studies were in European populations and used amoxicillin skin test concentrations up to 25 mg/mL.

The conclusion of this cumulative research seems clear. Without all five components of the penicillin skin tests used in these studies, some sensitized patients would not have been discovered. And presumptively some subset of these “minor sensitized” patients will be at risk of systemic allergic reaction. A definitive determination of positive predictive value (PPV) for minor determinant skin test positivity would require treating skin-test-positive subjects, with no clinical benefit, which is an unacceptable ethical hazard.^{70,71}

The safety of penicillin skin testing was assessed in a review of 54 studies published over a period of 49 years.^{13-22,24-26,30,32-34,36-39,41-50,52-58,72-87} All 19,259 patients in these studies were exposed to PPL and benzylpenicillin; 7,749 (40.2%) were exposed to PPL as well as benzylpenicillin, benzylpenicilloate, and benzylpenilloate; and 4,824 (25.0%) were exposed to PPL, benzylpenicillin, benzylpenicilloate, benzylpenilloate, and amoxicillin reagent. The rate of allergic reactions secondary to penicillin skin testing in this large body of patients with a reported history of penicillin allergy was extremely low, involving only 31 patients (0.16%). For the studies in which severity, treatment, and outcome were reported, all of the adverse reactions were mild or moderate and responded to treatment, and no severe adverse reactions were

reported. Only five (9.3%) of the 54 studies had an incidence of reported adverse reactions to the penicillin skin test $\geq 1\%$.

Negative Predictive Value (NPV) of Penicillin Skin Testing

The validity of the negative skin test is confirmed by the administration of a penicillin—i.e., by drug challenge. Table 5 summarizes the published results in 2,680 history-positive, skin-test-negative patients who were challenged by the administration of a penicillin. The incidence of reported IgE-mediated reactions ranged from 0 to 6.0% in individual studies, with an overall false-negative rate of 2.1% across studies. The 55 (2.1%) patients with adverse drug reactions experienced mild, probably IgE-mediated reactions within 72 hours following administration of a penicillin. These adverse reactions were not serious and were largely self-limiting cutaneous reactions.

[Insert Table 5]

Conclusion

An extensive body of research conducted around the world over a period of more than 50 years has shown that properly conducted penicillin skin testing, using both the major and minor determinants of penicillin, has proven effective in identifying patients who, despite a history of penicillin allergy, are at very low risk of reactions to penicillins. The use of PPL alone is not sufficient to establish low-risk for penicillin treatment in these patients. A combination of minor determinants is also required, preferably including an MDM of benzylpenicillin, benzylpenicilloate, and benzylpenilloate as well as separately administered amoxicillin reagent. The use of penicillins in patients with a history of acute penicillin allergy who have negative skin test results using all of these reagents is considered safe from immediate hypersensitivity reactions to re-administration.

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FIGURE LEGEND

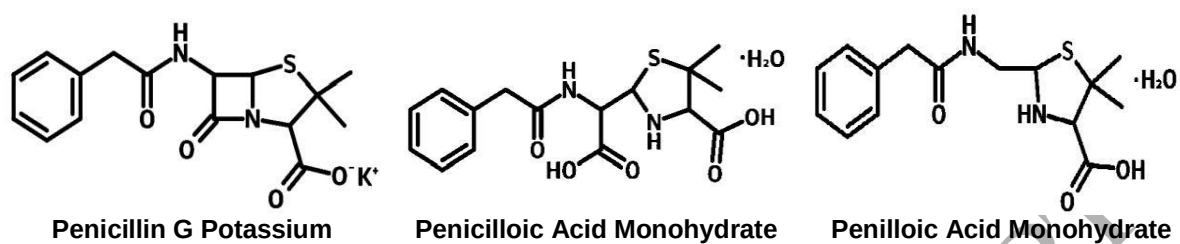


Figure 1. Chemical Structures of the Principal Minor Penicillin Determinants

TABLES

Table 1. Progression of Clinical Research with Various Combinations of Penicillin Skin Test Reagents

Reagent(s) Studied	Investigators
PPL alone	Brown et al., 1964 ⁷
PPL + benzylpenicillin	Budd, Parker et al., 1964 ⁸ Green et al., 1977 ⁹ Arroliga et al., 2003 ¹⁰ del Real et al., 2007 ¹¹ Rimawi et al., 2013 ¹² Chen et al., 2017 ¹³ Macy and Shu 2017 ¹⁴ McDaniel et al., 2017 ¹⁵ Ramsey and Staicu, 2017 ¹⁶ Sundquist et al., 2017 ¹⁷ Vyles et al., 2017 ¹⁸ Dorman et al., 2018 ¹⁹
PPL+ benzylpenicillin + benzylpenicilloate	Levine et al., 1966 ⁵ Warrington et al., 1978 ²⁰ Solley et al., 1982 ²¹ Valyasevi and Van Dellen, 2000 ²² Nadarajah et al., 2005 ²³ Park et al., 2006 ²⁴
PPL+ benzylpenicillin + benzylpenicilloate + ampicillin + other reagents	Van Dellen and Gleich, 1970 ²⁵ Sullivan et al., 1981 ²⁶ Romano et al., 1995 ²⁷ Romano et al., 1997 ²⁸
Benzylpenicillin + benzylpenicilloate	Sarti, 1985 ²⁹
PPL + benzylpenicillin + benzylpenicilloate + benzylpenilloate + penicilloyl-N-propylamine	Levine and Zolov, 1969 ³⁰
Octa-penicilloyl-octalysine + benzylpenicillin + benzylpenicilloate + penicilloyl-N-propylamine	VanArsdel, Jr., et al., 1986 ³¹ Sogn et al., 1992 ³²
PPL+ benzylpenicillin + benzylpenicilloate + benzylpenilloate	Adkinson, Jr., et al., 1971 ³³ Chandra et al., 1980 ³⁴ Mendelson et al., 1984 ³⁵ Gadde et al., 1993 ³⁶ Pichichero and Pichichero, 1998 ³⁷ Klaustermeyer and Gowda, 2005 ³⁸ Treudler et al., 2007 ³⁹ Frigas et al., 2008 ⁴⁰ Nolan et al., 2008 ⁴¹ Raja et al., 2009 ⁴²
PPL + benzylpenicillin + benzylpenicilloate + benzylpenilloate + amoxicillin	Macy et al., 1997 ⁴³ Macy et al., 2010 ⁴⁴ Lin et al., 2010 ⁴⁵ Kopac et al., 2012 ⁴⁶ Geng et al., 2017 ⁴⁷ Marwood et al., 2017 ⁴⁸
PPL+ benzylpenicillin + benzylpenicilloate + amoxicillin	Fox and Park, 2014 ⁴⁹

Reagent(s) Studied	Investigators
PPL + benzylpenicillin + benzylpenicilloate + benzylpenilloate + amoxicillin MDM + ampicillin MDM + cloxacillin MDM	Silviu-Dan et al., 1993 ⁵⁰
PPL + benzylpenicillin + benzylpenicilloate + benzylpenilloate + amoxicillin + other reagents	Torres et al., 2001 ⁵¹ Matheu et al., 2007 ⁵² Romano et al., 2007 ⁵³ Romano et al., 2009 ⁵⁴ Romano et al., 2010 ⁵⁵ Richter et al., 2011 ⁵⁶ Al-Ahmad et al., 2014 ⁵⁷ Bourke et al., 2015 ⁵⁸

Abbreviations: MDM, minor determinant mixture ; PPL, penicilloyl-polylysine

Table 2. Skin Test Results with PPL and Two or More Minor Determinants in Patients with a Reported History of Penicillin Allergy

Investigators	Reagents ^a	History-Positive Patients, N	Positive n (%)	Negative n (%)	Equivocal n (%)
Levine and Zolov, 1969 ³⁰	A	218	32 (14.7%)	185 (84.9%)	1 (0.4%)
Van Dellen and Gleich, 1970 ²⁵	C ^a	240	57 (23.8%)	183 (76.3%)	NR
Adkinson Jr. et al., 1971 ³³	B	66	16 (24.2%)	50 (75.8%)	0
Warrington et al., 1978 ²⁰	C ^b	253	29 (11.5%)	224 (88.5%)	NR
Chandra et al., 1980 ³⁴	B	300	48 (16.0%)	252 (84.0%)	NR
Sullivan et al., 1981 ^{c; 26}	G	740	469 (63.4%)	205 (27.7%)	66 (8.9%)
Solley et al., 1982 ²¹	C ^a	778	108 (13.9%)	670 (86.1%)	NR
Mendelson et al., 1984 ^{d; 35}	B	223	20 (9.0%)	203 (91.0%)	0
Sogn et al., 1992 ³²	D	726	167 (23.0%)	559 (77.0%)	NR
Gadde et al., 1993 ³⁶	A	776	55 (7.1%)	700 (90.2%)	21 (2.7%)
Silviu-Dan et al., 1993 ⁵⁰	K	112	21 (18.8%)	87 (77.7%)	4 (3.6%)
Macy et al., 1997 ⁴³	E	348	60 (17.2%)	288 (82.7%)	NR
Pichichero and Pichichero, 1998 ^{e; 37}	B, F	247	53 (21.5%)	194 (78.5%)	NR
Valyasevi and Van Dellen, 2000 ²²	C	1,710	86 (5.0%)	1,624 (95.0%)	NR
Klaustermeyer and Gowda, 2005 ³⁸	B	122	10 (8.2%)	112 (91.8%)	NR
Raja et al., 2009 ⁴²	B	150	13 (8.7%)	137 (91.3%)	0
Lin et al., 2010 ⁴⁵	E	1,068	243 (22.8%)	825 (77.2%)	NR
Kopac et al., 2012 (some pediatric) ⁴⁶	E	274	14 (5.1%)	260 (94.9%)	NR
Al-Ahmad et al., 2014 ⁵⁷	H	124	44 (34.9%)	80 (64.5%)	NR
Fox and Park, 2014 (pediatric) ⁴⁹	I	778	66 (8.5%)	703 (90.4%)	9 (1.2%)
Bourke et al., 2015 (some pediatric) ⁵⁸	J	341	42 (12.3%)	299 (87.7%)	NR
Geng et al., 2017 ⁴⁷	E	528	107 (20.3%)	421 (79.7%)	NR
Marwood et al., 2017 ⁴⁸	E	103	16 (15.5%)	87 (84.5%)	0

Investigators	Reagents ^a	History-Positive Patients, N	Positive n (%)	Negative n (%)	Equivocal n (%)
TOTAL	—	10,225	1,776 (17.4%)	8,348 (81.6%)	101 (1.0%)

Abbreviations: Hx, history; MDM, minor determinant mixture; N, number; NR, not reported; PPL, penicilloyl-polylysine.

Note: Skin testing involved a prick/scratch test, usually with the major and minor determinants and suitable controls. If the prick/scratch test response was negative, this was followed by intradermal injection of the reagents. Reagents were:

A = PPL, benzylpenicillin, benzylpenicilloate, benzylpenilloate, penicilloyl-alpha-amide.

B = PPL, benzylpenicillin, benzylpenicilloate, benzylpenilloate.

C = PPL, benzylpenicillin, benzylpenicilloate.

D = PPL, benzylpenicillin, benzylpenicilloate, benzylpenilloate, penicilloyl-n-propylamine.

E = PPL, benzylpenicillin, benzylpenicilloate, benzylpenilloate, amoxicillin.

F = PPL, benzylpenicillin, benzylpenicilloate, benzylpenilloate, ampicillin, cefazolin, cefuroxime, ceftriaxone (130 patients treated by Pichichero and Pichichero 1998).

G = PPL, benzylpenicillin, benzylpenicilloate, ampicillin, cephalothin, carbenicillin.

H = PPL, benzylpenicillin, benzylpenicilloate, benzylpenilloate, ampicillin, amoxicillin.

I = PPL, benzylpenicillin, benzylpenicilloate, amoxicillin

J = PL, benzylpenicillin, benzylpenicilloate, benzylpenilloate, amoxicillin, cefazolin, ceftriaxone, and other agents if indicated

K = PPL, benzylpenicillin, benzylpenicilloate, benzylpenilloate, ampicillin MDM, amoxicillin MDM, cloxacillin MDM.

^a Includes reagents derived from benzylpenicillin, ampicillin, and methicillin.

^b Includes reagents derived from benzylpenicillin, ampicillin, cloxacillin, methicillin, and cephalothin.

^c Approximately 95% of the patients tested by Sullivan et al. 1981 were history-positive.

^d Approved by the University of Connecticut Institutional Review Board as IRB no. 667-79. All patients gave informed verbal consent to an information sheet.

^e An additional 26 (10.5%) patients were positive on repeat skin testing following an oral challenge.

Table 3. Positive Penicillin Skin-Test Patterns Among Patients Reporting a History of Penicillin Allergy: Results in Three Studies Using PPL, Benzylpenicillin, Benzylpenicilloate, Benzylpenilloate, and Amoxicillin Reagents

Reagent	Macy et al. 1997 ⁴³ N = 60 ^a n (%)	Lin et al. 2010 ⁴⁵ N = 243 ^b n (%)	Geng et al. 2017 ⁴⁷ N = 107 ^b n (%)
<i>Positive to Specified Reagent, Alone or in Combination</i>			
Penicilloyl-polylysine (PPL) ^c	41 (68.3%)	157 (64.6%)	39 (36.4%)
Benzylpenicillin	9 (15.0%)	111 (45.7%)	24 (22.4%)
Benzylpenicilloate	5 (8.3%)	90 (37.0%)	58 (54.2%)
Benzylpenilloate	8 (13.3%)	84 (34.6%)	23 (21.5%)
Amoxicillin	4 (6.7%)	75 (30.9%)	41 (38.3%)
<i>Positive to Specified Reagent Only</i>			
PPL only	24 (40.0%)	45 (18.5%)	13 (12.1%)
Benzylpenicillin only	2 (3.3%)	16 (6.6%)	2 (1.9%)
Benzylpenicilloate only	4 (6.7%)	7 (2.9%)	25 (23.4%)
Benzylpenilloate only	7 (11.7%)	16 (6.6%)	3 (2.8%)
Amoxicillin only	1 (1.7%)	14 (5.8%)	8 (7.5%)
<i>Positive to One or More Specified Reagents Only</i>			
Benzylpenicilloate and/or benzylpenilloate only	12 (20.0%)	39 (16.0%)	28 (26.2%)
PPL and/or benzylpenicillin only	32 (53.3%)	Not reported	Not reported
Benzylpenicilloate, benzylpenilloate, and/or amoxicillin only	16 (26.7%)	Not reported	Not reported
Benzylpenicillin, benzylpenicilloate, and/or benzylpenilloate only	15 (25.0%)	55 (22.6%)	30 (28.0%)

^a Outpatients.

^b Inpatients.

^c Macy et al. used commercially available PPL, whereas, because PRE-PEN was not commercially available in 2004, Lin et al. synthesized the PPL for their trial. The site whose retrospective data Geng et al. reported used PRE-PEN[®] or PPL synthesized by the site according to published methods.

Table 4. Results of Penicillin Skin Tests Using PPL, Benzylpenicillin, Benzylpenicilloate, and Benzylpenilloate, Including Challenge Results from Skin-Test-Negative Patients.

Investigators, Year Published	Patients, ^b No./Age	MDM ^a	Skin-Test-Positive, n (%)	Skin-Test-Positive to MDM Only, n (% of Pos.)	Oral Challenge, Skin-Test-Negative Patients, N	ADRs to Oral Challenge, n (%) of Challenged
Adkinson et al., 1971 ³³	169 16-72 yr	Mix	43 (25.4%)	10 (23.3%)	54	0 ^c
Chandra et al., 1980 ³⁴	163 ^b 300 children 50 children ^d	Mix	10 (6.1%) ^b 48 (16%) 6 (12%)	1 (10.0%) ^b 11 (22.9%) 4 (66.7%)	150 ^b 56	0 2 (3.6%)
Mendelson et al., 1984 ³⁵	240 children, adolescents	Comb	21 (8.8%)	3 (1.3%)	219, 10-day course, oral penicillin	3 (1.4%)
Sogn et al., 1992 ³²	726	Mix	167 (23.0%)	27 (16.2%)	566	7 (1.2%)
Gadde et al., 1993 ³⁶	776 (mean 25 yr) 4287 ^b	Mix ^e	55 (7.1%) 73 (1.7%) ^b	5 (9.1%) 8 (11.0%) ^b	649 ^f 4201 ^{b,f}	54 (8.3%) ^h 74 (1.8%) ^{b,i} follow-up 10 days follow-up 72 h
Silviu-Dan et al., 1993 ⁵⁰	112	Mix	21 (18.8%)	4 (19.0%)	NA	NA
Macy et al., 1997 ⁴³	348 ^j 38 ± 2 yr	Sep	60 (17.2%)	12 (20.0%)	215, single dose of 250 mg amox	13 (6.0%) to amox challenge ^k
Pichichero and Pichichero, 1998 ³⁷	247 children, adolescents	Comb	53 (21.5%) on initial test	2 (3.8%)	194: 10-day course of Pen VK or Pen VK + 2nd drug	5 (2.6%) Follow-up 6 months-8 years
Klaustermeyer and Gowda, 2005 ³⁸	122	Sep	10 (8.2%)	1 (10.0%)	110	4 (3.6%)
Raja et al., 2009 ⁴²	150, 42 ± 16 yr	Mix	13 (8.7%)	3 (23.1%)	NA	NA
Lin et al., 2010 ⁴⁵	1068	Comb + Amox	243 (29.1%)	55 (22.6%)	NA	NA
Macy et al., 2010 ⁴⁴	150	Sep	6 (4.0%)	0	144	3 (2.3%)
Kopac et al., 2012 ⁴⁶	274	Mix	14 (5.1%)	6 (42.9%)	260	19 (4.5%)
Al-Ahmad et al., 2014 ⁵⁷	124	Mix	44 (34.9%)	5 (11.4%)	46	1 (2.2%)
Bourke et al., 2015 ⁵⁸	341	Mix	42 (12.3%)	0	301	3 (1.0%)
Geng et al., 2017 ⁴⁷	528	Sep	107 (20.3%)	30 (28.0%)	NA	NA
Marwood et al., 2017 ⁴⁸	103	Mix	16 (15.5%)	NA	84	4 (4.8%)
TOTAL: History-positive	5828	—	969 (16.6%)	178 (18.4%) ^l	2898	118 (4.1%)
History-negative	4450	—	83 (1.9%)	9 (10.8%)	4351	74 (1.7%)

Abbreviations: ADR, adverse drug reaction; amox, amoxicillin; cep, cephalosporin; comb, combination; h, hours; MDM, minor determinant mixture; NA, not available; pen, penicillin; pos., positive; sep, separate; yr, years.

^a MDM is defined as including benzylpenicillin, benzylpenicilloate, and benzylpenilloate, which were tested in each case. However, in "Mix," they were tested as a mixture; in "Sep," each separately; in "Comb," benzylpenicilloate and benzylpenilloate as a mixture, penicillin separately. In some studies, additional reagents were also used.

^b All patients had a history of a reaction to penicillin/analog except for 163 in Adkinson et al., 1971, and 4287 in Gadde et al., 1993, who were history-negative.

^c Urticaria and arthralgias within 24 h in a patient with active lupus.

^d History-positive to ampicillin.

^e Schwarz Pharma lyophilized MDM.

^f The majority were treated with high-dose parenteral penicillin (Pen G procaine, 73%; Pen G benzathine, 8%) with oral probenecid; 19% received 3.5 g ampicillin and probenecid orally.

^g Includes one anaphylactic subject in whom puncture testing had been inadvertently omitted.

^h Probable IgE-mediated, 2.9% (1.4% immediate + 1.2 % accelerated) reactions. These were urticaria (3), pruritus (8), local swelling (1), mild, treatable anaphylaxis on receiving parenteral Pen G-procaine (2). Delayed reactions (1.2%) generally were cutaneous, non-urticarial rash or pruritus.

ⁱ Possible IgE-mediated, 0.5% (0.08% immediate + 0.4% accelerated) reactions.

^j History-positive to amoxicillin, 69%.

^k Includes mild, acute reactions, 2 (0.9%) of which were possibly IgE-mediated. There were 2 (0.9%) delayed reactions of non-urticarial skin rashes.

^l Denominator excludes the 16 skin-test-positive patients in Marwood et al. 2017.

Table 5. Summary of Published Studies in Which History-Positive Patients Were Challenged with Penicillins After Negative Skin Tests with a Variety of MDMs

Investigator	Reagent	Skin-Test-Negative Patients	Challenged with Penicillin	Serious Reaction	Probable IgE-Mediated Reactions Occurring in ≤72 hr n (%)
Levine and Zolov, 1969 ³⁰	C	185	185	0	1 (0.5%)
Adkinson et al., 1971 ³³	B	66	54	0	1 (1.9%)
Warrington et al., 1978 ²⁰	A	224	169	0	2 (0.2%)
Chandra et al., 1980 ³⁴	B	252	57	0	1 (1.8%)
Sullivan et al., 1981 ²⁶	A	204	61	0	1 (1.6%)
Solley et al., 1982 ²¹	A	682	290	0	7 (2.4%)
Mendelson et al., 1984 ³⁵	B	219	219	0	0 (0.0%)
Sogn et al., 1992 ³²	D	656	566	0	7 (1.2%)
Gadde et al., 1993 ³⁶	B	700	649	0	17 (2.9%)
Macy et al., 1997 ^{a, 43}	E	288	215	0	13 (6.0%)
Klaustermeyer and Gowda, 2005 ³⁸	B	110	110	0	4 (3.6%)
Abrams et al., 2016 ⁸⁸	F	105	105	0	1 (1.0%)
TOTAL		3691	2680	0	55 (2.1%)

Abbreviation: IgE, immunoglobulin E; MDM, minor determinant mixture.

Note: Major and minor determinants were as follows:

A = PPL, benzylpenicillin, benzylpenicilloate

B = PPL, benzylpenicillin, benzylpenicilloate, benzylpenilloate

C = PPL, benzylpenicillin, benzylpenicilloate, benzylpenilloate, benzylpenicilloyl-amine

D = PPL, benzylpenicillin, benzylpenicilloate, penicilloyl-N-propylamine

E = PPL, benzylpenicillin, benzylpenicilloate, benzylpenilloate, amoxicillin

F = PPL, benzylpenicillin, and ampicillin

^a Patients in Macy et al. 1997 were challenged with a single dose of amoxicillin.