Delabeling, safety, and impact of β-lactam allergy testing: A systematic review

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Background: To improve β-lactam delabeling outcomes, we need to understand current practice and the evidence base regarding its outcomes, safety, and impact.

Objectives: We sought to assess the existing published evidence reporting on the effectiveness of penicillin allergy testing and delabeling.

Methods: We conducted a systematic review of studies reporting β-lactam delabeling practices and outcomes after testing, including β-lactam use and patient understanding of the delabeling result. Searches of the PubMed, Scopus, and Embase databases; clinical trial registries; and websites of professional organizations were conducted. Data were extracted from the included studies in duplicate, with a third extraction if discrepancies remained.

Results: We included 284 publications (covering 98,316 participants); 173 were prospective studies, with no randomized controlled trials. The overall study quality was low. In all, 95.6% of individuals who underwent provocation testing were delabeled. Factors associated with successful delabeling could not be determined because of significant heterogeneity between studies. Anaphylaxis due to testing occurred in 0.3% of participants (95 of 31,667). Subjects who did not undergo skin testing (6,980 patients in 31 studies) before challenge had higher rates of provocation test positivity (8.8% vs 4.1% [$P < .0001$]) and anaphylaxis (15.9% vs 2.7% [$P < .0001$]) than those subjects who underwent skin testing (51,607 patients in 177 studies). Six studies (2.1%) followed patients after testing to assess their adherence to prescribing recommendations. In all, 136 participants (20.6%) were actively avoiding β-lactams despite delabeling.

Conclusions: The available data suggest that penicillin allergy testing is safe and effective in delabeling most individuals, but the evidence base is incomplete and more work is required to assess the role of skin testing and the impact that delabeling is having on prescribing habits. (J Allergy Clin Immunol Global 2023;2:100160.)

Key words: *Drug allergy, drug reactions, penicillin*

A history of adverse reactions to β-lactams are reported by 18% to 25% of hospitalized patients in Australia.[1] With the increasing use of antibiotics over the past 2 decades,[2] the presence of these allergy histories has led to greater use of broad-spectrum, non–β-lactam antibiotics. Use of broad-spectrum antibiotics in patients with an antibiotic allergy label is associated with longer hospital stays; more *Clostridioides difficile*, methicillin-resistant *Staphylococcus aureus,* and vancomycin-resistant *Enterococcus* infections; and a greater chance of intensive care admission and in-hospital death.[3,4] These patients will incur higher costs than patients without an antibiotic allergy label.[5] Moreover, up to 90% of people with histories of β-lactam allergy can be delabeled after proper evaluation,[6,7] so testing individuals with a reported β-lactam allergy has become an important strategy to minimize the use of broad-spectrum antibiotics.

Guidelines regarding β-lactam allergy delabeling have focused on helping clinicians delineate those patients who require further allergy assessment from those who do not.[8,9] Guidelines regarding testing procedures are based on limited nonrandomized studies or clinician experience. None address the issues of post-testing follow-up or the importance of communication and how delabeling translates outside the allergy clinic. We demonstrated[10] that as few as half of patients who undergo penicillin allergy testing understand the implications of their test results, including the possibility that they may be able to receive β-lactam antibiotics ("penicillins") in the future.

β-Lactam allergy delabeling can be a costly, time-consuming, and labor-intensive process. Previous reviews of the process have focused on the accuracy of diagnostic tests,[11] but a systematic review is required to assess the safety of testing, subsequent β-lactam use, and patient understanding of the outcome.

METHODS

Electronic search query

The literature search was conducted in April 2018; the PubMed, Embase and Scopus electronic databases were searched by using the strategy outlined in Appendix 1 (in the Online Repository at www.jaci-global.org). The review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[12] and registered with the International Prospective Register of Systematic

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Abbreviation used
IQR: Interquartile range

Reviews (PROSPERO) (registration no. CRD42020140266). Ethical approval was not required, as this study utilized data from already-published studies.

Eligibility criteria

A study was eligible for review if it addressed the process of delabeling β-lactam allergy. We excluded studies reporting data for fewer than 20 subjects, studies addressing basic science without reference to a clinical intervention, or studies examining nonhuman subjects. Studies that were not reported in English but deemed eligible after review of a translated abstract were formally translated (n = 79) to allow for complete review.

Data extraction

Data for each study were extracted on to a standardized electronic data collection form using Research Electronic Data Capture (RedCAP).[13] The following data were extracted: study population, index reaction, penicillin/β-lactam allergy assessment, and participant perception of allergy status and antibiotic use after delabeling (for the data collection form, see Appendix 2 in the Online Repository at www.jaci-global.org). Data were extracted in duplicate by 2 independent investigators. To resolve discrepancies that existed following these extractions, a third extraction was undertaken. Definitions for reactions (eg, anaphylactic vs nonanaphylactic) and test positivity were based on the definitions reported in individual studies, but nonanaphylactic IgE-mediated reactions were defined as reactions with symptoms typical of IgE-mediated reactions (eg, urticaria, angioedema) without cardiovascular or respiratory compromise. Non–IgE-mediated reactions were typically defined as delayed reactions or reactions with maculopapular rashes only.

Quality assessment

All eligible studies were assessed for their quality by using the revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool.[14]

Outcomes

The main outcomes were the proportions of patients with penicillin allergy, as determined by skin testing and by direct provocation. The secondary outcomes were the safety of skin testing and provocation testing and maintenance of the removal of the allergy label in the posttesting period. These outcomes were reported by using descriptive statistics, including proportions and medians with interquartile range (IQR). Data were further analyzed by test modality and population subgroups via chi-squared and *t* tests to establish whether significant differences in outcome existed between these subgroups. Data regarding skin and provocation testing results were also analyzed for heterogeneity and appropriateness for meta-analysis to assess the strength of evidence for both procedures.

RESULTS

Literature search

The search strategy identified 10,794 citations. After removal of the duplicate citations, publications that did not meet the criteria, and publications for which we could not locate either the abstract or full text, 284 studies were reviewed (Fig 1). The included studies consisted of 176 original articles, 105 abstracts, and 3 letters to the editor. In all, 173 studies (60.9%) had prospective data acquisition. No randomized controlled trial was identified. The studies were published between 1955 and 2018 (median year of publication 2011).

Data quality

The recruitment strategy was unclear in 175 studies (61.6%), with 151 of them (53.3%) identified as being at risk of recruitment bias owing to unclear patient selection criteria. An additional 170 studies (59.9%) did not clearly avoid inappropriate exclusions.

Only 59.4% of the studies (169 of 284) clearly used the same reference standard for all participants. There was a high or unclear risk of test interpretation bias in 38.8% of the studies (110 of 284), and more than a quarter (78 of 284 [27.5%]) did not include all participants in the analysis. Only 15 studies (5.2%) covering 3519 participants (3.5% of all participants) had no clear concern regarding possible bias in testing, participant selection, or interpretation (see Appendix 3 in the Online Repository at www.jaci-global.org).

Population

A total of 93,316 participants (Table I) were enrolled in the studies (median enrolment 131 per study [IQR = 70-313]). In all, 56 studies (19.7% [n = 11,483 participants]) included both pediatric and adult participants, 123 (43.3% [n = 59,388 participants]) had adult participants only, and 243 (85.6%) were performed in outpatient settings.

Initial reaction

Initial reaction was reported in only 129 studies (45.4%) (Table II). Anaphylaxis was the initial reaction in 4.4% of the studies reporting results (IQR = 0-14). Nonanaphylactic IgE-mediated reactions occurred in 42.8% of the studies (IQR = 21.2-56.8) and non–IgE-mediated reactions occurred in 43.3% (IQR = 21.0-67.9). Severe cutaneous adverse reactions were listed as exclusion criteria in 41 studies (14.4%). Participants were assessed a median of 24 months (IQR = 9.3-51.7 months) after their initial reaction.

Skin testing

Skin testing was performed in 251 studies (83.9%). This included 1 or more of types of testing: skin prick testing, intradermal testing, and patch testing. The most frequently used reagents were the major and minor penicillin determinants (in 79.6% and 66.4% of studies, respectively), followed by benzylpenicillin (in 64.7%) and amoxicillin (in 40.7%). The results of testing were reported in 242 studies (96.4%). The results of skin prick testing were positive in 0.9% of the reported cases (568 of 63,255) (Table III). The results of intradermal tests and patch tests were positive in 2.6% of cases (1,300 of 49,666) and 9.3% of cases (657 of 7,048), respectively.

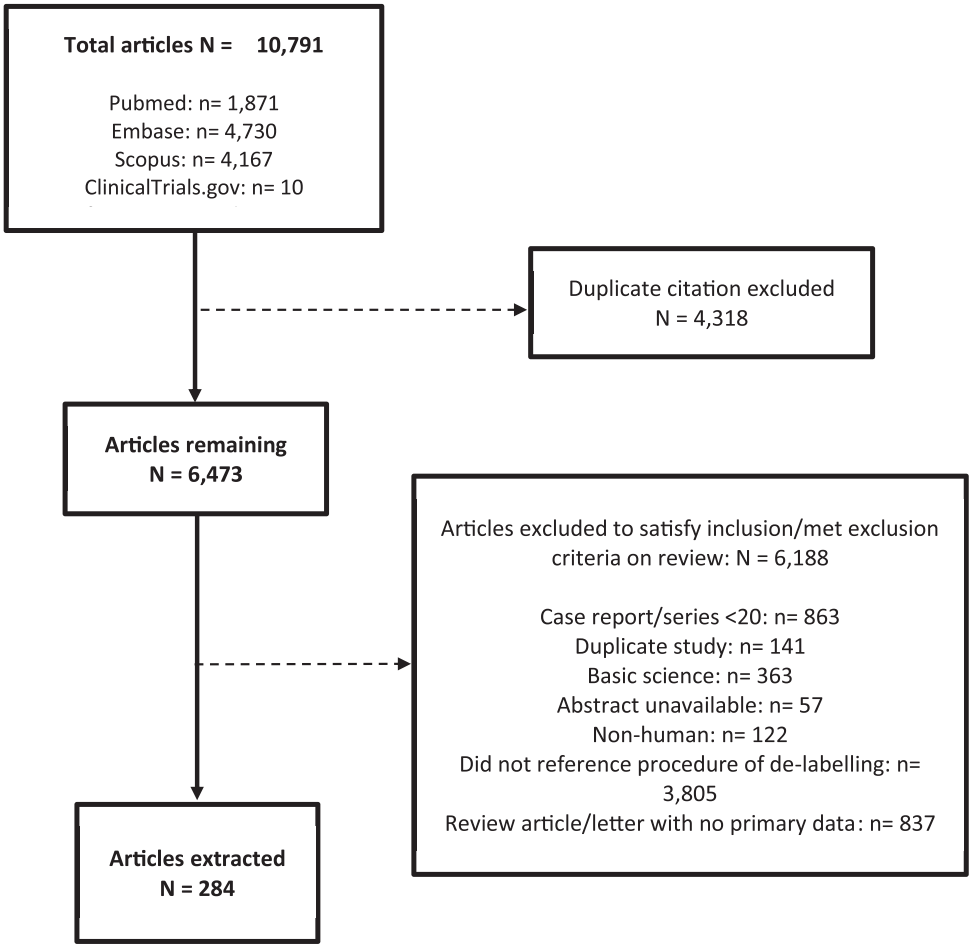

FIG 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

TABLE I. Study population by age group

Age group (y)	No. of studies (%)	No. of participants (%)	Studies with missing data, no. (%)
Adult	124 of 268 (42.6%)	59,388	16 of 284 (5.6%)
Pediatric	91 of 268 (33.9%)	22,445	
All ages	57 of 268 (19.9%)	11,483 (adult, 2,742; pediatric, 1,447)	

Data reported for 284 studies covering 93,316 participants, including 54,123 females (accounting for 58% of all participants). Notably, 114 of the 284 studies (40.1%) are missing data on participant sex.

Provocation testing

In-clinic (immediate) drug provocation testing was performed in 194 studies (67.6%). Testing was performed in a single-step challenge in 52 studies (26.8%). Up to 8 steps were used in the multistep challenges. Extended multiday provocation tests outside the clinic were performed in 86 studies (30.3%) lasting for a median of 5 days (range 2-42 days). The proportions of provocation tests reported as positive are described in Table IV. The provocation test results were positive in 3.3% of the single-step challenges versus in 5.9% of the multistep challenges. Reactions to provocation tests occurred in 4.1% of the participants who underwent preceding skin tests (in 2,125 of 51,607, of which 22 reactions were anaphylactic) versus in 8.8% in those participants who had not undergone preceding skin tests (in 613 of 6,980, of which 45 reactions were anaphylactic) ($P < .0001$) (Table IV). Only 1 study performed direct provocation testing on participants regardless of their skin test results. All of the other studies performed provocation testing only if participants had negative skin test results.

Safety of provocation testing

No deaths were reported. Anaphylaxis due to provocation testing occurred in 0.3% of participants (95 of 31,667) in the 95 studies that reported the reactions to direct provocation test results. The other 117 studies that reported the percentage of positive direct provocation test results did not detail the nature of these reactions. Anaphylaxis occurred in 0.1% of single-step

TABLE II. Study participants by initial reaction and time to assessment

Variable	Median rate of occurrence across studies (IQR)	Studies with missing data, no. (%)
Reaction		
Anaphylaxis	4.4% (0%-14%)	155 of 284 (54.8%)
Nonanaphylactic immediate reaction	42.8% (21.2%-56.8%)	160 of 284 (56.3%)
Delayed reaction	41.3% (21.0%-67.9%)	171 of 284 (60.2%)
SCAR	0	221 of 284 (77.9%)
Time to assessment (mo), mean (IQR)	24 (9.3-51.7)	228 of 284 (80.3%)

SCAR, Severe cutaneous adverse reaction.

TABLE III. Results of testing

	All studies (N = 284)		Prospective studies only (n = 173)	
Testing method	Studies reporting results, no. (%)	With positive results, no. (%)	Studies reporting results (%)	With positive results, no. (%)
Skin prick test	95 of 284 (33.5%)	568 of 63,255 (0.9%)	56 of 173 (32.4%)	383 of 16,730 (2.3%)
Intradermal test	61 of 284 (21.5%)	1,300 of 49,666 (2.6%)	57 of 173 (32.9%)	1,024 of 17,847 (5.7%)
Patch testing	31 of 284 (10.9%)	657 of 7,048 (9.3%)	27 of 173 (15.6%)	549 of 5,391 (10.2%)
In-clinic provocation test	127 of 284 (44.7%)	1,078 of 30,233 (3.6%)	85 of 173 (49.1%)	1,999 of 22,280 (9.0%)
Extended provocation test	85 of 284 (29.9%)	544 of 25,952 (2.1%)	58 of 173 (33.5%)	666 of 21,064 (3.2%)

TABLE IV. Test positivity with or without skin testing

	All studies (N = 284)		Prospective studies only (n = 173)	
Testing method	Studies reporting results, no. (%)	With positive results, no. (%)	Studies reporting results, no. (%)	With positive results, no. (%)
Skin test only	59 of 284 (20.8%)	2,728 of 34,306 (8.0%)	36 of 173 (20.8%)	1,649 of 21,640 (7.6%)
Skin test + provocation test	177 of 284 (62.3%)	2,125 of 51,607 (4.1%)	106 of 173 (61.3%)	1,161 of 30,471 (3.8%)
Provocation test only	31 of 284 (10.9%)	613 of 6,980 (8.8%)	19 of 173 (10.9%)	235 of 3,519 (6.7%)
Skin tests vs no skin tests		$P < .0001$		$P < .0001$

challenges and 0.2% of multistep challenges. Anaphylaxis after provocation testing occurred in 76 patients with a provocation test after skin testing (2.7%) versus in 19 who underwent provocation test without skin testing (15.9%) ($P < .001$ [Table V]). Only 3 of the 11 studies that used intravenous challenges reported anaphylaxis rates, of which there were none. Of the 6 studies using intramuscular challenges, 3 reported anaphylaxis rates. Anaphylaxis occurred in 16 of the 171 patients (9.4%). There was a higher rate of anaphylaxis in adults than in children ($P < .0001$).

Follow-up after penicillin testing

A total of 10,537 participants (in 39 studies) underwent repeat provocation testing with the delabeled antibiotic after testing. Of these patients, 442 (4.2%) developed a reaction. However, the types of reactions were not reported.

Only 6 studies followed up participants (n = 660), but did not necessarily challenge them, to assess participants' perceptions of their allergy status 2 to 10 years after delabeling. Of these 660 patients, 243 received a therapeutic course of penicillins in the interim period, with 10 of them (4.1%) reacting to penicillin. In all, 136 of the followed participants (20.6%) were still actively avoiding β-lactams despite successful delabeling owing to either their own concern that they would react or their prescribing doctor's concern that they would react.

Meta-analysis

A total of 211 studies (74.3%) reported complete data regarding direct provocation test results. Attempts at meta-analysis demonstrated significant heterogeneity between studies with regard to direct provocation testing in those who had and had not undergone preceding skin tests (I^2 for all prospective studies = 93.9%; I^2 for prospective studies in past 20 years = 83.6%), meaning that it was inappropriate to derive an estimate of overall effect from these studies. With regard to anaphylaxis in those who had and had not undergone skin tests, 113 studies reported complete data (39.8%). Again, significant heterogeneity in these studies was seen ($I^2 = 72.6\%$). This heterogeneity was also seen when the 15 studies considered to be of high quality were analyzed alone ($I^2 = 92.68\%$).

DISCUSSION

To our knowledge, this study is the most comprehensive review of the existing evidence base of the performance and safety of penicillin allergy testing through all its stages. It demonstrates that the incidence of anaphylaxis due to provocation testing is low, but the data on which this is based are incomplete. It also demonstrates a lack of data regarding the follow-up of patients after penicillin allergy testing and whether the work done in the allergy clinics translates into the real world.

Our systematic review and attempts at meta-analysis demonstrated that the evidence base in β-lactam allergy delabeling is

TABLE V. Incidence of anaphylaxis

Variable	All studies (N = 284)		Prospective studies only (n = 173)	
	Studies reporting results, no. (%)	With anaphylaxis events, no. (%)	Studies reporting results, no. (%)	With anaphylaxis events, no. (%)
Testing method				
Skin test + provocation test	76 of 284 (26.8%)	22 of 814 (2.7%)	51 of 173 (29.5%)	47 of 654 (7.2%)
Provocation test alone	19 of 284 (6.7%)	45 of 283 (15.9%)	13 of 173 (7.5%)	45 of 212 (21.2%)
		$P < .0001$		$P < .0001$
Skin test results vs no skin test results by age group				
Pediatric	39 of 91 (47.6%)	3 of 600 (0.5%)	28 of 50 (56.0%)	7 of 390 (1.8%)
Adult	35 of 124 (40.2%)	57 of 463 (12.3%)	24 of 46 (52.2%)	55 of 357 (15.4%)
		$P < .0001$		$P < .0001$

poor. Of the large number of studies that we initially identified, only 15 could be clearly identified as having a low risk of bias across all aspects of the study, and there was a high number of studies with missing or incompletely reported data. Also, there were no randomized controlled studies of penicillin delabeling.

Of the studies identified, only 1 performed direct provocation testing on participants regardless of skin testing results. We cannot comment, therefore, on the utility of skin testing in identifying those who are more likely to react at direct provocation testing, as the positive and negative predictive values of skin testing cannot be appropriately assessed. This is important when considering the expense and time of undertaking specialized skin testing for β-lactam allergy, in terms of both the time and expense required for training clinical staff appropriately and the expense of minor and major determinants. The studies also had incomplete and conflicting approaches to determining which reagents were tested, the concentrations used for intradermal testing, and the place of patch testing in assessing delayed reactions. We need to require a uniform approach to skin testing (such as the use of determinants, benzylpenicillin, and amoxicillin for all patients) so that guidelines have a strong evidence base on which to make recommendations.

Also, we cannot appropriately comment on the safety of direct provocation tests. The data available demonstrated that the incidence of reaction at provocation testing was higher in those who did not undergo skin testing than in those who did, but this is significantly confounded by the fact that most people with positive skin test results did not proceed to direct provocation tests. The overall rate of anaphylaxis was low (0.3%), but again, it was lower in those who underwent skin prick testing before direct provocation tests. The same concerns regarding data on rates of provocation test positivity that we have already discussed also exist for these data. We also cannot compare the safety of different provocation protocols (ie, single-step vs multistep), because the histories of the participants were not clearly articulated. There was a higher rate of anaphylaxis in patients undergoing multistep challenge, but this may be because they were in a higher-risk cohort to begin with owing to selection bias. Clarity is required with future studies; in addition, randomized studies of the same cohort subjected to either single-step or multistep challenges are necessary to assess the true risk of these procedures.

There is also a lack of information regarding the real-world impact of β-lactam testing on future penicillin and β-lactam prescribing. Given the time and cost involved in testing, as well as the known impacts of persistent β-lactam allergy labels in patient outcomes, we need to be able to ensure that the work done in the allergy clinic translates to each patient's long-term care and ongoing health journey. We need to better assess a patients' understanding of the testing that they went through, the significance of the test results, and how we can best communicate this with them so they can play an active role in their care. We also need to understand hesitancy in posttesting prescribing in both patients and prescribers so that we can address concerns appropriately. We recognized this in our own work[10] and have undertaken long-term follow-up of a cohort of patients who underwent penicillin allergy testing to understand barriers to the appropriate prescribing of penicillins after delabeling. This process needs to be repeated in a variety of cohorts to comprehensively assess the issues and highlight further potential barriers to allergy delabeling.

Our systematic review was limited by the large amount of missing data, as well as by inconsistent reporting of the procedures, reagents, and outcomes of the studies. The studies also looked at significantly different populations and thus cannot be analyzed in a more rigorous manner. Additionally, results were often reported for the cohort as a whole, without differentiation between those who initially presented with immediate versus nonimmediate reactions. Given the anticipation that these 2 populations would differ greatly with regard to testing results, it is difficult to assess the significance of these studies. Future studies should be clear with regard to the population being assessed. If it is a mixed population, we suggest separate reporting based on historical reactions.

There is a need for future studies to look at the value of skin testing in patients with β-lactam allergy, including studies in which all participants undergo skin prick testing, intradermal testing, and direct provocation tests to assess the true utility of skin testing in the β-lactam allergy algorithm. Current clinical guidelines[8,15,16] suggest that those who are considered low-risk on the basis of our clinical history undergo direct provocation testing without skin testing, but this suggestion is based on an incomplete data base. To improve guidelines, we require studies that more rigorously assess for those who would be considered being at moderate or high risk in a trial in which individuals are randomized to direct provocation testing with or without preceding skin testing. Reporting on these trials needs to be clear, comprehensive, and uniform so that we can build a strong evidence base on which to build changes in our field.

It is also recognized that pediatric and adult presentations can differ significantly, and our data suggest that issues such as anaphylaxis are more common in adults. There remain concerns about subjecting children to inappropriate painful skin and intradermal tests, which may limit the number of suggested reagents

and dilutions. It is also suggested that children and adults be assessed separately so that the true risk of these procedures can be better appreciated.

An updated search of publications (using the same search strategy) between April 2018 and December 2022 found 27 articles with a total of 5301 participants that met our criteria. None of these studies were randomized; all of them were retrospective, and they were not additive to the current review. The literature needs to be scrutinized at regular intervals, and ideally, this review could form the basis for a living systematic review.

β-Lactam allergy testing is a field with an incomplete evidence base; however, there is scope for improvement to ensure that we are providing patients with clear and reasonable testing and management.

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