Original Article

# Long-Term Follow-Up After Penicillin Allergy Delabeling in Ambulatory Patients

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***What is already known about this topic?*** Some long-term studies have shown patient reluctance to use penicillins after ruling out penicillin allergy. A discrepancy between the recommendation to erase the label and its persistent appearance on medical files has also been noted.

***What does this article add to our knowledge?*** Penicillin allergy annulling is effective in the long-term—most patients have used penicillins after an uneventful allergy evaluation. There is a discrepancy between the process results and the allergy label in medical files.

***How does this study impact current management guidelines?*** Penicillin allergy evaluation is effective in the long-term. Rising awareness of delabeling procedures along with better communication methods between the allergy clinic and the primary physician could help enhance the effectiveness of this essential process.

**BACKGROUND: Unverified penicillin allergy label has negative health implications. To address this, several delabeling methods have been proposed.**

**OBJECTIVES: To appraise the long-term outcomes of the penicillin allergy evaluation in ambulatory patients, focusing on subsequent use of penicillins in individuals found not allergic. A secondary objective was to examine the consistency between the evaluation's recommendations and the allergy label.**

**METHODS: A retrospective medical records review and phone survey were carried out in ambulatory patients who were evaluated for suspected penicillin allergy in our allergy unit. Patients with an uneventful oral challenge test (OCT) were interviewed regarding subsequent use of penicillins. Medical records were examined for antibiotic prescriptions and purchases. The records were also investigated for existing/erased penicillin allergy label and its consistency with the allergy evaluation.**

**RESULTS: Six hundred thirty-nine patients with an uneventful OCT were available for the survey. During a 56-month follow-up, 70% (447 patients) had used penicillins at least once. One hundred ninety-two patients (30%) did not use penicillins. The main reason for not using penicillins was lack of a clinical indication. Three hundred thirty-five patients (51.22%) carried a penicillin allergy label in their electronic medical file in spite of an uneventful OCT.**

**CONCLUSIONS: Penicillin allergy annulling via OCT has proven to be effective. Most of the patients who previously avoided penicillins have reused penicillins safely.** © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:231-5)

***Key words:*** *Allergy; Penicillin; Delabeling; Oral challenge test (OCT); Skin test (ST)*

## INTRODUCTION

Penicillin is the most common drug allergy, reported in 5% to 10% of individuals worldwide and the incidence seems to be climbing.[1,2] However, after thorough history, skin tests (STs), and an oral challenge test (OCT), 95% or more of individuals reporting penicillin allergy are in fact able to tolerate penicillins.[3]

The discrepancy between the high reported allergy rates and the significantly low rates of those clinically proven to be allergic can be explained by overdiagnosis due to benign nonallergic childhood rashes,[4] side effects reported as allergy, and the tendency of penicillin specific IgE levels to wane over time.[5]

Although alternative antibiotics are usually available, the growing prevalence of individuals with penicillin allergy has substantial negative implications. Penicillin- allergic patients require longer hospitalization periods,[6-8] and are more likely to receive second-line antibiotics such as fluoroquinolones, vancomycin, and clindamycin. Patients with penicillin allergy are more likely to develop serious infections caused by *Clostridium difficile*, methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant *Enterococcus*.[9]

Traditionally, removing an existing "penicillin allergy" label requires performing an ST and OCT with the culprit drug.[10]

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*Abbreviations used*
*HMO- health maintenance organization*
*MMC- Meir Medical Centre*
*OCT- oral challenge test*
*ST- skin test*

Various delabeling methods have been evaluated,[11-13] but only a few studies have looked into the long-term outcomes of these procedures and even fewer studies have assessed the subsequent use of penicillins of those proven nonallergic. Some long-term studies have shown patient reluctance to use penicillins even after ruling out their allergy. In a 10-year follow-up survey, Warrington et al[14] described penicillins avoidance in more than 50% of the patients tested negative on an ST only, without performing OCT. A recent article by Bourke et al[12] reported subsequent beta lactam use in only 64 out of a total of 182 patients (35.16%) who completed the full evaluation uneventfully including ST and OCT.

A different aspect of the allergy workup regards the ability to remove an existing penicillin allergy label from the patient's medical files. Some cohort studies on the matter reveal a discrepancy between the recommendation to erase the label and its persistence or reappearance on electronic medical files.[15,16] A recent cohort by Macy and Shu[8] reveals that although only 1.3% of 308 patients were tested positive for a penicillin allergy, more than 12% of them had an active allergy label noted at the end of the follow-up.

The aim of this study was to appraise the long-term outcomes of penicillin allergy evaluation in ambulatory patients, focusing on reuse of penicillins and its consequences in those individuals who were found not allergic and the consistency between the evaluation's recommendations and the allergy label on the medical files.

## METHODS

### Study population

Children and adults, considered to be allergic to penicillins, were evaluated in the Allergy and Clinical Immunology Clinic at Meir Medical Center (MMC), Israel. The full assessment protocol was recently published.[17] Briefly, the evaluation included ST followed by a 5-day OCT. After completion, a letter referred to the primary physician was issued to all patients. For patients with an uneventful OCT, the letter included a recommendation to remove the penicillin allergy label from the patient's electronic medical file.

### Medical files

All hospital admissions and community visits at primary physicians and consultations, as well as medical procedures, laboratory results, and medication purchases, are electronically filed into one electronic system, open for viewing only by all the physicians from the same health maintenance organization (HMO). However, modification of essential data regarding the patient, including drug allergies, can be done by the primary physician only.

### Long-term follow-up

Long-term follow-up was accomplished by phone survey and electronic medical records evaluation.

### Medical records evaluation

Medical records of all patients were reviewed for an existing penicillin allergy label. All purchased antibiotics dated after the allergy evaluation were documented, focusing on penicillins.

### Phone survey

A phone survey of all the patients in the study group was carried out. For patients younger than 18 years, parent/caregiver was contacted. The survey was aimed to complement the existing computerized data in determining whether penicillin antibiotics were consumed after the evaluation and if so, how many times, and whether there were any adverse reactions. For the individuals who did not consume penicillins, the reason for avoidance was explored. Individuals were also asked regarding their future intention to use penicillins if indicated (see Survey protocol in Appendix E1 in this article's Online Repository at www.jaci-inpractice.org).

Use of penicillins was considered positive if it was verified by either phone survey or evidence of purchase was found in the electronic medical file.

### Statistical analyses

Data are presented as numbers and percentage for nominal parameters and as mean and SD for continuous variables. Comparisons between 2 groups were performed with Student *t* test for continuous variables and with chi-square test or Fisher exact test for categorical variables, each when appropriate. All tests of hypotheses were considered significant when 2-sided probability values were $P < .05$.

All statistical analyses were done with IBM, SPSS-24 (Armonk, NY).

The study was approved by the MMC ethical committee (approval no. 0190-16-MMC).

## RESULTS

### Patient demographics

Between May 2011 and January 2016, 784 patients were evaluated for penicillin allergy in the allergy and clinical immunology unit at the MMC. Seven hundred forty-one patients who continued to an OCT were followed. All patients with uneventful OCT were considered as the study group (Figure 1). Their demographic parameters are summarized in Table I.

### Data availability

Data were collected from medical records and/or telephone survey in 714 of the 741 patients who underwent an OCT (96.35%) (Figure 2). There were no available data on 27 patients who belonged to a different HMO and efforts to reach them by phone were unsuccessful. Oral challenge was uneventful in 654 patients, of whom 639 (97.7%) were available for the survey—either by phone and/or by medical files. A telephone survey was completed by 579 patients. On 324 patients data were collected both by telephone survey and by medical files (43.72%). One hundred thirty-five patients (18.21%) have had records of antibiotics purchase in their medical file, but could not be reached by phone. Data from telephone survey only were collected on 255 patients (34.41%) (Figure 2).

### Penicillins use

Four hundred forty-seven patients (70%) have used penicillins at least once since the OCT and of them 189 (42.28%) patients have used penicillins twice or more.

Data regarding the outcome of subsequent use of penicillins were confirmed via phone survey in 344 patients, with 19 of

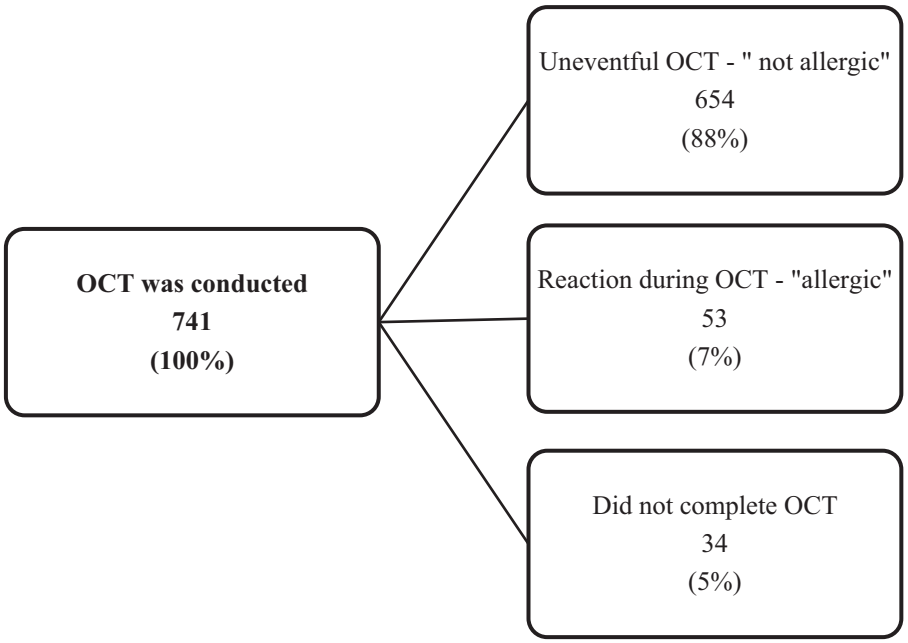


**FIGURE 1.** Number of patients who conducted an OCT and division according to OCT results.

them (5.5%) reporting adverse reactions. A late reaction manifested as benign rash was reported by 14 patients (4%), 2 patients (0.6%) described immediate reaction manifested as swollen tongue or face that resolved spontaneously, and 3 patients (0.9%) described adverse reactions such as abdominal pain and a general bad feeling. As reported by the patients, all these reactions appeared during the first course of penicillin treatment after the allergy evaluation (even though the OCT was uneventful).

A significant difference was found in reuse of penicillins when comparing the time elapsed between the alleged reaction and the OCT. Patients who were evaluated during the first year after the reaction returned to use penicillins significantly more than those who were evaluated after 3 years or longer (72.4% vs 62.9%; $P < .05$). No significant differences in the reuse of penicillins were found when comparing other subgroups including male versus female and age groups (younger than and older than 18 years).

### Penicillins avoidance

One hundred ninety-two patients (30%) did not use penicillins according to the patient's electronic medical files and/or phone survey. The reasons for penicillins avoidance were available in 163 (84.9%) patients. The main reason for not using penicillins was "lack of indication," with a total of 103 patients (63.2%). When they were asked regarding their future intention to use penicillins, if indicated, 96 of them (93.2%) expressed willingness.

Sixty patients out of the 163 who were questioned by phone (36.8%) refused to use penicillins. The main reason for refusal was lack of personal conviction that penicillins could be safely consumed (17%). Other reasons include inadequate understanding of the evaluation's results (10%) and refusal of the family physician to prescribe them penicillins (4%) (Figure 3).

### Penicillin allergy label

Three hundred thirty-six patients of the 654 (51.37%) who uneventfully completed the OCT still had a penicillin allergy label in their electronic medical file. Of them, penicillins were prescribed and purchased by 238 patients (71%) despite the allergy label present in the electronic medical files.

### Failed OCT

Although it was not the main focus of this study, 53 patients failed the OCT (Figure 1); 11 of them (20.75%) lack the allergy label and another 11 (20.75%) used penicillins after they failed the OCT. Of these, only 1 patient reported an allergic reaction described as a late-onset benign rash.

## DISCUSSION

Unverified penicillin allergy is a public health concern, with proven negative clinical implications.[2] The current criterion standard to rule out a penicillin allergy includes a negative ST result followed by an uneventful OCT.[10] This study was conducted to evaluate the long-term effectiveness of a 5-day OCT in an ambulatory setting.

Overall, the results presented show that most of the patients who completed the OCT uneventfully returned to use penicillins without any adverse events. The relatively high rates of reuse of penicillins were consistent between all subgroups; no differences were found between men and women or adults and children. These rates are higher than previously described by Bourke et al[12] who reported subsequent use of penicillins in 64 of 182 patients, 35.16%. This may be explained by the longer time elapsed between the evaluation and the survey, median of 37 months in our study, compared with 15 months in Bourke et al's study.

Patients evaluated during the first 12 months after the index reaction used significantly more penicillins than those evaluated

**TABLE I.** Demographic parameters of the patients with an uneventful OCT

| Parameter | Total | Age | |
|---|---|---|---|
| | | <18 y | >18 y |
| Total (%) | 654 | 447 (68) | 207 (32) |
| Male (%) | 310 (47.4) | 259 (57.9) | 51 (24.6) |
| Female (%) | 344 (52.6) | 188 (42.1) | 156 (75.4) |
| Age (y), mean ± SD | 19.02 ± 23.2 | 5.03 ± 4.3 | 49.2 ± 17.9 |
| Symptoms of the index reaction (% of total) | 589 (90) | 429 (96) | 161 (77.7) |
| Rash | 154 (23.5) | 88 (19.7) | 65 (31.4) |
| Pruritus | | | |
| Dyspnea | 24 (3.7) | 10 (2.3) | 13 (6.3) |
| Gastrointestinal | 13 (2) | 9 (2) | 4 (2) |
| Angioedema | 44 (6.7) | 21 (4.7) | 23 (11.1) |
| No recollection | 206 (31.5) | 105 (23.5) | 99 (47.8) |
| Antibiotic that caused the reaction (% of total) | | | |
| Amoxicillin (% of total) | 431 (65.9) | 366 (81.9) | 65 (31.4) |
| Phenoxymethyl penicillin | 25 (3.8) | 7 (1.6) | 18 (8.7) |
| Amoxicillin-clavulonic acid | 62 (9.5) | 39 (8.7) | 23 (11.1) |
| Penicillin | 58 (8.9) | 13 (2.9) | 45 (21.7) |
| Cephalosporins | 6 (0.9) | 4 (0.9) | 2 (1) |
| Unknown | 55 (8.4) | 8 (1.8) | 47 (22.7) |
| More than 1 antibiotic | 17 (2.6) | 10 (2.2) | 7 (3.4) |
| Time between original allergic reaction and OCT (y) | | | |
| Mean ± SD | 7.18 ± 12.58 | 2.46 ± 3.36 | 17.56 ± 18.05 |
| Median | 1.15 | 1 | 15 |
| Range | 0-75 | 0-18 | 0-75 |
| Time between OCT and survey (mo) | | | |
| Mean ± SD | 34.5 ± 14.9 | 34.1 ± 15 | 35.6 ± 14.8 |
| Median | 37 | 34 | 38 |
| Range | 7-63 | 7-63 | 7-63 |

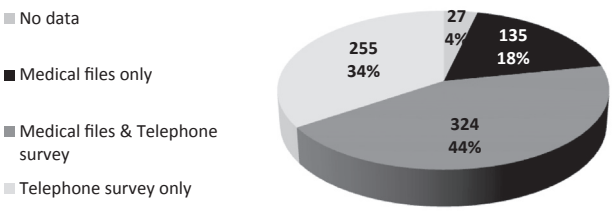


**FIGURE 2.** Data availability according to the methods used to extract the information. Medical files only—Patients who could not be reached by phone, but had information in the electronic medical files. Telephone survey only—Patients without electronic records of purchasing antibiotics, but who have answered the telephone survey. Medical files and telephone survey—Patients with electronic data and telephone survey.

afterwards. Exploring the reasons for this difference was beyond the scope of this study, but one can only assume that after prolonged avoidance of penicillins, there might be a greater tendency to continue using alternative antibiotics. Regardless of the reasons, these results suggest that there is an advantage for an earlier penicillin allergy evaluation, preferably within a year of the initial reaction.

In terms of safety, 4.6% of the patients reported a suspected allergic reaction after reuse of penicillins. Most of them reported a delayed benign rash. This is in accordance with previously published data by Phillips et al[18] who found that 4% of patients suffer from allergic reactions in spite of an uneventful OCT. It is unknown whether the patients developed a reaction *de novo* or an allergic reaction because of recurrent exposures to penicillins.[10]

The current data point toward high confidence of the examinees in the process: at the time the survey was conducted, most of the patients have already used penicillins. Most patients who had no subsequent use of penicillins have not done so simply because there was no medical indication. When those patients were asked regarding their future intention to use penicillins, if indicated, almost all of them answered positively. These results show a significantly higher rate of confidence in evaluations that include ST and a 5-day OCT than those based on ST only, as described by Warrington et al,[14] which have shown avoidance rates as high as 50%.

A second important aspect of this study regards documentation of allergy and labeling accuracy. As recently described,[8,19] penicillin allergy false labeling carries substantial negative implications such as longer hospitalization days, more emergency department and outpatient visits, and higher use of broad-spectrum antibiotics. In this current study, high rates of false labeling were found in both the allergic and the nonallergic groups. Half of the patients who were classified as nonallergic maintained their penicillin allergy label in their medical file. Surprisingly, this did not have a major effect on the tendency to

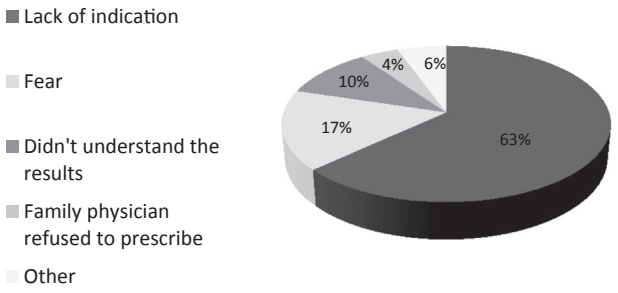


**FIGURE 3.** Reasons for no subsequent use of penicillins after uneventful OCT.

prescribe penicillins. In more than half of these patients, penicillins have been prescribed and subsequently taken despite having maintained the allergy label.

To complete this mismatch, not all patients who failed the OCT had a penicillin allergy label in their medical file. Even more bothersome are those who did have a penicillin allergy label and yet were prescribed and used penicillins. This lack of consistency to the label and the prescribed medications further emphasizes the need to better adhere to the allergy labels in the personal medical file.

In the electronic medical system used by the HMOs, erasing the allergy label can be done only by the primary treating physicians and not by the consultants or hospital physicians (this may be considered atypical when compared with other HMOs in the world, where all providers, including nurses and pharmacists, can update the "allergy" lists). One can speculate that as opposed to the patient's confidence in the evaluation, the physicians remained skeptical and chose not to remove the label. Nonetheless, this does not explain prescribing penicillins to those patients with an allergy label. Further investigation of this lack of adherence was beyond the scope of this study.

A thought-provoking aspect is the fact that only 1 of 11 patients who used penicillins after failing the OCT had a late-onset allergic reaction. The explanation for this result is speculative. One can assume that the subsequent treatment course was shorter than the OCT. Another possible explanation is that enough time elapsed since the OCT and as expected from penicillins skin reactions, it waned over time.

This study is subject to the limitations inherent to phone surveys and the boundaries of patients' memory. However, the integration of subjective data from the survey and objective data extracted from medical files may attenuate its effect. Another limitation consists of an internal selection bias of the patients arriving actively to the allergy clinic for evaluation.

Despite these limitations, the study group is quite large and heterogeneous, supporting the effectiveness of the allergy evaluation procedure.

In conclusion, this study has found penicillin allergy evaluation by using ST and 5-day OCT to be effective in the long-term. Most of the patients who avoided penicillins because of previous allergy diagnosis have proven reuse of penicillins safely. Furthermore, patients who avoided penicillins because of lack of indication expressed their readiness to use it in the future, if indicated, and by this expressed their confidence in the evaluation.

However, in terms of allergy label modifications, there seems to be a discrepancy between the allergy evaluation and its documentation in patients' electronic medical files. Rising awareness of this matter among all practicing physicians, along with better communication methods between the allergy clinic and the primary physician, could help enhance the effectiveness of this essential process.

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## ONLINE REPOSITORY

## APPENDIX E1. PHONE INTERVIEW

1 . Verification of patient details and evaluation results.
2. Have you received penicillins antibiotics since your visit to the allergy clinic?
   a. Yes:
      i. Were there any allergic reactions?
      ii. What was the nature of these reactions?
   b. No—please specify why not:
      i. There was no need to use penicillins since.
         1. In the future, if a need does arise, do you intend to use penicillins?
            a. Yes.
            b. If not—why?
      ii. I still prefer to avoid penicillins.
      iii. My physician prefers that I avoid penicillins.
      iv. I did not fully understand the allergy clinic's recommendations.
      v. Other.
3. Do you have any questions or further remarks?