REVIEW

How Far Are We From Achieving Delabeling of False Penicillin/ß-Lactam Allergy Alerts? A Population Problem

Tejedor-Alonso MA[1,2], Perez-Encinas M[3], Sanz Márquez S[3], Martinez Simon JJ[3], Moreno-Nuñez L[4], Gonzalez-Moreno A[1], Macias-Iglesias J[1], Rosado-Ingelmo A[1,5]

[1]Allergy Unit, University Hospital Fundación Alcorcon, Alcorcón, Spain
[2]Facultad Ciencias de la Salud, Department Public Health and Medical Specialties, Universidad Rey Juan Carlos, Alcorcón, Spain
[3]Pharmacy Area, University Hospital Fundacion Alcorcón, Alcorcón, Spain
[4]Infectious Diseases Unit, University Hospital Fundación Alcorcón, Alcorcón, Spain
[5]International Doctoral School, Faculty of Health Sciencies Ciencias de la Salud, University Rey Juan Carlos, Alcorcón, Spain

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Abstract

Interest in finding efficient ways to remove penicillin allergy alerts has grown as a result of awareness of the considerable excess of false-negative diagnoses in patients with penicillin allergy labels (90%-95%), the poorer course with non–ß-lactam antibiotics, the increase in bacterial resistance, and the fact that these problems can affect up to 20% of the population in some countries. The strategies proposed have generated many publications in countries where the number of allergists to conduct such studies is low.

In many cases where delabeling is performed, the risk of ß-lactam allergy is low, and a single penicillin challenge is sufficient to delabel the alert. However, other less "ultrarapid" strategies can be used to administer a ß-lactam during an admission for infection and thus postpone delabeling until traditional drug allergy consultations.

However, the definitive withdrawal of ß-lactam alerts is threatened by nonremoval of alerts in electronic health records and by the reactivation or nonsynchronization of alerts between electronic systems at different levels of care.

Allergy departments need to reflect on how to implement practices that enable rapid and efficient delabeling of drug allergy alerts, especially in patients with major comorbidities.

Key words: Penicillin. ß-Lactam. Allergy. Label. Barriers. Effectiveness.

Resumen

El interés por encontrar formas eficaces de eliminar las alertas de alergia a penicilina ha crecido como consecuencia de la concienciación sobre el considerable exceso de diagnósticos falsos negativos en pacientes con etiquetas de alergia a la penicilina (90%-95%), la peor evolución de enfermedades infecciosas con antibióticos no betalactámicos, el aumento de las resistencias bacterianas, y el hecho de que estos problemas pueden afectar hasta al 20% de la población en algunos países. Las estrategias propuestas han generado muchas publicaciones en países donde el número de alergólogos para llevar a cabo este tipo de estudios es bajo.

En muchos casos en los que se lleva a cabo la retirada de la etiqueta, el riesgo de alergia a betalactámicos es bajo, y una única provocación con penicilina es suficiente para suprimir la alerta. Sin embargo, pueden utilizarse otras estrategias menos "ultrarrápidas" para administrar un betalactámico durante un ingreso por infección y posponer así el desetiquetado hasta las consultas tradicionales de alergia a medicamentos.

Sin embargo, la retirada definitiva de las alertas de betalactámicos se ve amenazada por la no retirada de las alertas en los historiales médicos electrónicos y por la reactivación o no sincronización de las alertas entre los sistemas electrónicos de los distintos niveles asistenciales.

Los servicios de Alergia deben reflexionar sobre cómo implantar prácticas que permitan la retirada rápida y eficaz de las alertas de alergia a medicamentos, especialmente en pacientes con comorbilidades importantes.

Palabras clave: Penicilina. Beta-lactámicos. Alergia. Etiqueta. Barreras. Efectividad.

Introduction

In the last 10 years, interest has grown in the use of ß-lactam antibiotics in patients with penicillin allergy labels. This has been accompanied by a notable increase in the number of publications from allergy and other specialties (eg, primary care, pharmacy, anesthesiology, infectious diseases) on the need for strategies to delabel penicillin allergy. These publications are a consequence of the knowledge that penicillin allergy is not true in more than 95% of cases, the greater toxic effects and reduced efficacy of alternative antibiotics, and the increased frequency of bacterial resistance in affected individuals.

Therefore, this "explosion" in interest is accompanied by a series of controversial questions surrounding whether we should change the way we assess patients with penicillin allergy labels. Should skin testing (ST) be performed in all suspected cases independently of the risk of true penicillin allergy, or should only the drug provocation test (DPT) be performed in cases of low risk of true penicillin allergy? Should we not wait for the failure of antibiotics other than ß-lactams before assessing whether an admitted patient will tolerate the best ß-lactam for the infection responsible for the admission? [1].

Epidemiology of Penicillin Allergy

General Data

Studies show that 35.7% and 50% of hospitalized patients in Scotland and the US, respectively, need at least 1 course of antibiotic treatment during admission [2].

Macy and Adkinson [3] report a new, predictable penicillin allergy within 30 days after approximately 0.5% of all classes of penicillin treatment. Penicillin-associated anaphylaxis is extremely rare, occurring in only about 1 in 255 000 oral exposures and 1 in 124 000 parenteral exposures [2].

Recent studies of large populations in the United States and Denmark, Spain, and Portugal show that the clinical records of admitted patients contain a penicillin allergy label in 10-12%, 2.6%, and 0.9% of patients, respectively [4-7]. In addition, 5.9% of the general population in the UK have a penicillin allergy [8]. Recent studies of a large electronic health records database found the frequency of drug-induced anaphylaxis to be 1.1% in the USA, with the most common culprit being penicillin, and reported that, in Spain, a drug was involved in 5.3% of all patients admitted with anaphylaxis [4,7-11].

However, only 1%-2% of people who report penicillin allergy are confirmed to have a true IgE-mediated allergy to penicillin. Individuals whose penicillin allergy label has been removed based on a negative oral challenge are still at least twice as likely to report a new allergy with any future penicillin use [3].

Differences between countries have been reported with respect to diagnosis of penicillin allergy. Southern European populations have a lower rate of reactivity to the major determinant penicilloyl-polylysine with penicillin ST, likely owing to the higher prevalence of amoxicillin allergy, with patients being sensitized to the R-group side chain. Populations in the United States and Scandinavia are more likely to develop hypersensitivity to the ß-lactam core [12]. While penicillin allergy can be ruled out in the USA based on ST with penicillin, followed by a simple dose of amoxicillin, in many European countries, it is necessary to establish tolerance to the ß-lactam antibiotic involved in the adverse reaction and tolerance to penicillin using graded drug challenge when appropriate [13-17].

The positive predictive value has classically been considered low when the prevalence of penicillin hypersensitivity is low. Therefore, in these populations, false positives can arise [11,18-20].

Several studies have shown that IgE-mediated penicillin hypersensitivity decreases in a significant percentage of patients at a follow-up of 5-10 years [21-24]. On the other hand, the risk of resensitization after oral courses of penicillin is absent in the USA [25] and present in 2% to 15.9% of European studies [24-27].

These differences may explain the different strategies used for delabeling in these geographical areas.

Health Implications and Burden of the Penicillin Allergy Label

Castells et al [26] studied the repercussions of the penicillin allergy label using 2 approaches: first, in terms of personal health, owing to the use of less effective antibiotics, which are associated with more toxic effects and a greater presence of surgical site infection; and second, in terms of public health, with increases in bacterial resistance to antibiotics (methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*), higher rates of *Clostridioides difficile* infection, use of more costly antibiotics, and increased length of hospital stay [26,27]. Some studies reported a small increase in mortality after long-term follow-up. Gray [28] and Blumenthal et al [29] reported a small increase in mortality risk (hazard-ratio, 1.08 and 1.14, respectively) in patients labeled as allergic to ß-lactams or other, non–ß-lactam antibiotics. These findings should affect only 5% of cases labeled as penicillin allergy, that is, patients with true allergy [26,30].

In the US, a penicillin allergy label is applied to 20% of the population and 15% of patients admitted to hospital (7 million people) [26]. However, the problem is much less serious in countries such as Spain and Portugal, where the prevalence of patients admitted with penicillin allergy is only 2.5% and 0.9%, respectively [5,6].

Table 1 summarizes studies addressing the consequences of a penicillin allergy label. Analysis of the consequences of not using ß-lactam antibiotics reveals significant results—albeit with an OR<2—in studies based on data from a single hospital with 1 research protocol to obtain data directly from cohorts comprising 300-1000 admitted patients and studies with clinical-administrative databases for cohorts comprising >105-106 patients [6,9,27,31-39].

For the above reasons, several large American clinical societies and public institutions recommend evaluation of penicillin allergy and delabeling where possible [40-42].

Table 1. Studies Assessing Various Aspects of Events Described in Patients With a Penicillin Allergy Label.

	West/ UK/2019/ General Practice/ Health System [8]	Charneski/ USA/2011/ 1 hospital [52]	MacFadden/ Canada/ 2016/ 1 hospital [31]	Blumenthal/ USA/2018 General Practice/ Health System [32]	Blumenthal/ USA/ 2018/ 1 hospital [33]	Savic/ UK/2019/ 1 hospital [35]	Macy/USA/ 2014/HMO [9]
MRSA	1 in 1000 more patients with MRSA.		Global marker (readmission, CDI, drug reaction, or AKI) 3.43/95%CI, 1.28.7.89)	Adjusted HR=1.69 (95%CI, 1.12-1.40), 55% caused by alternative ß-lactam antibiotics			OR, 1.14 (95%CI, 1.07-1.32)
VRE							OR, 1.30 (95%CI, 1.13-1.504)
Surgical site infection					Increased odds of SSI (adjusted OR [aOR], 1.51; 95%CI, 1.02-2.22)		
Duration of admission/ Readmission if penicillin allergy label		Average all ages 1 d longer. 20-39 years 4.5 d longer Adjusted readmission OR=0.71 (0.63-0.80)	Penicillin-allergic patients who did not receive ß-lactams, adjusted OR=3.42 (95%CI, 1.28-7.89) due to readmission and adverse effects				
Deaths	6 in 1000 more deaths	Adjusted OR=1.56 (1.20-2.04)					
Clostridioides difficile infection	No increased risk			Adjusted HR=1.26 (95%CI, 1.12-1.40) 35% caused by alternative β-lactam antibiotics			1.23 (95%CI, 1.16-1.32)
Costs and toxicities of alternative drugs							The increased hospital use accounted for 30 433 extra hospital days. This amounts to $64 626 630.48 more in health care expenditure

(continued)

Table 1. Studies Assessing Various Aspects of Events Described in Patients With a Penicillin Allergy Label (*continuation*).

	Ramsey/USA/2020/ 1 hospital [53]	DuPlessis/New Zealand/2020/ 1 hospital-outpatients /randomized [37]	Mustafa/USA/2019 [38]	Chua/Australia/ 2021/ 2 hospitals [39]	Perez-Encinas /Spain /2021/ Spanish hospital system [6]
MRSA					
VRE					
Surgical site infection					
Duration of admission/ readmission if penicillin allergy label		Median length of stay of 6 d (IQR, 2-8 d) vs patients who were confirmed allergic median (9 days (IQR, 3-13.5 d) *P*=.0015			Increase in length of stay 6% (5 d vs 4 d)
Deaths					Less mortality in allergic patients
Clostridioides difficile infection					
Costs and toxicities of alternative drugs	Total cost avoidance, $23 375.27		ST cost a total of $29 092.80 for the 80 patients DPT cost a total of $4239.14 for the 79 patients	355 patients delabeled in the inpatient setting, with a total cost of $6825; if this been performed in the outpatient clinic, the total cost would have been $60 447	

Abbreviations: AKI, acute kidney injury; CDI, *Clostridioides difficile* infection; DPT, drug provocation test; MRSA, methicillin-resistant *Staphylococcus aureus*. SSI, surgical site infection; ST, skin test; VRE, vancomycin-resistant enterococcus.

Strategies to Enable Fast and Total Delabeling in Penicillin Allergy

The need to delabel penicillin allergy has led to various initiatives to overcome the nonuse of ß-lactam antibiotics in patients with a penicillin allergy label, above all in patients with a low risk of true allergy. In this review, we analyzed several systematic reviews and meta-analyses addressing various aspects of delabeling.

In summary, a dilemma can be observed in international publications over whether challenges should be performed with penicillins after ST, with penicillin determinants, or with other ß-lactam antibiotics.

Publications on direct DPTs use structured questionnaires. A systematic review of the safety and efficacy of delabeling penicillin allergy in adults using direct oral challenge revealed the following [43]:

- Eleven of the studies in the review used a similar standardized questionnaire or screening tool to assess the patients' history and thus determine the risk of true allergy.
- Devchand et al [44] and Trubiano et al [45] validated 2 tools designed to be used by nonspecialist clinicians for stratifying the risk of reaction after a challenge.
- According to the authors, adoption of a validated tool with appropriate training could help nonspecialist clinicians to assess and delabel patients in whom it is unknown whether they have true penicillin allergy. However, there is no evidence published in its favor.

The most common nonallergy specialties involved in delabeling [43] were general/internal medicine, intensive care, oncology-hematology, and general surgery (Table 2). The participation of obstetrics and pediatrics in these studies is remarkable, since studies involving pregnant women were previously not recommended because of the risk for the fetus and the usual tolerance to ß-lactam antibiotics in ß-lactam–experienced children who have had exanthems. Pharmacists also played a key role in delabeling and, in the USA, are considered the specialists of reference in the absence of support from an allergist. Likewise, most studies involved patients with a low risk of true penicillin allergy, although some studies were performed in high-risk patients [43]

In another meta-analysis [46], tolerance to ß-lactams was assessed in terms of the history of penicillin allergy and challenge with or without previous ST. A total of 5056 patients with a reported penicillin allergy were challenged, mainly with aminopenicillins and natural penicillins. The

Table 2. Specialties and Risk for a True Allergy in the Systematic Review of Powell et al [43].

Specialty involved	No.
General/internal medicine	23
Intensive care	12
Oncology	11
Surgery/general surgery	10
Hematology	9
Emergency department	8
Pediatrics	6
Perioperative assessment study	6
Obstetrics and gynecology	5
Emergency department	4
Outpatient clinics	3
Transplant services	3
Cardiology	2
Maxillofacial surgery	1
Neurology	1
Urology	1
Risk of a history of true allergy	**No.**
Low risk of allergy history	26
Moderate risk of allergy history	21
Unclear risk	18
Low and moderate risk of allergy history	2
Low, moderate, and high risk of allergy history	2

pooled weighted average tolerance calculated with random effects was 94.4%. Dose challenge was tolerated more frequently in patients based on direct provocation alone than in those where prior ST was used: the patients were probably higher-risk and were selected to undergo ST prior to dose challenge. The authors conclude that the studies safely identified low-risk patients who were candidates for dose challenge without prior ST, thus supporting this practice in settings without specialist allergy support.

These results are similar to those of another systematic review [47] of 19 studies of inpatient populations assessing the accuracy of ST in penicillin, where the percentage of negative results among inpatients ranged between 79% and 100%.

In a meta-analysis [43] that assessed the effectiveness of interventions performed in adult and pediatric patients by nonallergy specialists, the authors reported the percentage of delabeling to be under 40% of the initial approximate assessment for delabeling, because the delabeling procedure was not carried out in more than 60% of cases (Table 3). However, when the procedure is performed, the percentage of delabeling is over 95%. These results are repeated in more recent studies such as those of Chua et al [39] and Moreno-Rosado et al [48]. Likewise, the study populations were older and had major comorbidities [48].

The same meta-analysis [43] revealed high heterogeneity between studies, probably resulting from the different assessments of patient factors and allergy history, the route of DPT administration, the location where testing was performed, and the different specialists undertaking testing.

All these strategies are characterized by fast delabeling (simple oral drug administration is usually shorter with direct challenge, requires fewer staff, making it less costly overall than with ST followed by single or multiple grading doses) and a short duration (maximum 2-3 hours) [2,46,47], and most cases prove to be low-risk for true penicillin allergy. Many publications based on this approach are from English-speaking countries, where hypersensitivity is mainly to the ß-lactam nucleus or the proportion of allergy labels is higher (frequencies higher in hospitalized patients than some European countries) and the number of allergists available to study the huge number of people claiming to be allergic to penicillin is low (in the USA, 1 per 17 500 allergic people) [49]. This contrasts with the Madrid region in Spain, where each allergist would have to assess 1500 patients with a penicillin allergy label (Table 4) [50].

Strategies to Slow and Partially Delabel Penicillin Allergy

Other less resolutive strategies have been assayed to enable the use of some ß-lactam antibiotics in patients with a penicillin allergy label. In a hospital in Castellon, Spain [51], pharmacists identified admitted patients with a penicillin allergy label and

Table 3. Approximate Percentage of Delabeling of Penicillin Allergy on Initial Assessment According to The Meta-Analysis by Powell et al. [43].

Type of delabeling	No. of studies	No. assessed for testing	No. (%) of total delabeled patients	No. of patients suitable for drug delabeling	No. (%) patients suitable for drug delabeling with successful delabeling
Total delabeling	47	11 856	3720 (31.4%)		
Delabeling based on history alone	11	4350	689 (15.8%)	713	701 (100%; 95%CI, 99%-100%), with no reports of harm.
Direct DPT	12	4027	844 (27%; 95%CI 18-37%)	1336 patients tested,	1288 (98%; 95%CI, 97%-99%).
SPT and DPT 12 studies	12	2890	925 (41%; 95%CI 24-59%)	1294	1177 (95.0%; 95%CI, 90%-99%)

Abbreviations: DPT, direct provocation testing; SPT, skin prick testing.

Table 4. Number of Allergists Available to Assess Penicillin Allergy Label (Assessment of Adverse Reactions, All Diagnostic Tests Including Drug Provocation Tests) in the Region of Madrid, Spain and the United States Of America [50,54].

Geographical area	Number of allergists per 100 000 inhabitants	Prevalence of penicillin allergy label in the hospital	No. of penicillin-allergic patients per allergologist
Region of Madrid, Spain with 132 allergists in the public health system	2	2.5%-3%	1500 In our hospital, there would be 2300 patients in the >65-year age group with activated penicillin allergy alerts [64]. In 2016, 500 penicillin allergy studies were carried out in the Allergy Unit of the authors' review, ie, work for 4-5 years [63]
United States of America, 2000 allergists performing drug allergy studies (40% of the population with access to penicillin allergy testing)	0.5	10%-15%	350*106*0.1/1500=17 500

referred them to the allergy department for classic drug allergy assessment (ST and DPT). The authors reported efficacy data for 176 patients collected over 21 months that were similar to those reported for faster strategies [51]

In our hospital [48], the strategy is aimed at assessing the tolerance of chosen ß-lactam through the antibiotic stewardship program. After discharge, the patient is referred to the allergy department to complete a classic study for drug allergy assessment. Once again, the results for safety, elective population, and percent of delabeling were similar to those of previous studies with faster delabeling [43,46].

A health management organization in the east of the USA [28] published findings for a strategy where information on administration and tolerance of ß-lactam antibiotics is found by algorithms based on natural language processes. The results were good with the most ambitious algorithm (F1 score=0.90).

Towards Local Strategies for Delabeling Penicillin Allergy

Our overview of these strategies indicates that in countries such as the USA or Australia, delabeling penicillin allergy is a cause of some concern. Therefore, it is necessary to find safe and efficient strategies for delabeling, for example, DPTs with a single dose of amoxicillin and performance of testing by nonallergists in patients with a low risk of true penicillin allergy. In other countries, on the other hand, especially those with more human capital in allergology, the concern may be less urgent than in the above-mentioned countries. Consequently, the usual practice is to maintain the classic drug allergy tests with ST and DPT.

In any case, the current capacity of health systems with both low and high frequencies of penicillin allergy labeling is exceeded by the huge number of people who report being allergic to penicillin. Therefore, realistic strategies are mandatory (Table 4).

Effectiveness of Delabeling

The effectiveness of delabeling penicillin allergy is usually assessed based more on changes in the antibiotic use profile and less on measures of effectiveness such as length of stay.

In an exact matched analysis after 12 months of follow-up, West et al [8] reported that patients with a record of penicillin allergy received 5% more antimicrobial prescriptions than those without. Charnesky et al [52] noted that patients with a penicillin allergy label had an adjusted OR of 1.51 for use of >1 antibiotic compared with patients without the label.

Likewise, patients with penicillin allergy were less often prescribed any ß-lactam antibiotic than patients without a history of penicillin allergy (adjusted incidence rate ratio, 0.30). In addition, these patients more frequently received macrolides (4.15), clindamycin (3.89), fluoroquinolones (2.10), and tetracyclines (1.75) [31].

Several studies have shown that patients with penicillin allergy do not receive the antibiotic of choice for prevention of surgical site infection (usually cefazolin, owing to a favorable spectrum of antibacterial effect and good distribution in the skin). In their observational study, Blumenthal et al [33] found that patients with a reported penicillin allergy were significantly less likely to receive cefazolin before surgery (12.2% vs 92.4%; $P<.001$) and more likely to receive clindamycin (48.8% vs 3.1%; $P<.001$), vancomycin (34.7% vs 3.3%; $P<.001$), gentamicin (24.0% vs 2.8%; $P<.001$), and fluoroquinolones (6.8% vs 1.3%; $P<.001$).

In addition, in cases where cefazolin or vancomycin was used (n=8085), 97.5% did not receive vancomycin within the time frame for administration recommended by guidelines, whereas only 1.7% of patients did not receive cefazolin within the recommended time frame ($P<.001$) [33].

Studies that have assessed the change in antibiotic use profile after delabeling report a decrease in prescription of aztreonam, quinolones, and macrolides and an increase in prescription of all classes of ß-lactams.

In a meta-analysis analyzing clinical changes among inpatients who had undergone penicillin allergy testing, Sacco et al [47] found that 25 studies (36%) reported increased use of ß-lactams, and 22 (33%) reported the use of narrower-spectrum ß-lactams or the preferred regimen. The authors also observed reduced use of glycopeptides, quinolones, aztreonam, carbapenems, clindamycin, cephalosporins, macrolides, and aminoglycosides.

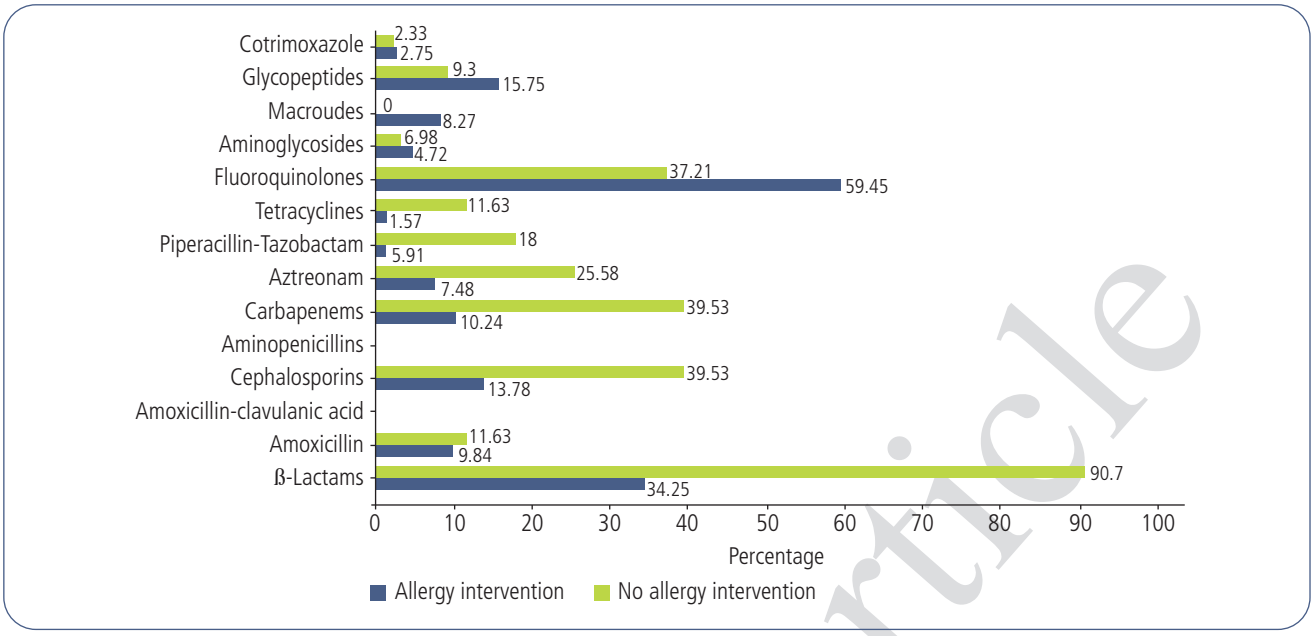
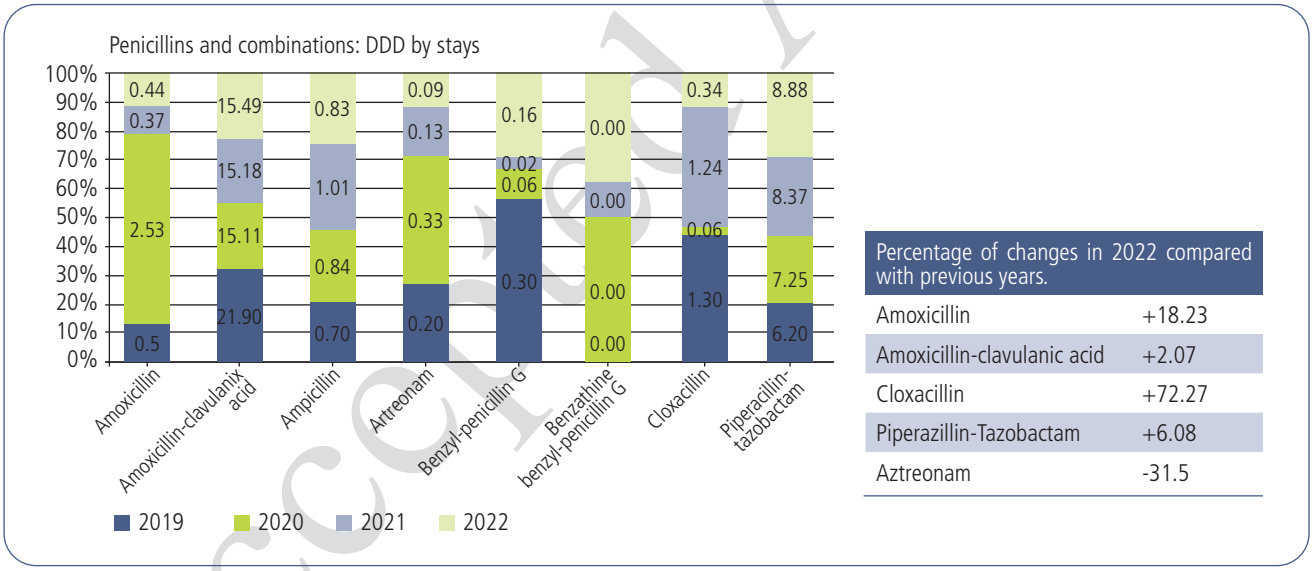


Figure 1. Changes in the profile of antibiotic use in Hospital Universitario Fundación Alcorcon after an intervention by the Allergy Department in the hospital's multidisciplinary antibiotic stewardship program.



Percentage of changes in 2022 compared with previous years.	
Amoxicillin	+18.23
Amoxicillin-clavulanic acid	+2.07
Cloxacillin	+72.27
Piperazillin-Tazobactam	+6.08
Aztreonam	-31.5

Figure 2. Changes in the antibiotic use profile at Hospital Universitario Fundación Alcorcon after an intervention by the Allergy Department in the hospital's multidisciplinary antibiotic stewardship program. We highlight the decrease in the use of aztreonam and the increase in the use of amoxicillin and amoxicillin-clavulanic acid in 2022, 1 year after the start of the intervention by the Allergy Department. DDD indicates defined daily dose.

Likewise, Du Plessis et al [37] noted that prescription of penicillin antibiotics changed during the year after the intervention in the delabeled group: penicillin antibiotics were prescribed for 28% of courses before surgery compared with 62% of courses after surgery in this group (P=.0001).

Similar results are reported by other studies and groups [39,53], including that of Moreno-Nuñez et al [48] (Figures 1 and 2).

Other analyses of effectiveness, for example the meta-analysis of Powell et al [43], showed that hospital length of stay was reduced in 3 studies, although mortality and readmission rates remained unchanged.

Safety of Delabeling

In the meta-analysis of DesBiens et al [46], 228 of the total number of patients (4.5%) reported reactions that may be compatible with hypersensitivity. In mild syndromes, 85 participants developed only urticaria, 129 developed mild rash,

4 noted only pruritus, 1 developed facial erythema, 1 developed facial and hand swelling, 1 noted shortness of breath, and 1 reported a metallic taste. More severe adverse reactions were detected in 6 patients: 5 participants were coded as having anaphylaxis, although all 5 of these reactions occurred 1 hour after the dose challenge, and none of the 5 patients had systemic symptoms or required epinephrine.

In the meta-analysis of Powell et al [43] the rate of adverse reactions was lower: 1.5% for all 47 studies and 3720 patients, 2% for direct drug provocation testing, and 0.03% for ST and DPT.

In the systematic review of Cooper et al [2] , which was based on DPT, of the 1202 patients challenged, 41 (3.41%) experienced a reaction to direct DPT; of these, 17 reactions (41%) were immediate and 24 (59%) were delayed. All reactions were reported as mild or intermediate, with no reports of anaphylaxis in any of the studies analyzed. Participants in the direct challenge group experienced 8.7% fewer positive results than those randomized to the SPT plus challenge group (P=.079).

The evidence level of these studies is low owing to their observational design. However, no statistically significant differences in the number of adverse reactions observed were reported a recent international randomized noninferiority trial [54] carried out in 6 Australian and North American hospitals in patients with a low risk for penicillin allergy and where patients were randomly assigned to a direct challenge or ST and challenge (both 0.5%).

Who Should Perform Delabeling?

According to the literature reviewed, direct oral DPT can be performed safely in hospitalized patients considered low-risk for true penicillin allergy based on their allergy history. This approach is effective in delabeling patients with an unverified allergy label. Only patients who were classified as low-risk according to individual study criteria can be offered direct DPT.

Those who reported a recent allergic reaction and those who reported severe symptoms associated with IgE-mediated hypersensitivity are considered high-risk and cannot be offered direct DPT; consequently, they must be referred for specialized allergy evaluation.

Efficiency of Delabeling

In the meta-analysis of Powell et al [43], several studies ascertained the length of the intervention. Nine studies reported staff time taken with ST patients and found that an hour or less was necessary per patient. One study reported the time requirement as 0.15 full-time equivalent pharmacists, with 30 minutes a week for a pharmacy technician. In our hospital, the patient interview, data collection, obtaining written consent from the patient's family, and performance of ST and drug challenge take only 5% of time from the usual activity of the outpatient allergy clinic, with 2 hours necessary for completion of the procedure.

Powell et al [43] analyzed 13 studies reporting antibiotic cost savings and found that between $225 and $7800 was saved per delabeled patient. The annual hospital drug saving was between $12 400 and $26 000. Another study reported antibiotic costs to be 2.5 times greater for inpatient and outpatient allergy. Three studies reported the cost of ST to be between $137 and $175, and the cost of DPT was reported to be AUS$35.18.

Perez-Encinas et al [6,55] calculated an excess length of stay for patients with a penicillin allergy label in the Spanish hospital system of 19 486.64 days in 2014 and 2015, reporting an avoidable expense of €13 880 130.80. In 104 patients in our hospital, where delabeling of penicillin allergy was carried out as part of an antibiotic stewardship program, the number of antibiotics after delabeling was 1.15, and the daily expenditure on antibiotics was €7.06, compared with 1.72 antibiotics used and €16.96 per day before delabeling.

After Delabeling

Use of Penicillins After Delabeling

Some long-term studies have shown patient resistance to using penicillins when penicillin allergy has been ruled out.

In a 10-year follow-up survey, Warrington et al [56] reported penicillin avoidance in more than 50% of patients with a negative ST result, without performing oral DPT. Likewise, Bourke et al [57] reported ß-lactam use in only 35.16% of 182 patients who completed the full evaluation uneventfully, including ST and DPT.

Other studies [58] show a significantly higher rate of confidence in evaluations that include ST and oral DPT than in those based on ST only, as described by Torres et al [14].

Reporting data from Israel, Lachover-Roth et al [58] performed a long-term follow-up of penicillin allergy delabeling and found that 447 patients (70% of the total) had used penicillin at least once. An interesting finding was that patients who were challenged during the first year after the reaction began using penicillin again significantly more frequently than those who were evaluated after 3 years or more (72.4% vs 62.9%; P<.05).

The same Israeli group [58] investigated reasons for avoidance of penicillin use among delabeled patients. According to the patient's electronic clinical records and/or phone survey, 192 patients (30% of all those whose allergy was delabeled) did not use penicillin. The reasons for penicillin avoidance were available in 163 patients (84.9%). The main reason for not using penicillin was "lack of indication" (103 patients [63.2%]). When patients were asked about their future intention to use penicillin, 96 of them (93.2%) expressed willingness, while 60 out of the 163 (36.8%) refused. The main reason for refusal was lack of personal conviction that penicillin could be safely consumed (17%). Other reasons included inadequate understanding of the results of the evaluation (10%).

Nonremoval and Reactivation of the Label

Lachover-Roth et al [58] investigated whether the label was removed and found that in 51.37% of patients who completed the oral DPT without a reaction, the penicillin allergy label remained active in their electronic clinical record. However, of

these, penicillin was prescribed and purchased by 238 patients (71%), despite the allergy label being present in the electronic medical record.

Some cohort studies on the matter reveal a discrepancy between the recommendation to remove the label and its persistence or reactivation in electronic clinical records [59]. A cohort study by Macy and Shu [60] revealed that although only 1.3% of 308 patients tested positive for penicillin allergy, more than 12% had an active allergy label at the end of follow-up.

One systematic review [2] showed that the penicillin allergy label had been removed from the patient's electronic clinical record [61]. In one study, the participants' general practitioners confirmed that 47/55 patients (85%) had the correct revised allergy status recorded on their medical files [35]. However, in another study, only 33% of patient medical records had been updated to reflect the correct allergy status [62].

Lo et al [63] used natural language tools to develop a solution/intervention to help remove drug allergy alerts at the General Hospital of Massachusetts, USA. The authors created an algorithm with the name of the medication and test results from a flowsheet of forms where the DPT results are recorded and from the clinical notes containing information about the DPTs. This information was compared with the drug allergy lists to identify discrepancies and suggest reconciliation between both sources of information. The authors found 2.9% nonconcordance, mainly with respect to nondeletion of drug allergy alerts (2.7%).

The experience of our group and of other authors shows that ≤20% of removed penicillin allergy alerts are reactivated [64,65].

In the study by Khan [64] the authors evaluated multiple interventions to prevent the penicillin allergy label from reactivation, including counseling at the time of testing, post–hospital discharge counseling, best practice advisory pop-up alerts, wallet cards, and chart review. All interventions led to a <2% rate of penicillin allergy relabeling. A criticism of this initiative is that it is not feasible to constantly remind patients that they are not allergic.

Also problematic is the lack of synchronization of the penicillin label update or removal of penicillin allergy label between different attending clinical settings with differences in their electronic clinical records system [58,59].

Barriers to a Reliable Drug Allergy Alert System

- Need to give permission to activate alerts to groups of health professionals with different degrees of knowledge of drug allergy.
- Failure to update health alerts, especially when they have to be removed, and controversy over responsibility for this activity.
- Carry-over of annotations from previous reports to reports made after negative test results ("copy and paste").
- Different electronic clinical record platforms at different care levels or in care networks that do not synchronize updated information.
- Patient resistance to accepting negative allergy test results when an allergy label has been maintained for decades.
- Baseline patient situations that do not permit allergy assessment in the allergy outpatient clinic.
- No published studies on whether the practice of delabeling has spread to specialties outside allergy and nonallergy specialists with a strong interest in delabeling.
- The considerable magnitude of the problem, even in countries with a lower prevalence of drug allergy alerts.
- Opportunity costs in allergy departments when prioritizing diseases or clinical situations.

12. Summary

- Penicillin allergy labels are false in more than 95% of cases, potentially leading to bacterial resistance, with worse outcomes and higher health care costs.
- Most admitted patients can receive the ß-lactam of choice for the causative infectious processes at a lower cost.
- For patients at low risk of an allergic reaction, the considerable available evidence indicates that nonallergists can test for tolerance, albeit with a small proportion of adverse reactions, which are generally not serious.
- However, the frequency of delabeling of penicillin allergy is less than 40% for all potential candidates where an alert is identified.
- Delabeling/cancelations of alerts can be reactivated owing to patient-related factors and nonsynchronization of telematic systems between care levels.
- Differences in the approaches for delabeling penicillin drug allergy in different geographic areas and health systems can be explained by differences in the resources available for patients with penicillin allergy.
- Allergy units should initiate reflections to improve efficiency, with fast and early assessment of penicillin allergy, especially in patients with a high frequency of comorbidities and other risk groups, where ß-lactam antibiotics are the first choice for antibiotic treatment at admission, for specific surgical procedures, and in obstetric protocols.

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Miguel Ángel Tejedor Alonso

https://orcid.org/0000-0003-3618-8220
Allergy Unit
Hospital Universitario Fundación Alcorcón
C/ Budapest, 1
28922 Alcorcón (Madrid), Spain
E-mail: M914674227@telefonica.net
miguelangel.tejedor@salud.madrid.org