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The Role of Clinical Pharmacists in Patients with Suspected Allergy to β-Lactams: A Systematic Review

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Abstract: Objective: To analyze the role played by the clinical pharmacist and its impact in antibiotic stewardship facing suspected allergy to beta-lactam antibiotics. Method: We performed 2 different independent bibliographic searches. A total of 35 articles were found, and the final number included in the study was 12. We analyzed the articles and collected variables of efficacy, safety, and applicability of evaluation tools applied to patients with suspected allergy to beta-lactams. Also, the variation in the consumption and prescription profile of alternative antibiotics was analyzed. Results: The selected studies analyzed questionnaires, allergy delabeling, intradermal tests, and oral challenge tests performed by pharmacists. Significant differences in the efficacy endpoint were found in 4 studies in favor of pharmaceutical intervention. In the study of Kwiatkowski et al., cefazolin use increased in surgical patients after pharmacist intervention (28% vs 65%; P < 0 .01). In a quasi-experimental study, the mean defined daily dose of aztreonam and the mean days of therapy per 1,000 patients/day decreased (21.23 vs 9.05, P < 0.01) and (8.79-4.24, P = 0.016), pre- and post-intervention, respectively, increasing antibiotic de-escalations (P < 0.01). In another quasi-experimental study, the prescription of restricted use antibiotics decreased (42.5% vs 17.9%, P < 0 .01) and the use of pre-surgical prophylactic antibiotics alternative to cefazolin (81.9% vs 55.9%, P < 0.01) in another study. Other study showed that the mean time per interview was 5.2 min per patient. No adverse events were reported in any study. Conclusion: The pharmacist intervention in the evaluation of the patient with suspected allergy to beta-lactams is effective, safe, and feasible to implement on daily clinical practice. The standardization of protocols to clarify the history of allergies and development of evaluation tools represents simple screenings to perform delabeling or refer to the immunoallergology service, improving penicilin use and reducing the need for second-line antibiotics. More studies are needed to standardize the desensitization tests made by pharmacists. However, despite these results, the involvement and leadership of the pharmacist in this area is limited and constitutes a future challenge for the profession.

Key words: beta-lactams (β-Lactams); allergy; antibiotic stewardship; antibiotic administration; pharmacist; pharmacy

1. Introduction

β-lactam antibiotics are the most widely used drugs in the treatment of infectious diseases due to their efficacy,

spectrum of activity, and safety. Their prescription can be limited by bacterial resistance and the appearance of adverse reactions, among which hypersensitivity is of special relevance. Penicillin allergy is the most commonly reported type of drug allergy. [1]

About 10% of patients report a history of allergy; however, it is estimated that less than 1% of the population is actually allergic. According to the American Academy of Allergy, Asthma, and Immunology, 80% of patients with IgE antibody-mediated penicillin allergy lose sensitivity after 10 years. [2] Of note, the rate of cross-reactivity between penicillins and cephalosporins is less than 1%. [3] Nevertheless, β-lactam therapy is often completely avoided in patients with no real allergies or with mild reactions.

Of greater relevance are IgE-mediated allergic reactions (type I allergic reactions), which usually occur within the first hour of drug administration. Symptoms include urticaria, angioedema, shortness of breath, wheezing, and anaphylaxis. Other severe reactions, which are not IgE-mediated (late allergic reactions, type II, III, and IV), include Stevens-Johnson syndrome, toxic epidermal necrolysis, interstitial nephritis, hemolytic anemia, acute serum sickness, or drug sensitivity syndrome with eosinophilia and systemic symptoms (DRESS).

The unwarranted avoidance of β-lactam antibiotics is of concern in several respects: it may lead to the use of potentially less effective antibiotics (e.g. vancomycin is less effective than cloxacillin against methicillin-sensitive Staphylococcus aureus), and it may promote the use of agents with a broader spectrum of activity and a higher likelihood of resistance development, potentially leading to an increased risk of toxicity (e.g. the selection of Clostridioides difficile [CD], and methicillin-resistant S. aureus). Furthermore, poorly characterized allergies are associated with delays in the first administration of antibiotic therapy, higher rates of rehospitalization, prolonged hospitalizations, an increased risk of surgical site infections, increased adverse reactions, mortality, and higher associated costs. [4]

2. Pharmacists as Agents in Antimicrobial Stewardship Programs

Antibiotic resistance is a worldwide public health problem. It has been estimated that in the United States, 2.8 million infections are caused by resistant bacteria every year resulting in over 35, 000 deaths. [5] It has also been estimated that in the European Union, 670 ,000 infections are caused by resistant bacteria each year, resulting in 33, 000 deaths. [6]

The inappropriate use of antibiotics has been found to be the most relevant modifiable risk factor for resistance development. Therefore, the promotion of the appropriate use of antibiotics in all clinical settings is essential, and the pharmacists' role is integral to achieving this goal. Antimicrobial Stewardship Programs (AMSP) comprise a set of strategies that promote the appropriate use of antibiotics. These strategies attempt to optimize the effectiveness of antibiotics, minimize adverse events and toxicities associated with their use, limit the development of resistant bacteria, and reduce unnecessary costs associated with the excessive and inappropriate use of antibiotics. [7-10]

Pharmaceutical organizations such as the American Society of Health-System Pharmacists (ASHP) and the Society of Infectious Diseases Pharmacists (SIDP) have published guidelines on the role of pharmacists in AMSPs in hospital and outpatient settings, respectively. [11-13] Currently, establishing protocols for managing suspected β-lactam allergies is a high priority for hospital infection control groups; however, despite their multidisciplinary profile, the role of pharmacists remains underdeveloped in these groups. The main objective of this review was to analyze the role played by clinical pharmacists and its impact on AMSPs in the setting of suspected allergy to β-lactam antibiotics.

3. Material and Methods

3.1 Literature search

A bibliographic search for MeSH terms was performed in the main biomedical databases: MEDLINE (PubMed) and EMBASE. The strategies and terms used in the searches were as follows: ("β-Lactams" [Mesh] AND "Hypersensitivity"

[Mesh]) AND "Pharmacists" [Mesh]) AND/OR "Antimicrobial Stewardship" [Mesh]. The years 2018-2022 (last 5 years) was established as the search period. A literature search was also conducted by the Centro de Informação do Medicamento da Ordem Dos Farmacêuticos de Portugal (CIM-OF).

3.2 Selection of studies

The studies were selected according to the following criteria:

Inclusion criteria: studies were included that: (a) described the role played by clinical pharmacists in AMSPs in the setting of suspected allergy to β-lactam antibiotics; (b) evaluated the clinical parameters of patients in terms of efficacy and/or safety; (c) analyzed the feasibility of the procedures implemented by pharmacists; and (d) described information about changes in the pattern of antibiotic use, cost, hospital stay, and/or patient perception.

Exclusion criteria: studies were excluded that: (a) did not include pharmacist participation; (b) only analyzed differences in the pattern of antibiotic prescription; (c) only analyzed costs; (d) were not written in Spanish, Portuguese, or English; and (e) studies were excluded for which the complete text could not be located. Regarding the last 2 criteria, no studies have analyzed or described the role played by clinical pharmacists in AMSPs in the setting of suspected allergy to β-lactam antibiotics.

3.3 Data analysis

Following the selection procedure, a team of 2 researchers independently analyzed the studies and collected data on the following variables: country of publication, design, pharmaceutical intervention, patient sample, and results of the intervention (efficacy, safety, and/or other variables such as applicability or analysis of consumption). The data were then pooled by consensus and, in its absence, a third researcher participated in the procedure. The studies were selected and analyzed using the Prisma 2020 [14] guideline as a reference.

4. Results

In total, 35 studies were identified that met the search criteria. After applying the inclusion and exclusion criteria, 12 studies were finally selected. Fig. 1 shows the study selection process.

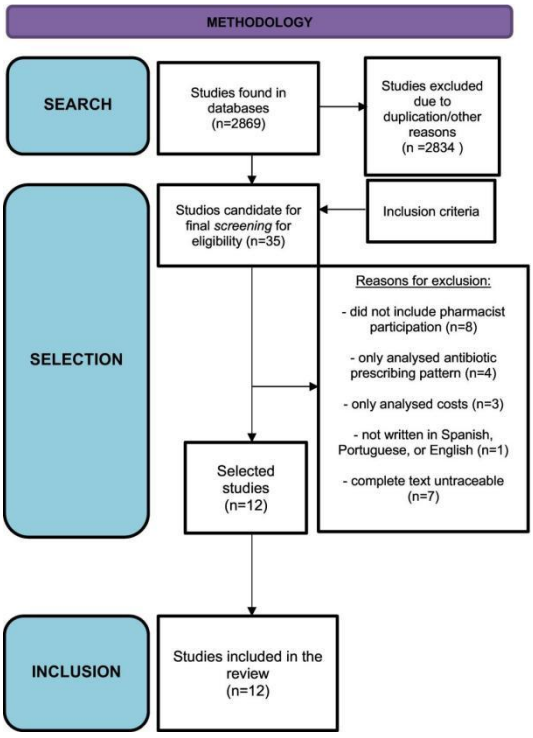

Figure 1. Selection of studies.

A number of studies were excluded on the following grounds: 8, because they did not include pharmacist participation; 4, because they only analyzed differences in the pattern of antibiotic prescription; 3, because they only analyzed costs; 1, because it was not written in Spanish, Portuguese, or English; and 7, because the complete texts could not be located. Of the included studies, 11 were quasi-experimental studies and 1 was an observational study.

Table 1. The results of the studies

Author, year, country	Design	Pharmaceutical intervention	n (sample)	Direct de-labeling	Oral challenge/ intradermal test	Referral to IA service	Consumption of ABs	Safety
Tanya du Plessis et al.[15] *J Antimicrob Chemother 2018 (New Zealand)*	Quasi-experimental	Structured questionnaire, de-labeling, and oral challenge	250 adults, admitted	64%, of which 50% had already tolerated a penicillin-containing antibiotic	12.4%	20% (47% with confirmed allergy)	N/A	No adverse effects reported in 98% of patients after 1 year of follow up
Mitchell et al.[16] *Fed Pract 2021 USA*	Observational	Structured questionnaire, de-labeling, and oral challenge	278 adults, admitted	22%	8.6%	N/A	N/A	N/A
Harmon S et al.[17] *Hospital Pharmacy 2020 (USA)*	Quasi-experimental	Intradermal test	31 adults, admitted	N/A	96%	N/A	Average daily savings of US $74.75 per patient	2 patients with adverse effects after intradermal test: skin rash and local reaction
Turner NA et al.[18] *JAMA, 2021 (USA)*	Quasi-experimental: case control	Structured questionnaire, de-labeling, penicillin skin testing and interpretation, referral to IA	273 adults, admitted	17.2%	68%	0.4%	Reduced use of alternative and high CD infection-risk antibiotics after applying the questionnaire (RR 0.87; 95% CI, 0.79–0.97) and (0.91; 95% CI, 0.85–0.98), respectively	N/A
Mann KL et al.[19] *J Antimicrob Chemother 2019 USA*	Quasi-experimental	Structured questionnaire, direct de-labeling	175 adults	1.1% (at patient's own request) +13%	N/A	N/A	N/A	No adverse effects reported
Clark KE et al.[20] *J Pharm Pract 2019 (USA)*	Quasi-experimental	Structured questionnaire	95 adults preintervention vs 65 postintervention	N/A	N/A	N/A	Decrease in DDD aztreonam/ 1000 patients/d: 21.23 vs 9.05; $P = 0.003$)	No adverse effects reported
Devchand M et al.[21] *J Antimicrob Chemother 2019 (Australia)*	Quasi-experimental	Structured questionnaire, de-labeling, oral challenge, and skin prick testing	106 adults, admitted	13%	18.8% (oral) 3.8% (skin)	25.4%	N/A	One patient reported late cutaneous rash in response to oral amoxicillin challenge; new record added to patient's allergy history
Vaisman et al.[22] *J Antimicrob Chemother 2017 (Canada)*	Quasi-experimental	Structured questionnaire	485 adults, prior to elective surgery	N/A	N/A	N/A	Decrease in AB alternatives, 81.9% vs 55.9% ($P = .001$) pre-postintervention	No adverse effects reported after cefazolin administration
Ham Y et al.[23] *Allergy Asthma Proc 2021 (USA)*	Quasi-experimental	Structured questionnaire and oral challenge	50 adults, admitted	40%	56%	N/A	N/A	2 patients with mild adverse effects after oral challenge
Louden NJ et al.[24] *J Pediatr Pharmacol Ther, 2021 USA*	Quasi-experimental	Structured questionnaire, direct de-labeling, and referral to IA	11 pediatric patients	18%	N/A	82%	N/A	N/A
Kwiatkowski S et al.[25] *Am J Health Syst Pharm 2021 (USA)*	Quasi-experimental: case control	Telephone questionnaire prior to elective surgery	87 adults	N/A	N/A	N/A	Use of augmented cefazolin ($P = .001$) 65% vs 28%	N/A
Song YC et al.[26] *2021 USA*	Quasi-experimental	Structured questionnaire	66 adults, admitted	18%	N/A	N/A	N/A	N/A

Note: IA: immuno-allergology service; AB: antibiotic; N/A: non-applicable/no mention of result; CD: Clostridioides difficile; 95% CI: 95% confidence interval; DDD: defined daily dose.

4.1 Pharmaceutical intervention

In 11 studies, the pharmacist interviewed the patient with suspected β-lactam allergy, collected the complete history of the allergic reaction and evaluated it using standardized questionnaires [15, 16, 27]; in 1 study, skin tests were performed without prior interview. [17] The interventions performed after the interview were as follows: direct de-labeling (6 studies);

oral challenge tests (4 studies); skin prick/intradermal tests in inpatients or outpatients (3 studies); and referral to the immuno-allergology service (2 studies).

In 10 studies, interventions were performed in hospitalized patients with records of β-lactam allergy. Only 2 interventions were performed on patients who had not yet been admitted prior to elective surgical procedures, and only 1 study included pediatric patients.

4.2 Identification of patients who were candidates for interview

Candidates were identified through entries of suspected allergic reaction to β-lactams in their electronic medical record. Some studies refer to the creation by pharmacists of automated tools to facilitate daily searches for these patients. [16, 17, 19, 26] One study included patients pending elective surgery with reported allergies, who were expected to be given β-lactam antibiotic prophylaxis. [25] Patients meeting criteria were informed of the completion of the questionnaire 1 week before pre-operative anesthesia consultation.

4.3 Questionnaires, risk stratification, and previous training

The structured questionnaires referred to in the studies collected information on the antibiotics involved, characteristics of the reactions, time since they occurred, and any subsequent administrations of β-lactam antibiotics to confirm that they were well-tolerated. [16, 19, 20, 21, 24, 26] Subsequent risk was stratified at 3 or 4 levels: no risk, low-, moderate-, and high risk. Each category was associated with a recommended action: de-labeling, oral challenge, skin test followed by challenge, or avoidance of β-lactams.

The results of the questionnaires and the recommendations were recorded in the electronic medical records. [16, 19, 20, 21, 24, 26] In 1 study, an electronic assessment tool was created that removed information from the clinical process and automatically categorized the level of risk. [24] Several studies refer to previous pharmacist training of varying duration, [20, 24] which was given by infectionists [22] or immuno-allergologists, [23] who were always available to resolve questions. Training comprised 2 components: theoretical and practical, with case-by-case discussion.

4.4 Skin testing

A previous study [17] described the skin tests, which comprised 3 steps: a skin prick test; an intradermal test with diluted penicillin; and a challenge dose of oral amoxicillin 250 mg or intravenous ampicillin if patients were intolerant to oral administration. These tests were performed by resident pharmacists and previously trained specialists, and followed a protocol approved by the Pharmacy and Therapeutics Commission. Previous studies identified potential drugs that could mask histamine release. [16]

4.5 De-labeling

When de-labeling was indicated, the AMSP pharmacist recorded the result of the assessment and updated the allergy profile in the electronic medical record. [16, 18, 21] In 1 study, this information was added to the original medical record. [16] In some cases, the patients were provided with a card to alert family physicians of this update. [18]

4.6 Efficacy

(1) Efficacy variables

The efficacy of the intervention were assessed using the following main outcome measures: percentage of de-labeling (in 8 studies); antibiotic consumption (β-lactam or alternative) (in 4 studies); CD rate (in 1 study); and overall mortality (in 1 study). The following efficacy variables were also included: the number of patients whose antibiotic regimen was de-escalated; the cost of antibiotic treatment; and the probability of prescribing β-lactams, first-generation cephalosporins, or high CD infection-risk antibiotics.

(2) De-labeling

The percentage of patients who underwent direct de-labeling (following clarification of their allergy history via interview) ranged from 13% to 64% (median: 18%). The study by du Plessis et al. [15] had the highest percentage of de-labeling; 50% of patients had tolerated 1 course of a penicillin antibiotic prior to inclusion. After skin testing or oral challenge, the de-labeling rates ranged from 8.6% [16] to 96%. [17]

(3) Antibiotic consumption

In 4 of the studies, significant differences were found in the primary endpoint in support of the pharmaceutical intervention. There was a decrease in the mean defined daily dose (DDD) of aztreonam/1000 patient-days and mean days on therapy/1000 patient-days (21.23 vs 9.05; $P < 0.01$) and (8.79-4.24; $P = 0.016$); these results are based on pre- and post-implementation data obtained from the questionnaire and associated recommendations, respectively. [20] A significant decrease was found in the prescription of restricted-use antibiotics (42.5 vs 17.9%; $P < 0.01$). [21] A decrease was reported in the use of pre-operative prophylactic antibiotics alternative to cefazolin (81.9 vs 55.9%; $P < 0.01$). [22] An increase was found in cefazolin use from 28% to 65% ($P < 0.01$). [25] No significant differences were found between pre- and post-intervention periods in the consumption of narrow-spectrum β-lactams (amoxicillin, amoxicillin-clavulanic acid) and restricted-use antibiotics, including high CD infection-risk antibiotics (e.g., ceftazidime, ceftriaxone, ciprofloxacin, and clindamycin). [18] The only difference was related to the decreased consumption of antibiotics alternative to penicillins (aztreonam, ciprofloxacin, etc), with a higher probability of β-lactams being prescribed before discharge.

(4) Safety variables

Two studies found no adverse events during the study period, [19, 20] and 1 study found no adverse events at 1 year follow-up. [15] In total, 98% percent of patients who were de-labeled had no adverse events after repeated administration of penicillin-containing antibiotics. Likewise, 1 study found no adverse reactions after administration of cefazolin. [22] However, some of the studies reported adverse effects: 1 patient developed late rash [21]; 2 patients experienced mild adverse effects after oral challenge [23]; and 2 patients experienced adverse effects (skin rash and local reaction) after intradermal testing. [17]

(5) Other parameters

There was a mean decrease in overall antibiotic therapy costs ($74.75/d). [17] The mean time spent per interview was 5.2 min/patient. [26]

5. Discussion

Establishing protocols for managing suspected β-lactam allergies is one of the main priorities for hospital infection control groups. Several recent publications have analyzed the efficacy, safety, and cost-effectiveness of such measures. [24-26] Clinical pharmacists are members of these groups and, together with the rest of the team, are fully involved in this activity; however, there are few published reports of such activity being led by these professionals. In our review, the main pharmaceutical interventions were structured interviews (telephone or face-to-face) with patients with suspected allergy, skin tests, and oral challenge tests under surveillance, direct de-labeling of patients considered non-allergic after confirmation of the clinical history, and referral to immuno-allergology specialists for further specific tests.

After analyzing the results of studies reviewed, we found that they offer a certain degree of guidance or recommendations on the best course of action to take in patients with suspected allergies. However, they are not decisive or of sufficient scientific robustness to decide whether pharmacists are appropriate healthcare staff to provide leadership in this role.

Despite the lack of conclusive results, pharmacists have increasing presence and visibility in infection control groups, which is a situation endorsed by both international and national regulations. For example, in Portugal, the regulation Direçao geral de Saude (DGS) of September 2022 [28] requires the implementation of such groups in both public and private hospitals with the aim of promoting activity related to AMSPs and reducing the risk of antimicrobial resistance. It is mandatory that such groups include at least 1 pharmacy specialist.

In light of the results, simple measures such as computer tools or patient questionnaires to clarify histories of allergic reactions [29] can be used to de-label "low-risk" patients and refer them to immuno-allergologists, thus improving the use of penicillins and reducing the need for second-line antibiotics. This approach is likely to reduce the risk of iatrogenic and multidrug-resistant infections, and reduce healthcare costs. However, there is no consensus on clinical decision rules for de-labeling and classifying "false" allergies as intolerances. Furthermore, many of these decision rules, such as Pen-Fast, [29] are not specifically validated for use by healthcare staff other than physicians.

Although previous studies have reported pharmacists conducting oral penicillin challenge and desensitization skin tests, these are very specific cases in that the pharmacists received specialized training by immuno-allergologists. However, no details on such training are provided regarding the objectives, duration, or competencies to be acquired. [15-18, 21, 23, 30, 31] Furthermore, the highly heterogeneous nature of the health and policy frameworks in which these studies were conducted makes it difficult to extrapolate such training into the daily practice of hospital pharmacists.

In the case of Spain and Portugal, this activity is conducted by immuno-allergologists. In addition, of the 12 studies reviewed, only 7 refer to safety variables and the outcomes are not defined. However, the number of adverse effects reported was low and those reported were considered to be mild.

This review offers detailed and current information from published studies, specifically focussing on the role of well-trained clinical pharmacists. It assesses how this role impacts patients with suspected or reported β-lactam allergies, particularly in terms of directly de-labeling or referring patients to immuno-allergology specialists.

5.1 Limitations

The main limitation of this review is that no randomized clinical trials are available. Furthermore, some of the conclusions were based on low-quality quasi-experimental studies, the review did not evaluate any potential biases within the studies, and, after the exclusion were applied, the final number of studies was quite low. Another relevant limitation is that only 2 databases were used for the literature search. In order to obtain the most recent evidence on the study topic, the period 2018-2022 (last 5 years) was established as the search period; however, an additional search was conducted by the CIM-OF to minimize the risk of inclusion or selection bias.

6. Conclusion

The latest scientific evidence suggests that involving pharmacists in the evaluation of patients suspected of having β-lactam allergies is effective, safe, and applicable in clinical practice. Standardized protocols to clarify allergy histories and evaluation tools, such as structured questionnaires, would provide a straightforward screening method for de-labeling or referral to an immunology/allergy service in specific situations. Thus, patients with false allergies could be de-labeled and first-line antibiotics could be used safely. In addition, there would be a decrease in the consumption of alternative antibiotics, which carry a higher risk of the resistance development. However, these potential benefits are based on highly heterogeneous studies employing low-quality methodology. Randomized clinical trials with sound methodology are needed to provide higher quality results based on the available evidence. Specific training in this area would enable pharmacists to provide added value and broaden the range of competencies within our specialization, both in Portugal and Spain. This aspect represents a future challenge for the pharmaceutical profession.

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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