ORIGINAL ARTICLE

A Comprehensive Prospective Study of the Costs Associated With Evaluation of ß-Lactam Allergy

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Abstract

Background: Being labeled as allergic to penicillin (unverified ß-lactam allergy) can result in patients receiving broader-spectrum antibiotics than necessary that may be more toxic, less effective, and/or more expensive than alternative options.
Objective: We aimed to evaluate the real costs of evaluating ß-lactam allergy.
Methods: We performed a prospective real-life observational study designed to evaluate all adult patients who consulted for suspected ß-lactam allergy over a 1-year period. Direct and indirect costs were systematically recorded. Direct health costs were calculated based on the number of visits and all additional and diagnostic tests performed, direct nonhealth costs based on the number of visits and the distance from their homes to the Allergy Department, and indirect costs based on absenteeism.
Results: A total of 296 patients with suspected allergy to ß-lactams were evaluated in our outpatient clinic from June 1, 2017 to May 31, 2018. Total direct health care costs were €28 176.70, with a mean (SD) cost of €95.19 (37.20). Direct nonhealth costs reached €6551.73, that is, €22.13 (40.44) per patient. Indirect health costs reached €20 769.20, with a mean of €70.17 (127.40). In summary, the total cost was €55 497.63, that is, a cost per patient of €187.49 (148.14).
Conclusions: When all possible costs are taken into account, the evaluation of ß-lactam allergy is not expensive and can reduce future expense arising from unnecessary use of more expensive and less effective antibiotics.

Key words: ß-Lactam allergy. Delabeling. Costs. Pharmacoeconomics. Penicillin allergy evaluation.

Resumen

Introducción: Un diagnóstico no verificado de alergia a la penicilina o a los betalactámicos (BL) conlleva que los pacientes reciban antibióticos de amplio espectro, que pueden ser más tóxicos, menos efectivos, y/o de mayor coste.
Objetivo: Evaluar los costes reales de un estudio de alergia a los betalactámicos.
Métodos: Se diseñó un estudio observacional prospectivo en condiciones de práctica clínica habitual en el que se evaluaron todos los pacientes adultos que consultaron por sospecha de alergia a BL durante un año. Los costes directos e indirectos se recogieron sistemáticamente. Los costes directos sanitarios se calcularon teniendo en cuenta el número de visitas y todas las pruebas diagnósticas realizadas; en los costes directos no sanitarios se consideraron el número de visitas y los kilómetros desde el domicilio hasta el Servicio de Alergología; en los costes indirectos se evaluó el absentismo.
Resultados: Se evaluaron 296 pacientes remitidos desde el 1 de junio de 2017 hasta el 31 de mayo de 2018. Los costes directos totales sanitarios fueron 28.176,70 €: coste medio (desviación estándar, DS) de 95,19 € (37,20). Los costes directos no sanitarios alcanzaron, 6.551,73: coste medio 22,13 (40,44). Los costes indirectos fueron 20.769,20 €: coste medio (DS) 70,17 (127,40). En resumen, la cantidad total fue de 55.497,63 €, lo que supone un coste medio de 187,49 € (148,14).
Conclusiones: Considerando todos los costes posibles, la evaluación de la alergia a betalactámicos no es cara y puede ahorrar gastos futuros debido a una utilización innecesaria de antibióticos más caros y menos efectivos.

Palabras clave: Alergia a betalactámicos. Desetiquetado. Costes. Farmacoeconomía. Evaluación de alergia a penicilina.

Introduction

Drug allergy affects 7%-10% of the general population and constitutes a major public health issue [1-3]. Drugs are also an important cause of anaphylaxis [4]. ß-Lactam antibiotics are the drugs most frequently involved in immunological adverse reactions [5]. Nevertheless, most patients claiming to have ß-lactam allergy are shown not to be allergic after evaluation [1-3]. Unverified penicillin allergy results in patients receiving broader-spectrum antibiotics than necessary, which may also be more toxic, less effective, and/or more expensive. In addition, the unnecessary use of alternative antibiotics places patients at risk of adverse reactions, treatment failures, and health care–associated infections [6-13].

Blumenthal et al [6] estimated the cost of evaluating penicillin allergy prospectively in 30 outpatients and found that the base case cost was $220, which included penicillin skin testing and a 1-step amoxicillin drug challenge performed by an allergist. Even with varied assumptions adjusting for operational challenges, clinical setting, and expanded testing, the cost of penicillin allergy evaluation is still only about $540. This modest investment may be offset by that of patients treated with costly alternative antibiotics, which may also induce adverse events.

Rimawi et al [14] studied 146 patients with a history of penicillin allergy and negative skin prick test (SPT) results who were treated with ß-lactam antibiotics. The SPT-guided antibiotic choice for these patients resulted in an estimated annual savings of $82 000.

For all the above-mentioned reasons, it is important to reinforce the need for accurate diagnosis of ß-lactam allergy. The aim of this study was to prospectively evaluate the costs associated with a comprehensive evaluation of allergy to ß-lactam antibiotics.

Methods

We performed a prospective observational study of patients attending our outpatient clinic who consulted for suspected ß-lactam allergy. The study ran from June 1, 2017 to May 31 of the following year. The study protocol was approved by the local ethics committee (code PI4505/2017).

Inclusion Criteria

All patients aged ≥14 years and attending the Allergy Department outpatient clinic for suspected hypersensitivity reactions to ß-lactam antibiotics during the study period were invited to participate in the study. Those who voluntarily agreed to participate in the study signed a written informed consent document.

Methodology

Diagnostic procedures were carried out following the European Network of Drug Allergy/European Academy of Allergy and Clinical Immunology (ENDA/EAACI) protocol [15,16]. In addition to the history taken by the attending physician, this protocol included the following procedures:

In vivo tests

(*a*) SPTs, intradermal tests, and patch tests (Table 1 in the Supplementary Material).

(*b*) Single-blind, placebo-controlled challenge tests up to the therapeutic dose with various ß-lactams (see Table 2 in the Supplementary Material).

The clinical history was usually taken at a single visit. The patient then attended another visit for skin testing and drug challenge. If the result was negative and more than 6 months had passed since the reaction, another visit was arranged for re-evaluation (SPT and re-exposure test). In patients with a positive result, and depending on which drug was involved, additional visits could be arranged for challenge with alternative ß-lactams (for example, cephalosporins and/or meropenem in the case of patients with selective reactions to amoxicillin). All visits were prospectively recorded for each patient. Moreover, the number of visits to our outpatient clinic changed depending on whether the reaction was immediate (those reactions that appeared within the first hour) or nonimmediate (those with a latency period greater than 1 hour).

In vitro tests

(*a*) Determination of total IgE and specific IgE in some patients (ImmunoCAP, Thermo Fisher Scientific, Phadia Spain SL).

Data and Variables Collected

Data were collected using a structured questionnaire (Table 3 in the Supplementary Material) and stored in a dissociated database to guarantee patient anonymity.

Assessment of Costs

Data relating to staff, materials, and infrastructure costs were provided by the Bureau of Management of University Hospital of Salamanca, Salamanca, Spain.

Data concerning the medication used for the study (consumption and costs) were collected in a structured way; these data were provided by the hospital pharmacy (Table 2 in the Supplementary Material).

To assess the costs in monetary terms, the data considered were as follows:

- Reagents used for skin testing and drugs used for challenge tests
- Reagents used for laboratory tests
- Remuneration for doctors, nurses, auxiliary health personnel, and administrative staff
- Building maintenance expenses (eg, water, electricity)
- Patient transport to the clinic
- Loss of working hours

Direct health costs

Direct health costs were based on the number of visits, additional and diagnostic tests performed, and cost of the personnel and materials used during the study.

In this regard, all the diagnostic tests performed were taken into account, ie, in vivo tests (skin tests, patch tests,

and controlled drug challenge tests) and in vitro tests (total and specific IgE) (Text 1 and Table 4 in the Supplementary Material).

To estimate the costs per patient derived from personnel fees, the costs were divided by the overall number of patients seen in the outpatient clinic during 2017. As the remuneration of staff in the Spanish National Health Service does not depend on medical acts, it was assumed that the cost of each patient was the same (Text 1 and Table 5 in the Supplementary Material).

The total amount attributed to the patients of the study, including remuneration of personnel and building maintenance expenses, was calculated proportionally on the basis of the total amount attributed to the Allergy Department and the number of visits to the outpatient clinic during this period. This information was provided by the hospital administration (Table 6 in the Supplementary Material).

Direct nonhealth costs

Direct nonhealth costs were calculated based on the number of patient visits and kilometers from their homes to the Allergy Department, with an estimated cost per kilometer of €0.19. This is the amount that Spanish Authorities pay to public officials for the use of their private car and was considered as travel expenses [17]. Most patients lived in the province of Salamanca (331 000 inhabitants).

To attribute this cost to a single patient, the distance from the place of residence to the outpatient clinic was estimated. Patients living in the city of Salamanca, which is a small town of 144 000 inhabitants located in the west of Spain, were considered to have come to the hospital on foot (in most cases). The remaining patients living in the province of Salamanca were considered to have come by car.

Indirect costs

Indirect costs were based on loss of working hours (absenteeism). We obtained this amount by taking into account daily labor costs in the European Union (EU).

The average hourly labor cost for 2018 in the EU was estimated at €27.40. However, this average masks significant differences between EU member states, with hourly labor costs ranging between €5.40 in Bulgaria and €43.50 in Denmark (the average labor cost in Spain was €21.50) [18].

Gross earnings are the largest part of labor costs. Across EU member states, the highest national median gross hourly earnings were 15 times higher than the lowest when expressed in euros [18]. Spain ranked number 13 of the 28 countries of the EU both in hourly labor costs and in median gross hourly earnings [18].

Statistical Analysis

Data were analyzed using IBM SPSS Statistics Version 25.0 (IBM Corp.). Statistical significance was set at $P<.05$. Quantitative variables were expressed as means and qualitative variables as relative frequencies. A nonparametric test (Mann-Whitney test) and a parametric test (*t* test for independent samples) were used to compare mean values for quantitative variables.

Results

A total of 296 patients with suspected allergy to ß-lactams were evaluated in the allergy outpatient clinic between June 1, 2017 and May 31, 2018. Of these 296 patients, 273 (92.23 %) completed the study.

The percentage of women was 65.54%, and age ranged between 14 and 91 years. Mean (SD) age was 52 (20.39) years (median [IQR], 55 [36-69] years).

The demographic characteristics of the study population are presented in Table 7 of the Supplementary Material.

Allergy to ß-lactams was demonstrated in 46 out of 296 patients (15.54%). The mean and median ages of those who were found to be allergic were 53.22 (19.73) and 57 (37-70) years, respectively (values similar to those of all patients studied). Of the 46 patients who were found to be allergic, 29 (63.04%) had previously had an immediate reaction, 16 had a delayed reaction (34.78%), and in 1 patient the latency period could not be established (2.17%).

Of the 46 allergic patients, 35 (76.09%) were detected by skin tests (skin prick tests were positive in 5 patients, intradermal tests in 29 patients, and patch tests in 1). Of these 35 patients, 23 experienced immediate reactions and 12 delayed reactions. A further 6 patients (13.04%) were detected by challenge test: 3 experienced delayed reactions, 2 immediate reactions, and 1 an unknown reaction. The remaining 5 patients (10.87%) were considered to be allergic based on the clinical history (4 and 1 with immediate and delayed reactions, respectively).

Concerning the type of reaction, 23 patients (50%) experienced skin reactions (10 immediate and 13 delayed), 20 anaphylaxis (43.48%), and the remaining 3 (6.52%) a respiratory reaction, a cardiovascular reaction, and an unknown reaction.

Of the 46 allergic patients, 29 had amoxicillin-selective reactions (63.04%); 24 (82.76%) tolerated alternative ß-lactams (cephalosporins and meropenem), and in 5, challenge testing could not be performed with the alternative antibiotics or patients refused to undergo challenge testing.

In addition to the descriptive statistics indicated above, we assessed statistical inference. The percentage of allergic patients who had an immediate reaction was significantly higher than percentage of those who had a delayed reaction ($P=.0263$).

We also compared the number of visits of the different groups of patients using an independent-samples *t* test (2-sided), which revealed significant differences in both cases. In the overall sample, the mean number of visits until diagnosis was 2.41 (range 1 to 7). The mean number of visits up to completion of the diagnosis was significantly different in patients who were eventually diagnosed with ß-lactam allergy (2.13) than in patients who were not (2.46) ($P=.039$). Furthermore, the mean number of visits of patients who experienced immediate reactions (1.95) and delayed reactions (2.76) was also significantly different ($P<.001$).

Direct Health Costs

We calculated personnel and materials costs, which reached €20 614.64. Of this amount, €1413.88 corresponded

Table. Total Costs and Percentages by Item and Type of Costs

Item	No.	Cost, %	Type of Cost	Total Cost, %	Mean (SD) Cost
Skin and patch tests	267	€6271.99 (11.30)	Direct health costs	€28 176.70 (50.77)	€95.19 (37.20)
Challenge tests	260	€888.30 (1.60)			
Specific IgE	30	€401.77 (0.72)			
Materials	296	€1413.88 (2.55)			
Medical personnel fees	296	€19 200.76 (34.60)			
Travel expenses	296	€6551.73 (11.81)	Direct nonhealth costs	€6551.73 (11.81)	€22.13 (40.44)
Loss of working hours	296	€20 769.20 (37.42)	Indirect health costs	€20 769.20 (37.42)	€70.17 (127.40)
		Total		€55 497.63 (100)	€187.49 (148.14)

to materials, whereas €19 200.76 corresponded to health care personnel costs (personnel expenses, including payroll and insurance) (Tables 5 and 6 in the Supplementary Material).

The costs of performing skin tests (267 patients), patch tests (32 patients), and controlled exposure tests (260 patients) were €7160.29. Overall, the costs of the ß-lactam drugs used in the challenge tests were €831.68, and specific IgE testing (30 patients) cost €401.77, reaching an average amount of €13.39 per patient. Finally, total direct health care costs reached €28 176.70, with a mean cost per patient of €95.19 (37.20) (Table).

Direct Nonhealth Costs

With an estimated cost of €0.19 per kilometer [17], direct nonhealth costs reached €6551.73 (Table).

Of the 296 patients studied, 146 came to our outpatient clinic from areas outside that of the hospital, and it was assumed that they came by car; therefore, the cost per kilometer was applied. The mean distance traveled per patient to attend the visits was 236.18 kilometers (252.18), with a cost per patient of €44.87 (47.92).

Data on travel expenses were very asymmetrically distributed (Figure 1 in the Supplementary Material). Therefore, the mean figure of average travel expenses was €22.13 (40.44), although this value was highly influenced by a few high outliers. The median per patient was €0, since more than half of the patients lived within walking distance of the hospital.

Indirect Health Costs

We measured indirect health costs taking into account only work absenteeism. Total costs reached €20 769.20 (Table). The mean loss of income for the 296 patients studied was €70.17 (127.40).

Nevertheless, only 82 patients (27.70%) were employed. When the analysis was restricted to this group, the mean loss of income was €253.28 (110.48). Of these 82 patients, those who had immediate reactions (23 [28.05%]) had a mean loss of income of €215.63 (49.09). In the case of patients who had nonimmediate reactions (43 [52.44%]), the mean loss of income was €286.11 (124.17), whereas in those whose reaction latency period was unknown (16 [19.51%]), the mean loss of income was €219.20 (116.25). Loss of income was greater in patients who had delayed reactions than in those who had had immediate reactions (Mann-Whitney 1-tailed test; *P*=.006).

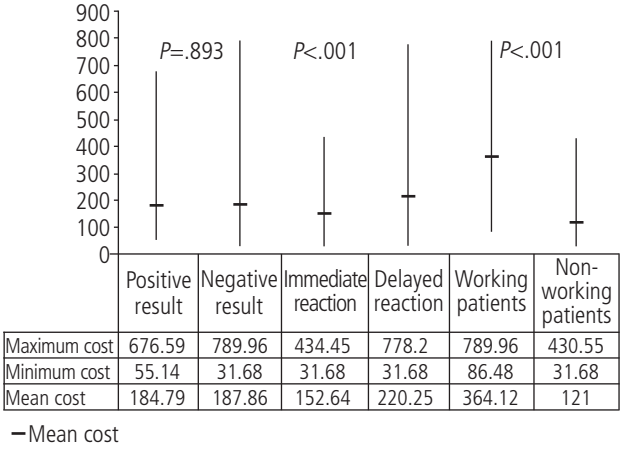

Figure. Total cost per patient (€) according to different variables.

Total Costs

In summary, the total study costs amounted to €55 497.63, with a mean cost of €187.49 (148.14) per patient (Table). The minimum cost was €31.68, the maximum €789.96.

Distinguishing between patients with positive and negative study results, the mean cost was €184.79 (138.50) and €187.99 (150.40), respectively; the differences were not statistically significant (*P*=.893). The mean cost was €152.64 (106.73) in patients with immediate reactions and €220.48 (171.79) in those with delayed reactions (*P*<.001) (Figure). Finally, mean costs differed significantly (*P*<.001) between working patients (€364.12 [156.38]) and nonworking patients (€121.28 [68.18]).

Discussion

We performed a prospective, real life, 1-year, comprehensive study evaluating the direct and indirect health costs of evaluating 296 patients with suspected ß-lactam allergy. Overall, the mean cost of evaluating ß-lactam allergy was

€187.49 per patient, meaning that evaluation can now be considered inexpensive. The various costs that contributed to the final figure were as follows: (*1*) direct health costs, accounting for more than half, reaching a total per patient of €95.19 (37.20); (*2*) direct nonhealth costs, which reached €22.13 (40.44) per patient; and (*3*) indirect costs, which were based on absenteeism and reached €70.17 (127.40) per patient.

In a Spanish prospective study that estimated the direct and indirect costs of allergic rhinitis in patients attending specialized clinics (the FERIN study) [19], the distribution of costs was very different: indirect costs were almost 3-fold higher than direct costs (24% vs 76%), because, in contrast to drug allergy, presenteeism in allergic rhinitis accounts for the main part of indirect costs.

To our knowledge, only 1 prospective study addresses the costs of evaluating penicillin allergy. Blumenthal et al [6], who prospectively estimated the cost of evaluating penicillin allergy in 30 outpatients found the cost of the base case to be $220, which, with varied assumptions after adjusting for operational challenges, clinical setting, and expanded testing, could reach $540.

However, our results are not completely comparable for the following reasons: (*1*) the per capita incomes of the United States and Spain differ considerably (€53,341 and 25,900, respectively, in 2018); (*2*) differences in the National Health System (mainly private in the United States and mainly public in Spain); and (*3*) currency exchange, ie, absolute figures are not the same (1 EUR=1.1250 USD). Notwithstanding, in our study, costs also varied between a minimum of €31.68 and a maximum of €789.96.

Two main factors influenced the final cost of the study, the type of reaction and employment status. With respect to type of reaction, we found a statistically significant difference between patients who had immediate reactions (€152.64) and those who had delayed reactions (€220.48) (P<.001). This difference was mainly related to the number of visits (193 [average, 1.95] and 383 [average 2.76], respectively). As for employment status, the costs of absenteeism were recorded only for patients who were employees. Thus, differences between working and nonworking patients were also statistically significant (P<.001), reaching an average loss of income of €364.12 and €121.28, respectively. Finally, costs were not significantly different between patients with a final diagnosis of penicillin allergy and patients in whom ß-lactam allergy was excluded (P=.893).

The main advantages of performing a study of ß-lactam allergy are delabeling false penicillin-allergic patients and correctly diagnosing patients with real ß-lactam allergy. We emphasize that there was a high prevalence of anaphylaxis in patients with positive results (43.48%). In addition, all patients with amoxicillin-selective reactions who underwent challenges with cephalosporins and meropenem (82.76%) tolerated alternative ß-lactams. Therefore, most patients could benefit from treatments with other ß-lactams, thus contributing to reduce the serious world health problem of antimicrobial resistance.

All patients mislabeled as allergic to ß-lactams would have received alternative drugs, which are usually less effective in terms of both symptoms and costs. Picard et al [9] showed that additional antibiotic costs increased by more than $15 000 in 1738 patients receiving non–ß-lactam antibiotics over 1 year, and Sade et al [10] identified 38% higher costs for the antimicrobial treatment regimen to be followed upon discharge. Furthermore, MacLaughlin et al [11] showed that the mean antibiotic cost for patients labeled with ß-lactam allergy was significantly higher than that of patients without ß-lactam allergy ($26.81 vs $16.28 respectively). Moreover, Sastre et al [20] evaluated 505 hospitalized patients with reported drug hypersensitivity, concluding that changes in drugs increased mean treatment costs 4-fold (range, 2-11; mean, €273.47 per patient per day).

In addition to increased costs, treatment with non–ß-lactam antibiotics has multiple clinical implications: higher incidences of infection by *Clostridium difficile*, vancomycin-resistant *Enterococcus*, and methicillin-resistant *Staphylococcus aureus*, along with an increased number of hospital days as inpatients [7] and readmissions. There are several explanations for these findings. Alternative therapies are often inferior to ß-lactams, for example, use of vancomycin to treat methicillin-susceptible *S aureus* bacteremia is more frequently associated with recrudescence of disease [8,12]. Adverse reactions to certain non–ß-lactam antibiotics occur with higher frequency than reactions to ß-lactam agents; these may also contribute to readmission during the course of treatment [13]. In addition, penicillin allergy labeling directly impacts the choice of antimicrobial by leading to use of less effective and broader-spectrum antimicrobials that are associated with antimicrobial resistance [21,22].

Our study is subject to a series of limitations. We made estimates according to the overall number of patients and not by medical act, because in the Spanish National Health Service, employee remuneration does not depend on medical acts. In addition, some estimates were made taking into consideration the whole year 2017, whereas the studies lasted from June 2017 to May 2018 (also 1 year); however, we believe that the deviation is negligible. Another limitation is the large number of unemployed patients, which clearly influences indirect costs. We included a total of 105 patients (35.47%) aged from under 16 years to over 65 years. Given that people of these ages are not usually employed in Spain, the mean global indirect cost in our study was lower. However, as ours was a real-life study, it was necessary to include these age groups. We also provide the costs in working patients notwithstanding. Finally, from a European perspective, it should be taken into account that gross earnings at work differ between the countries of the EU, thus implying that the indirect costs differ from those of other countries [18]. This also affects the total cost of the study.

In summary, our prospective and comprehensive real-life study, in which the direct and indirect health costs of evaluating penicillin allergy were systematically analyzed in an outpatient clinic in Spain, revealed a complete evaluation cost of €187.49 (148.14) per patient. We believe that this is an assumable figure, particularly given the consequences of incorrectly labeling a patient as allergic to ß-lactam.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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