A Comprehensive Prospective Study of Costs Associated to the Evaluation of beta-lactam Allergy

Running title: Delabelling beta-lactam hypersensitivity

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Abstract

Background: Being labelled as allergic to penicillin or unverified beta-lactam allergy result in patients receiving broader-spectrum antibiotics that may be more toxic, less effective, and/or with a higher cost.

Objective: We aimed to evaluate real costs of beta-lactam allergy evaluation.

Methods: A prospective real life observational study designed to evaluate all adult patients that consulted during one year for suspected beta-lactam allergy. Direct and indirect costs were systematically recorded. Direct health costs were calculated by taking into account the number of visits and all complementary and diagnostic tests performed; direct non-health costs by considering the number of visits and the kilometers from their homes to the Allergy Service; and indirect costs by considering the absenteeism.

Results: A total of 296 patients with suspected allergy to beta-lactams were evaluated in our outpatient clinic from June 1st, 2017 to May 31th, 2018. Total direct health care costs were €28,176.70, with a mean cost and a standard deviation (SD) of €95.19 (37.20). Direct non-health costs reached €6,551.73, 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, which means a cost per patient of €187.49 (148.14).

Conclusions: Even considering all possible costs, the evaluation of beta-lactam allergy is not expensive and can save future expenses due to unnecessary use of more expensive and less effective antibiotics.

Key words: Beta-lactam allergy, Delabelling, 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 can affect 7-10% of the general population and constitutes a Public Health issue [1-3] Drugs are also an important cause of anaphhylaxis [4]. Beta-lactam antibiotics are the drugs most frequently involved in immunological adverse reactions [5]. Nevertheless, most patients that claim to have beta-lactam allergy are determined not to be allergic after an allergy evaluation [1-3]. Unverified penicillin allergy results in patients receiving broader-spectrum antibiotics that may also be more toxic, less effective, and/or with a higher cost. In addition, the unnecessary use of alternative antibiotics places patients at risk for adverse reactions, treatment failures, and health care-associated infections [6-13].

Blumenthal et al [6] estimated the cost of penicillin allergy evaluation prospectively in 30 outpatients, reaching a cost of $220 the base-case, which includes 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, penicillin allergy evaluation still costs only about $540. This modest investment may be offset for patients treated with costly alternative antibiotics that also may result in adverse consequences.

Rimawi et al [14] studied 146 patients with a history of penicillin allergy and negative skin prick tests (SPTs) that were treated with beta-lactam antibiotics. The SPT-guided antibiotic election for these patients resulted in an estimated annual savings of $82,000.

All these reasons reinforce the need of performing an accurate beta-lactam allergy diagnosis. The aim of this study was to prospectively evaluate the costs associated to a proper evaluation of allergy to beta-lactam antibiotics comprehensively.

METHODS

This is a prospective observational study aimed to evaluate all patients of our outpatient clinic that consulted for suspected beta-lactam allergy. The study lasted from the 1st June 2017 to the 31st May of the following year. The study protocol was approved by the local Ethics Committee (code PI4505/2017).

Inclusion criteria

All patients from 14 year old that attended the Allergy Service outpatient clinic for suspected hypersensitivity reactions to beta-lactam antibiotics in that time period were proposed to participate in the study. All patients who voluntarily agreed to participate in the study signed an informed written consent.

Methodology of the study of beta-lactam allergy

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 anamnesis by the responsible physician, this protocol included the following procedures:

- In vivo tests

a) Skin prick test (SPT), intradermal and patch tests (see Table 1 in the Supplementary Material).

b) Single-blind, placebo-controlled exposure tests up to the therapeutic dose with different beta-lactams (see Table 2 in the Supplementary Material).

Usually, the clinical history was done in one visit. Then, the patient had another visit for skin testing and drug challenge. When negative result, if 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 it, additional visits could be arranged for challenging with alternative beta-lactams (for example, cephalosporins and/or meropenem in case of patients with amoxicillin selective reactions). All visits were prospectively recorded for each patient. Moreover, the number of visits to our outpatient clinic

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changed depending on the type of reaction: immediate reaction (those reactions that appeared within the first hour) or non-immediate reaction (those with a latency period greater than one hour).

- In vitro tests

a) Determination of total IgE and specific IgE in some patients (ImmunoCAP® Thermo Scientific™, Phadia Spain S.L., Barcelona, Spain).

Data and variables collected

For data collection, a structured questionnaire was handed out to all patients (see Table 3 in the Supplementary Material). Data obtained was stored in a dissociated database, so patients' anonymity was guaranteed.

Assessment of costs

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

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 Service (see Table 2 in the Supplementary Material).

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

- Reagents used for skin testing and drugs used for challenge tests.
- Reagents used for laboratory tests.
- Fees of doctors, nurses, auxiliary health personnel and administrative staff.
- Building maintenance expenses (water, electricity, etc.).
- Patients transport to the consultation.
- Loss of working hours.

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a) Direct health costs

Direct health costs were calculated taking into account the number of visits, complementary and diagnostic tests performed, and the costs for the personnel and materials used during the study.

In this regard, all the diagnostic tests performed were taken into account: *in vivo* tests (skin tests, patch tests and controlled drug exposure tests) and *in vitro* tests (total and specific IgE) (see Text 1 and Table 4 in the Supplementary Material).

To estimate the costs per patient derived of personal fees, these costs were divided by the global 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 (see Text 1 and Table 5 in the Supplementary Material).

Total amount attributed to the patients of the study, including fees and building maintenance expenses, was proportionally calculated on the basis of total amount attributed to the Allergy Service and the number of visits to the outpatient clinic during this period. This datum was provided by the Hospital Administration (see Table 6 in the Supplementary Material).

b) Direct non-health costs

The direct non-health costs were calculated considering the number of patients visits and the kilometers from their homes to the Allergy Service, estimating a cost of €0.19 per kilometer. This is the amount that Spanish Authorities pay to public officials for the use of their private car and has been considered as locomotion expenses [17]. The most of patients lived in the province of Salamanca that has 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 had come to the hospital by walk (most of them). It was considered that all the rest of patients living in the province of Salamanca had come by car.

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c) Indirect costs

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

The average hourly labor cost in 2018 was estimated at €27.4 in the EU. However, the average masks significant differences between EU Member States, with hourly labor costs ranging between €5.4 in Bulgaria and €43.5 in Denmark (in Spain average labor cost was €21.5) [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 labour costs as in median gross hourly earnings [18].

Statistical analysis

Data were analyzed using IBM® SPSS Statistics V25.0 (Armonk-IBM Corp., New York, USA) and it was considered a statistically significant result when $p<0.05$. Quantitative variables were described by means and qualitative variables in terms of relative frequencies. Nonparametric test (Mann-Whitney test) and parametric test (T test independent samples) were used to compare quantitative variables means.

RESULTS

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

The percentage of women was 65.54% and the age range between 14 and 91 years. Mean age and standard deviation (SD) was 52 years (20.39) (Median 55 and interquartile range, IQR, 36-69).

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

In 46 out of 296 patients, allergy to beta-lactams was demonstrated, representing 15.54% of cases. Mean and median ages of those who were found to be allergic were 53.22 (19.73) and 57 (IQR, 37-70) years, respectively (values similar to those of all patients studied). Out of the 46 patients that were found to be allergic, 29 (63.04%) had previously had an immediate reaction, 16 had a delayed reaction (34.78%) and in one patient the latency period could not be stablished (2.17%).

Out of these 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 one patient had positive patch tests). Of these 35 patients, 23 had had immediate reactions and 12 delayed reactions. Other 6 patients (13.04%) were detected by challenge test: 3 of them had had delayed reactions; 2 of them had had immediate reactions and the remaining one, an unknown reaction. The remaining 5 patients, 10.87%, were considered as allergic by the clinical history (4 and 1 with immediate and delayed reactions, respectively).

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

Out of these 46 patients, 29 had amoxicillin selective reactions (63.04%); 24 of these (82.76%) tolerated alternative beta-lactams (cephalosporins and meropenem). In 5 patients, challenges with the alternative antibiotics could not be performed or patients did not accept them.

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In addition to the descriptive statistics parameters indicated above, now we comment on some statistical inference results. Percentage of the allergic patients who had an immediate reaction is significantly higher than percentage of those who had a delayed reaction (p-value=0.0263).

We also compared the number of visits of the different groups of patients using the independent-samples bilateral T test, obtaining in the two cases significant differences. In the global 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 that finally had a diagnosis of beta-lactam allergy (2.13) than in patients that did not (2.46) (p=0.039). And the mean number of visits of patients that had had immediate reactions (1.95) and that had had delayed reactions (2.76) was also significantly different (p<0.001).

Direct health costs

We calculated the costs for the personnel and of materials used during the study, reaching a total of €20,614.64. Of them €1,413.88 were the cost of materials, whereas 19,200.76 corresponded to health care personnel costs (personnel expenses, including payroll and insurances) (see Table 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. Globally, the costs of beta-lactam drugs used in challenge tests were €831.68; and specific IgE (30 patients) were €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) (See Table 1).

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Direct non-health costs

With an estimated cost of €0.19 per kilometer [17], direct non-health costs reached €6,551.73 (see Table 1).

Of the 296 patients studied, 146 came to our outpatient clinic from localities different to the hospital setting and it was assumed that they came by car, so the cost per kilometer was applied. The mean number of kilometers traveled per patient to attend all the consultations was 236.18 kilometers (252.18), with a cost per patient of €44.87 (47.92).

Data of travel expenses had a very asymmetrical distribution (see Figure 1 in the Supplementary Material). So, the mean figure of average travel expenses was €22.13 (40.44), although was highly influenced by a few high outliers. The median per patient was €0, due to it should be taken into account that more than half of patients lived in a ranged that allowed them coming to the hospital by walking.

Indirect health costs

We measured indirect health costs taking only into account work absenteeism. Total costs reached €20,769.20 (see Table 1). The mean income loss of the 296 studied patients was €70.17 (127.40).

Nevertheless, only 82 patients (27.70%) of the sample were employed. Analyzing only employed patients, the mean income loss was €253.28 (110.48). Of these 82 patients, those who had had immediate reactions, 23 (28.05%), had an mean income loss of €215.63 (49.09). In the case of patients that had had non-immediate reactions, 43 (52.44%), the mean income loss was €286.11 (124.17), whereas in those whose reaction latency period was unknown, 16 (19.51%), the mean income loss was €219.20 (116.25). Patients who had had delayed reactions had higher income loss than who had had immediate reactions (Man- Whitney's U one tailed test; p=0.006).

Total costs

In summary, total costs of the study were €55,497.63, with a mean cost of €187.49 (148.14) per patient. (see Table 1). The minimum cost was €31.68, the maximum €789.96.

Distinguishing between patients with positive or negative study results, the mean cost were €184.79 (138.50) and €187.99 (150.40) respectively; these amounts were not significantly different (p-value=0.893). The mean cost in patients with immediate was €152.64 (106.73) and with delayed reactions was €220.48 (171.79). There were statistically significantly different (p-value<0.001) (See Figure 1). And, finally, the mean costs in working [€364.12 (156.38)] and non-working patients [€121.28 (68.18)] were significantly different (p-value<0.001).

DISCUSSION

This is a prospective, real life, one year long, comprehensive study evaluating all direct and indirect health costs of studying 296 patients with suspected beta-lactam allergy. Overall, the mean cost of beta-lactam evaluation was €187.49 per patient, meaning that penicillin allergy evaluation is a non-expensive study. Different costs contributed to the final figure: (i) direct health costs that accounted for more than half, reaching a total per patient of €95.19 (37.20), (ii) direct non health costs per patient that reached €22.13 (40.44) and (iii) indirect costs were based on absenteeism that reached €70.17 (127.40) per patient.

In a prospective study that estimated direct and indirect costs of allergic rhinitis in patients attending specialized clinics performed also in Spain (the FERIN study) [19] the distribution of costs was highly different: indirect costs were almost threefold direct costs (24% vs 76%). This is because, in contrast to drug allergy, in allergic rhinitis presenteeism is important and most part of indirect costs.

To our knowledge there is only one prospective study addressing the costs of penicillin allergy evaluation. Thus, Blumenthal et al [6], who prospectively estimated the cost of penicillin allergy evaluation in 30 outpatients found a cost of $220 for the base-case, which with varied assumptions adjusting for operational challenges, clinical setting, and expanded testing, could reach up to $540.

However, our results are not completely comparable because: (i) the per capita incomes of the United States and Spain are highly different (€53,341 and 25,900 respectively in 2018), (ii) differences in the National Health System (mainly private in the United States versus mainly public in Spain); and (iii) currency exchange, i.e., absolute figures are not the same, (1 EUR=1,1250 USD). In our study not with standing costs also varied between a minimum of €31.68 and a maximum of €789.96.

There were two main factors that influenced the final cost of the study. On the one hand, the type of reaction: we found statistically significant differences between patients that had immediate (€152.64) and delayed reactions (€220.48) with a p-value<0.001. This difference was mainly related to the number of visits (193 –average 1.95- and 383 average 2.76-, respectively). On the other hand, the fact of being

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employed or not: costs of absenteeism were only present in patients that worked for hire. Thus, differences between working and non-working patients were also statistically significant, with a p-value<0.001 reaching an average income loss of €364.12 and €121.28, respectively. Finally, costs were not significantly different in patients that had a final diagnosis of penicillin allergy that in those patients in which beta-lactam allergy was excluded (p=0.893).

The main advantages of performing a study of beta-lactam allergy are de-labelling false penicillin allergic patients and correctly diagnosing patients with a real beta-lactam allergy. We want to emphasize that there was a high prevalence of anaphylaxis in patients with positive results (43.48%). In addition, all of our patients with amoxicillin selective reactions in which a challenge with cephalosporins and meromepen were performed (82.76%) tolerated alternative beta-lactams. So, most patients could benefit from treatments with other beta-lactam, contributing to reduce the serious world health problem of antimicrobial resistance.

All patients mislabeled as allergic to beta-lactams would have received alternative drugs, which are usually less effective clinically and economically. In this way, Picard et al [9] showed that additional antibiotic costs increased in more than $15,000 in 1,738 patients receiving non-beta-lactam antibiotics over one year, and Sade et al [10] identified 38% higher costs for the prescribed antimicrobial treatment regimen to be followed upon discharge. Also, MacLaughlin et al [11] showed that the mean antibiotic cost for patients labelled with beta-lactam allergy was significantly higher compared with those without a beta-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 the economic consequences, treatment with non-beta-lactam antibiotics has multiple clinical implications: higher incidences of *Clostridium difficile*, vancomycin-resistant *Enterococcus*, and methicillin-resistant *Staphylococcus aureus* infections along with an increased number of hospital days at inpatients [7] and readmissions, explained by several options. Alternative therapies often are inferior to

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beta-lactams, for example, vancomycin treatment for methicillin-susceptible *S. aureus* bacteremia is more frequently associated with recrudescence of disease [8,12]. Adverse reactions to certain non-beta-lactam antibiotics occur with higher frequency than reactions to beta-lactam agents, which may also contribute to readmission during the course of treatment [13].

In addition, penicillin allergy labelling directly impact on the antimicrobial choice by leading to use of less effective and broader spectrum antimicrobials that are associated with antimicrobial resistance. [21,22].

Finally, our study has some limitations. We have made estimates according to the overall number of patients and not by act. This is due to the fact that in the public Spanish National Health Service payment to employees is not dependent of medical acts. In addition, although some estimates have been done considering the whole year 2017 and the studies lasted from June 2017 to May 2018, as the period is also of one year, we believe that the deviation is neglectable. Another limitation of our study is the great number on unemployed patients, which clearly influences indirect costs. We had a total of 105 patients (35.47%) under 16 years of over 65 years. At these ages, people do not usually work in Spain, so this means that these patients are not employed and therefore, it implies a lower mean global indirect cost in our study. Nevertheless, this is due to the fact that our study is a real-life study. 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 are different between the different countries of EU, which implies that the indirect costs are different from other countries [18]. This also affects the total cost of the study.

In summary, in this prospective and comprehensive real-life study, in which direct and indirect health costs of evaluating penicillin allergy were considered in a systematic way in an outpatient clinic in Spain, a complete study reached €187.49 (148.14) per patient. We believe that this is an assumable figure, particularly taking into account the consequences of labeling a patient as allergic to beta-lactam.

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The authors declare that they have no financial sources.

CONFLICT OF INTEREST

The authors have no conflict of interests to declare.

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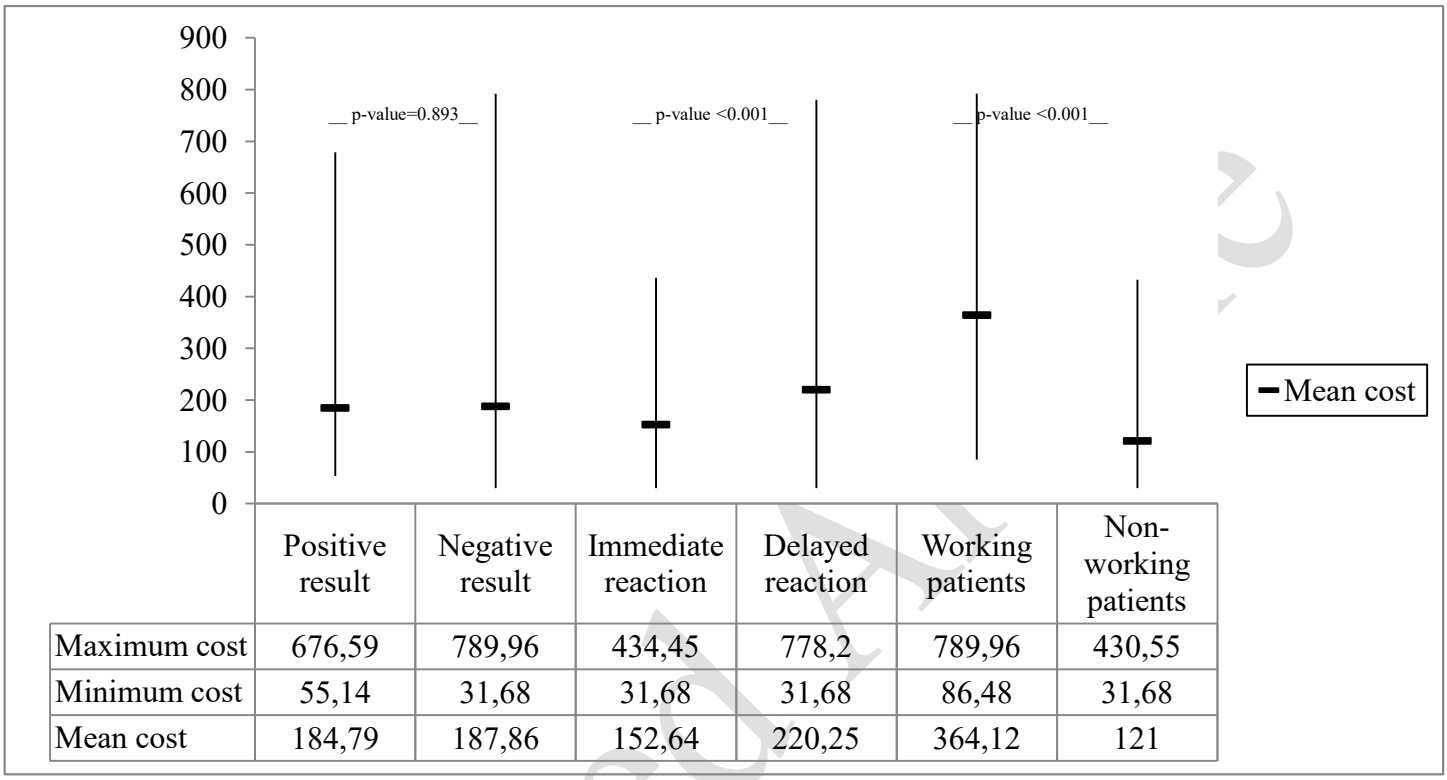
Table 1. Total costs and percentages disaggregated by items and types of costs.

Item	n	Cost (%)	Type of Cost	Total cost (%)	Mean cost (SD)
Skin and patch tests	267	€6,271.99 (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	€1,413.88 (2.55)			
Medical personnel fees	296	€19,200.76 (34.60)			
Travel expenses	296	€6,551.73 (11.81)	**Direct non-health costs**	€6,551.73 (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)

Figure 1. Total cost per patient (€) according to different variables.



	Positive result	Negative result	Immediate reaction	Delayed reaction	Working patients	Non-working patients
Maximum cost	676,59	789,96	434,45	778,2	789,96	430,55
Minimum cost	55,14	31,68	31,68	31,68	86,48	31,68
Mean cost	184,79	187,86	152,64	220,25	364,12	121

Figure 1. Box-plot of the distribution of direct non-health costs.

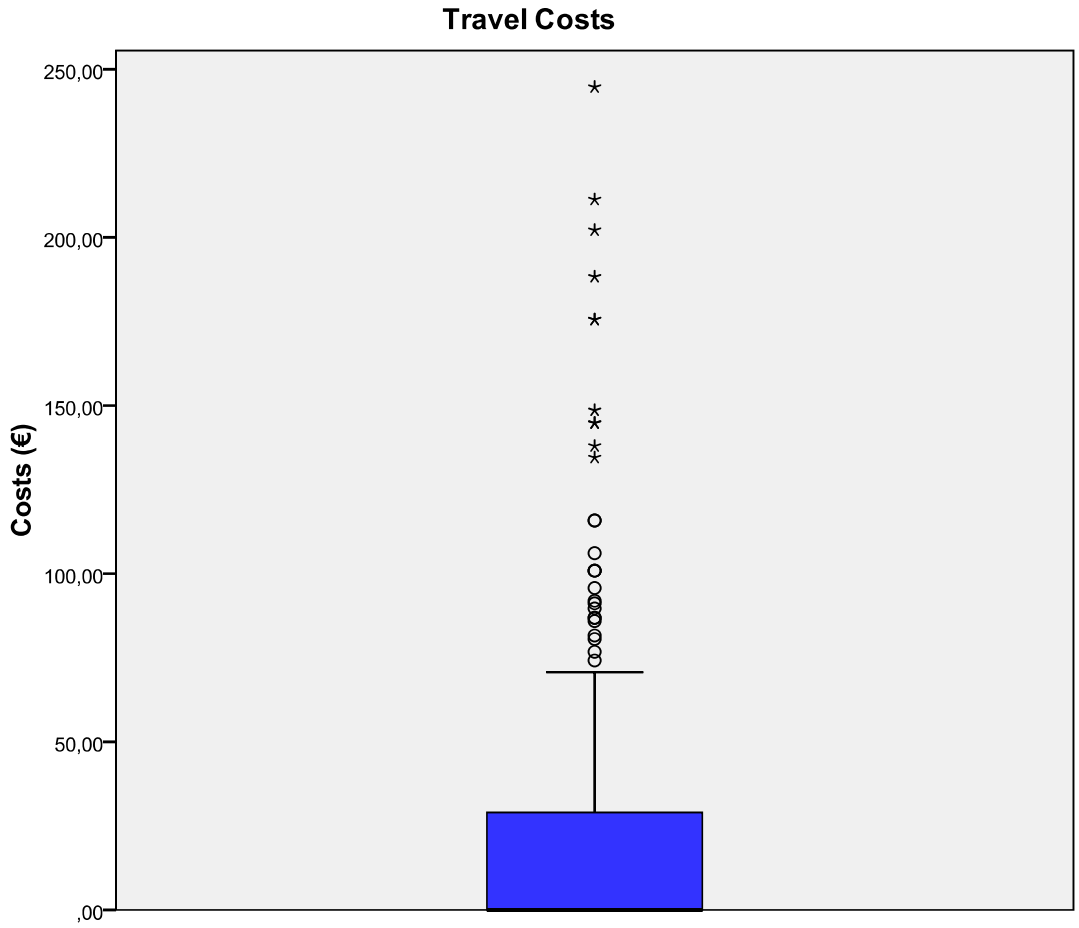


Table 1. Reagents and concentrations used for skin and patch tests

Reagent	**Concentration**
Bencylpenicilloyl Octa-L-Lysine (BP-OL)	0.04 mg/mL
Sodium Benzylpenycilloate **(**DM**)**	0.50 mg/mL
Benzylpenicillin	10,000 IU/mL
Amoxicillin	20 mg/mL
Amoxicillin + clavulanic acid	20 mg/mL + 2 mg/mL
Cefuroxime	2 mg/mL
Meropenem	1 mg/mL
Clavulanic acid	1 mg/mL

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Table 2. Raw data of the study medication consumption costs provided by the Hospital Pharmacy Service.

ACTIVE PRINCIPLE	SPECIALTY	COST (€)
Amoxicillin	Amoxicillin 500 mg, caps	-0.05
Amoxicillin	Amoxicillin 1g, sachets	15.94
Amoxicillin	Amoxicillin 250 mg/5 mL, suspension	10.49
Amoxicillin	Amoxicillin 250 mg, sachets	0.21
Amoxicillin	Amoxicillin 1g, vial	57.65
Ampicillin	Gobemicina® 500 mg, vial	1.09
Ampicillin	Gobemicina® 1000 mg, vial	1.21
Ampicillin	Britapen® 500 mg, caps	0.83
Benzylpenicillin	Penibiot® 1 million IU, vial	42.26
Penicillin combinations	Benzetacil® 6.3.3, vial	2.33
Phenoxymethylpenicillin	Penilevel® 250 mg, sachets	47.36
Cloxacillin	Anaclosil® 500 mg, caps	1.94
Cloxacillin	Cloxacillin 1g Normon®, vial	9.49
Cloxacillin	Cloxacillin 500 mg Normon®, vial	1.42
Amoxicillin/ clavulanic acid	Amoxicillin/ clavulanic acid 875 mg/125 mg, sachets	28.57
Amoxicillin/ clavulanic acid	Amoxicillin/ clavulanic acid 250 mg/62.5 mg, sachets	1.97
Amoxicillin/ clavulanic acid	Amoxicillin/ clavulanic acid 500 mg/125 mg, tablets	0.11
Amoxicillin/ clavulanic acid	Amoxicillin/ clavulanic acid 1g /100 mg, vial	79.08
Amoxicillin/ clavulanic acid	Augmentine® 100 mg/ 12.5 mg, suspension	16.64
Piperacillin/ tazobactam	Piperacillin/ tazobactam 2g /250 mg, vial	28.27
Piperacillin/ tazobactam	Piperacillin/ tazobactam 4g /500 mg, vial	23.35
Cefazolin	Cefazolin 1g Normon®, vial	7.95
Cefuroxime	Cefuroxime 750 mg, vial	49.97
Cefuroxime	Cefuroxime 500 mg, tablets	56.25
Cefuroxime	Zinnat® 250 mg/5 mL, suspension	11.80
Cefditoren	Spectracef® 200 mg, tablets	5.58
Cefditoren	Spectracef® 400 mg, tablets	2.78
Cefotaxime	Cefotaxime 1g,vial	7.12
Ceftazidime	Ceftazidime 1g, vial	12.44
Ceftriaxone	Ceftriaxone 1g, vial	13.15
Cefepime	Cefepime 1g, vial	2.29
Aztreonam	Azactam® 1g, vial	16.80
Ertapenem	Invanz® 1g, vial	74.77
Meropenem	Meropenem 1, vial	303.10
Meropenem	Meropenem 500 mg, vial	9.92
	TOTAL	**944.07**

Proportion of adults: 296/336. Adults medication consumption costs: (296/336)*944.07 = 831.68€

Table 3. Variables and data collected in the structured questionnaire

1. Sex	26. Assessment of visits to the Emergency Service
2. Age	27. Assessment of visits to the Health Center
3. First-degree family history of drug allergy	28. Treatment with antihistamines
4. First-degree family history of atopy	29. Treatment with corticosteroids
5. Personal history of atopy	30. Treatment with epinephrine
6. Personal history of drug allergy	31. Hospital admissions due to suspected drug allergy
7. Personal history of chronic disease	32. Number of days of hospitalization
8. Personal history of other diseases	33. Previous tolerance of the drug involved
9. Number of drugs regularly consumed	34. Consultations from the drug induced allergic episode
10. Drugs regularly consumed	35. Previous treatments
11. Treatment with beta-blockers	36. Number of visits to the physician in the Allergy Service
12. Treatment with ACE inhibitors	37. Number of visits to Nurse in the Allergy Service
13. Treatment with other drugs	38. Consultation in Allergy Service
14. Clinical Service that sent the patient	39. Treatments in Allergy Service
15. Reason for consultation	40. Skin prick test with aeroallergens
16. Indication for drug administration	41. Skin prick test with the involved drugs
17. Number of drugs involved in the reaction	42. Intradermal skin test with the involved drugs
18. Drugs involved in the reaction	43. Patch testing with the involved drugs
19. Route of administration	44. Total IgE
20. Number of doses administered	45. Specific IgE
21. Latency period until the onset of symptoms	46. Controlled exposure tests
22. Clinic Reaction	47. Result of controlled exposure tests
23. Duration of symptoms	48. Leaving the study
24. Number of episodes	49. Do you work for hire?
25. Number of visits to the Emergency Service	50. Hours of work lost for allergy diagnostic procedures

Table 4. Data of consumption (material and infrastructures)

MATERIAL	Total amount in 2017 (€)
Repairs, maintenance and conservation	1,771.69
Non inventoriable ordinary office material	152.44
Reprography and print material	701.23
Clothing	151.81
Supply of machinery spare parts	523.96
Lab's material	27,270.00
Generic healing material	403.05
General sanitary material	18,060.35
Cannules and tubes	172.15
Kitchen and dinette utensils	34.97
Cleaning	367.62
Non inventoriable ordinary office material	83.88
Electrical, electrical and communication material	138.67
Chemical products for laboratories	28.87
Kitchen and dinette utensils	23.52
Transportation cleaning	52.39
Total consumption transportation	42.35
TOTAL CONSUMPTION	**49,978.95**

Total number of visits to Allergy Service: 25,239
Number of patients that consulted for suspected beta-lactam allergy (older than 13) visits: 714
Consumption (material and infrastructures): (714/25,239)*22,507.93 = **1,413.88 €**

Table 5. Payroll of the Allergy Service personnel

CONCEPT	Total amount in 2017 (€)
Payroll of personnel	541,958.69
Insurance of personnel	136,763.94
TOTAL	**678,722.63**

Total number of visits to Allergy Service: 25,239

Number of patients that consulted for suspected beta-lactam allergy (older than 13) visits: 714

Payroll : (714/25239)* 678,722.63 = **19,200.76€**

Table 6. Consumption and payroll of the personal proportionally to the number of patients/visits

	Allergy Service		**Patients of the study**	
	Total cost (€) (y)	**nº visits** (N)	**nº visits** (n)	**Total cost (€)** (x)
Consumption	49,978.95	25,239	714	1,413.88
Personnel	678,722.63			19,200.76
			TOTAL	**20,614.64**

The equation for attributing the total consumption and personnel costs to the patients of the study was:

$$x = \frac{y}{N} * n$$

Where: *x*: costs attributed to the patients of the study

y: total costs attributed to all patients attended in the Allergy Service

N: number of visits of all patients who were attended in the Allergy Service

n: number of visits of the patients of the study

Table 7. Study population demographic characteristics.

Total Patients (n=296)		
Gender	Male (%)	102 (34.46)
	Female (%)	194 (65.54)
Age (years)	Range	14-91
	Mean (SD)	52.00 (20.39)
	Median (IQR)	55 (33)

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Text 1

Estimation of personnel fees, material and infrastructures

Data related to the costs of general materials and infrastructure costs (Table 4) and personnel (Table 5), were provided by the Bureau of Management of the University Hospital of Salamanca.

Only data of 2017 were available at the moment of the study. As our study lasted one year, these annual data were assumed for the study.

To estimate the cost per patient for personnel fees, the global figure attributed to the Allergy outpatient Clinic (that included the laboratory of allergy) was divided by the number of patients seen during 2017. Data for personnel, materials and infrastructures were also divided by the number of patients seen during 2017, with a total of 296 patients (it was impossible to obtain monthly data). Although the time dedicated by the staff to a particular patient varies with the disease, with the diagnostic or with the therapeutic procedure, as fees of staff are not paid per particular medical acts in Spain, it was assumed that the cost of each patient was the same.

The number of visits of patients valuated at the outpatient allergy clinic during 2017 was 25,239 (first and successive visits). We have calculated consumption and personnel costs proportionally to the number of visits of our patients (714 visits). Each time a patient assisted to the outpatient allergy clinic, a visit was considered.

Costs of general expenses (material and infrastructures) were equally attributed to all patients seen in 2017.

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