A Prospective Study of Costs Associated with the Evaluation of β-Lactam Allergy in Children

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Objective To evaluate the costs associated with evaluation of β-lactam allergy in children labeled as allergic.

Study design We performed a prospective year-long real life observational study designed to evaluate all pediatric patients with suspected β-lactam allergy who consulted for allergy evaluation. Direct and indirect costs were systematically recorded. Direct healthcare costs were calculated by taking into account the number of visits and all complementary and diagnostic tests performed. Direct nonhealthcare costs were calculated by considering the number of visits and the kilometers from their homes to the clinic. Finally, indirect costs were evaluated by considering the absenteeism of parents or other companions who took the children to the clinic.

Results A total of 40 children with suspected allergy to β-lactams were evaluated in our outpatient clinic from June 1, 2017 to May 31, 2018. Total direct healthcare costs were $5038.03, with an average cost per patient of $125.95. Direct nonhealthcare costs reached $901.87 ($22.55 per patient) and indirect nonhealthcare costs reached $6384.35 ($159.61 per patient). The total cost was $12 324.25, a cost of $308.11 per patient.

Conclusions Elective evaluation of β-lactam allergy and delabeling children who are not allergic is not expensive. In addition, it could save future expenses because of an unnecessary lifelong use of alternative antibiotics that are usually more expensive, less effective, and more frequently associated with antimicrobial resistance and different side effects. *(J Pediatr 2020;223:108-13)*.

About 10% of parents claim that their children are allergic to drugs, with β-lactam antibiotics the most frequently suspected of causing reactions, and probably related to high prescription rates.[1-3] However, only a small proportion of all suspected allergic reactions are true drug allergic reactions.[1] In this way, different studies revealed that fewer than 10% of patient claiming to be allergic really are, meaning that most children are inappropriately labeled as having a drug allergy.[4-6] The unnecessary use of alternative antibiotics places patients at risk for adverse reactions, treatment failures, increased rates of antimicrobial resistance, and healthcare-associated infections.[7-14] The evaluation and delabeling of β-lactam allergy in pediatric population constitute an important public health goal.[15]

Nevertheless, published studies about the costs of delabeling β-lactam allergy in children are scarce. Au et al estimated that the lifetime antibiotic costs per patient of subjects labeled as penicillin allergic prior to age 10 years compared with those who were not allergic to penicillin were $8171 and $6278, respectively, concluding that an elective evaluation study of suspected penicillin allergic reactions in children could be cost saving.[16]

There are a few studies addressing the cost of β-lactam allergic evaluation in adults.[7,17] We aimed to prospectively evaluate the costs associated with an elective evaluation of allergy to β-lactams in children.

Methods

This was a 1-year prospective real-life observational study aimed at evaluating the costs associated with the evaluation of all pediatric patients of our outpatient clinic who consulted for a suspected β-lactam allergy. Pediatric was defined as up to 14 years of age because this is the age limit for care by pediatric allergists in Spain. The study lasted from June 1, 2017 to May 31, 2018. The study protocol was approved by the local Ethics Committee (code PI4505/2017). This was a substudy of a global study of costs associated with drug allergy evaluation (not only β-lactams) that included both adults and children. Parts of this study have been published elsewhere.[17,18]

Inclusion Criteria

All pediatric patients who attended our allergy service outpatient clinic for suspected hypersensitivity reactions to antibiotics during that time period were

EU	European Union

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invited to participate in the study. The children's legal guardians who voluntarily agreed to participate in the study signed an informed written consent form.

As recommended, all testing was avoided in children with a history of a severe cutaneous nonimmediate reaction such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms, acute generalized exanthematous pustulosis, or serum sickness.

Methodology of the Study of β-lactam Allergy

Diagnostic procedures were performed following the European Network on Drug Allergy/European Academy of Allergy and Clinical Immunology protocol.[19,20] After detailed clinical history and exploration, children underwent the following procedures: skin prick and intradermal tests, and patch tests when advisable, using a standard set of reagents (**Table I**; available at www.jpeds.com). We decided to apply the same protocol to all patients, therefore, negative skin tests were mandatory before challenge tests.

When negative, children underwent single-blind, placebo-controlled oral challenge tests with the involved β-lactam up to a therapeutic dose. Usually, the clinical history was done during the first visit. Skin and drug challenge tests were performed in a subsequent visit. If negative, when the suspected reaction occurred more than 6 months before the allergy evaluation, skin tests and challenge test were repeated. In those patients with positive results, additional challenge tests with alternative β-lactams were performed (ie, cephalosporins and/or meropenem in patients with selective reactions to aminopenicillins). All visits were prospectively recorded.

Total IgE and specific IgE (ImmunoCAP; Thermo Scientific Phadia Spain S.L., Barcelona, Spain), and patch tests were only performed in some patients, depending on their allergist criterion. Skin prick, intradermal tests, and challenge tests were mandatory per protocol.

Data and Variables Collected

For data collection, a structured questionnaire was handed out to all patients (**Table II**; available at www.jpeds.com). Data obtained were stored in a dissociated database, guaranteeing the anonymity of the patients.

Assessment of Costs

Data relating to staff, material, and infrastructure costs were provided by the Bureau of Management at the University Hospital of Salamanca. Data concerning the medication used for the study were collected in a structured way; these data were provided by the hospital pharmacy service (**Table III**; available at www.jpeds.com).

To assess the costs in monetary terms, the following data were considered: reagents used for skin testing and drugs used for challenge tests; costs of laboratory tests; fees of doctors, nurses, auxiliary health personnel, and administrative staff; building maintenance expenses (water, electricity, etc); patient travel costs; and loss of working hours of the legal guardian.

Direct healthcare costs were calculated considering the number of visits, complementary and diagnostic tests, costs for personnel, and materials. All diagnostic tests were taken into account: in vivo tests (skin tests, patch tests, and challenge tests) and in vitro tests (total and specific IgE) (**Table IV**). Data of materials and infrastructures are detailed in **Table V** (available at www.jpeds.com). To estimate per visit cost derived of personnel fees, these costs were divided by the global number of visits to the outpatient clinic of patients seen during 2017. The 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 our allergy service outpatient clinic and their number of visits to the outpatient clinic during the study (**Table V**).

As staff remuneration in the Spanish National Health Service does not depend on medical procedures, it was assumed that the cost of each patient was the same (**Table VI**; available at www.jpeds.com). This datum was provided by the Bureau of Management of the University Hospital of Salamanca.

Direct nonhealthcare costs were calculated considering the number of patients' visits and kilometers from their residences to the allergy service outpatient clinic, estimating a cost of $0.21 per kilometer. This is the amount paid by Spanish authorities to public officials and was considered as travel expenses.[21] Usually, 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, were considered to have come on foot. It was considered that the remaining patients had come by car.

Indirect costs were based on loss of working hours (absenteeism). As pediatric patients do not work, we considered absenteeism of legal guardians who accompanied the children to clinic. We obtained this amount taking into account the hourly labor costs in the European Union (EU). The average hourly labor cost in 2018 was estimated at $30.67 in the EU,[22] when the legal guardian who attended the consultation with the child were employed by others. When legal guardians were unemployed, we considered the mean hourly minimum basic wages in Europe, which were estimated at $4.90 (SD $3.37).[23]

Statistical Analyses

Data were analyzed using IBM SPSS Statistics v 25.0 (IBM Corp, Armonk, New York). A statistically significant result was considered when P value was $< .05$. Quantitative variables were described by means and qualitative variables in terms of relative frequencies. Nonparametric test (Mann-Whitney test) and parametric test (t test

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

Items	n	Cost (%)	Type of cost	Total cost (%)	Average cost (SD)
Skin prick, intradermal and patch tests	40	$1053.62 (8.55)	Direct healthcare costs	$5038.03 (40.88)	$125.95 ($37.10)
Total and specific IgE*	6	$96.24 (0.78)			
Challenge tests	40	$107.19 (0.87)			
Materials and infrastructure	40	$259.33 (2.10)			
Health personnel fees	40	$3521.65 (28.57)			
Travel expenses	40	$901.87 (7.32)	Direct nonhealthcare costs	$901.87 (7.32)	$22.55 ($31.46)
Loss of working hours	40	$6384.35 (51.80)	Indirect healthcare costs	$6384.35 (51.80)	$159.61 ($139.43)
Total				$12 324.25 (100)	$308.11 ($184.35)

*The cost per unit of specific IgE to ampicillin or amoxicillin is $ 7.39 and the cost per unit of total IgE is $ 1.26.

independent samples) were used to compare quantitative variables means.

Results

A total of 40 children with suspected allergy to β-lactams were evaluated in our allergy service outpatient clinic between June 1, 2017 and May 31, 2018. All of the children completed the study. The mean age was 5.45 years (SD 4.22) and median age 4 years (0-13), and 45% were girls. Previous reactions were immediate in 8 children (20%), delayed in 29 (72.5%), and unknown in 3 (7.5%). Allergy to β-lactams was demonstrated in 3 children (7.5%). One of them had had urticarial, and the other 2 had experienced anaphylaxis previously.

None of the included children had positive results in skin prick tests, patch tests, or ImmunoCAP. Three patients definitively were diagnosed as allergic to β-lactams and had a positive intradermal test with amoxicillin. All patients underwent oral challenge tests. In those patients with negative intradermal tests, oral challenge tests were performed with the suspected drug. The 3 patients with positive intradermal tests with amoxicillin underwent oral challenge tests with cefuroxime, an alternative β-lactam; all had negative results. Furthermore, no patient required the study to be repeated, as they had all suffered the reaction within 6 months prior to the allergy assessment.

The median number of visits up to completion of the diagnosis was 3 visits. This was not statistically different between patients who had a diagnosis of β-lactam allergy than in patients who did not ($P = .762$). Also, the median number of visits between patients with suspected immediate reactions and delayed reactions was not statistically significantly different ($P = .723$).

Direct Healthcare Costs

Total attributed costs of personnel and of materials reached $3780.98. Of the total costs, $259.33 were the cost of materials and infrastructures (including maintenance, infrastructure, electricity, water, gas consumption, inventory material, laboratory equipment, kitchen, cleaning.), whereas $3521.65 corresponded to healthcare personnel costs (personnel expenses, including payroll and insurances) (Table V and Table VI). Costs of performing skin tests (40 patients), patch tests (8 patients), and controlled exposure tests (40 patients) reached $1053.62. Overall, the costs of β-lactams used in challenge tests reached $107.19; costs of total and specific IgE (6 patients) were $96.24. Finally, the total direct healthcare costs reached $5038.03, with an average cost per patient of $125.95 (Table IV).

Direct Nonhealthcare Costs

Of the 40 children studied, 24 came to our outpatient clinic from different localities. As it was assumed that they came by car the cost per kilometer was applied. The average cost and the average number of kilometers of those who had traveled were $37.58 (SD $37.00) and 176.70 km (SD 155.19 km), respectively. Overall, direct nonhealthcare costs reached $901.87 (Table IV). The travel expense data had a very asymmetrical distribution, with average travel expenses $22.55 (SD $31.46) strongly influenced by a few outliers.

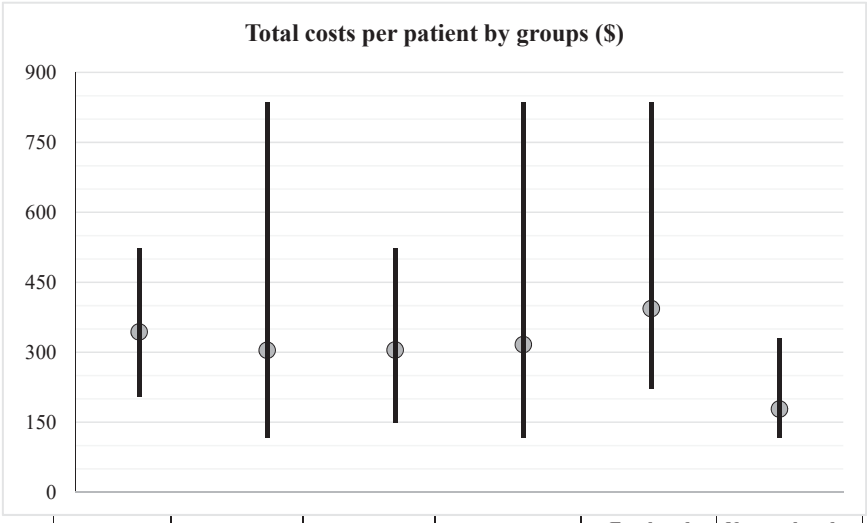
Indirect Healthcare Costs

In Spain, there is no salary deduction for employees who go for medical consultations; so, the loss of income refers to the labor costs lost by employers. Thus, we measured indirect healthcare costs taking into account only the work absenteeism of legal guardians raising 24 of our 40 children (60%); the rest of the legal guardians were unemployed, but it is reasonable to consider that it generates a cost similar to the minimum hourly wage because they may need another person to do their housework while attending the consultation with their child. Total indirect costs reached $6384.35 (Table IV). The average income loss was $159.61.

Total Costs

In summary, the total costs of the study were $12 324.25, with a mean a cost of $308.11 (SD 184.35) (Table I). The minimum cost was $116.44, and the maximum $835.86 (Figure).

Comparing patients with allergies and patients without allergies, the average cost were $343.87 (SD 163.08) and $304.55 (SD 187.93), respectively ($P = .521$). The average cost of patients who reported immediate ($304.90; SD 129.16) and delayed reactions ($316.70; SD 205.70) were also not significantly different ($P = .825$). However, as



	Allergic patients	Nonallergic patients	Immediate reaction	Delayed reaction	Employed parents /legal guardians	Nonemployed parents / legal guardians
Maximum cost	522.68	835.86	522.68	835.86	835.86	330.30
Average cost	343.87	304.55	304.90	316.70	393.76	178.11
Minimum cost	203.31	116.44	148.75	116.44	221.18	116.44

Figure. Total cost per patient ($) according to patients allergic patients vs nonallergic patients ($P = .521$), immediate vs delayed reactions ($P = .825$), and employed vs nonemployed parents or legal guardians accompanying the child to consultation ($P < .001$).

expected, the total expenses in the case of children who were brought to the outpatient clinic by a legal guardian who worked for pay ($393.76; SD 188.92) were significantly higher than that of those whose parents did not work ($178.11; SD 64.12) ($P < .001$) (**Figure**).

Discussion

The main advantage of performing a study of β-lactam allergy is delabeling β-lactam allergy, especially in pediatric patients in which verifiable penicillin allergy is less than 10%.[1] However, it is also important to know the cost of carrying out this delabeling and whether it represents or not a considerable financial burden on the health system.

In our prospective study, the average cost per child reached $308.11 (SD 184.35): direct healthcare costs were $125.95 (SD 37.10), direct nonhealthcare costs $22.55 (SD 31.46), and indirect healthcare costs $159.61 (SD 139.43) (**Table IV**). The median number of visits until completion of the diagnosis was 3 visits. Therefore, most of the costs were due to direct healthcare costs and indirect healthcare costs. The former were mainly determined by the number of visits, and the latter by the loss of wages of the parents or legal guardians, as well as by the cost of the minimum hourly wage. In summary, both are influenced by the number of visits.

These facts may explain the fact that we have not found differences in costs between patients in relation to different aspects. In this way, costs were not significantly different in children in whom β-lactam allergy was excluded than in patients with a final diagnosis of penicillin allergy. This is probably because all the patients, after skin tests, underwent a challenge test, either with the suspect drug or with an alternative drug. Thus, it was not expected that there would be a different number of visits between the 2 groups. Also, there were no differences in costs between children with immediate and delayed reactions; this could also be due to the fact that the median number of visits was not statistically different in patients with immediate or nonimmediate reactions.

In turn, the number of visits is also determined by the protocol used to study allergy to β-lactams. Recently, Abrams et al provided an approach to children who are mislabeled as β-lactam allergic, as well as offering salient examples of the importance of delabeling β-lactam allergy in the pediatric population.[15] These authors propose a diagnostic algorithm to manage children with suspected amoxicillin allergy, which relies predominantly on oral drug provocation tests unless the child is considered as high risk. Nevertheless, Macy et al considered that only a few studies reported on safety, and no clear recommendations have been promoted until now.[24] They state that a number of allergists still consider performing systematic skins tests before challenge tests, mainly for fear of severe reactions. According to this observation, we have always performed skin tests before challenge tests in all children to avoid unsuspected risks. Furthermore, no patient required repeat testing because they all had the suspected reaction within 6 months before the allergy evaluation. Presumably, the total costs would have been higher if it had been necessary to repeat the tests because the number of visits would also have been higher.

In our study, the total costs of delabeling β-lactam allergy were in the range of others previously performed in adult patients. To our knowledge, there are only 2 prospective studies addressing the costs of β-lactam evaluation, both performed in adults, and virtually none have addressed these costs in pediatric populations. Thus, Blumenthal et al prospectively estimated the cost of penicillin allergy evaluation in 30 adult outpatients, obtaining a cost of $220 for the base case that could rise up to $540.[7] In the base case, oral provocation tests were performed without previously performing skin tests, so the number of visits was lower than in the cases in which skin tests were performed and so were the costs. In addition, Sobrino et al prospectively evaluated 296 adult patients who consulted for β-lactams allergy, finding a mean cost of $209.85 per patient.[17] In this case, the authors followed the EAACI/ENDA protocol[19,20] that included prior skin tests.

The cost of delabeling β-lactam allergy in children should be weighted taking into account the consequences of not using β-lactams, and the costs of the treatment of possible further reactions. Thus, Au et al estimated the lifetime antibiotic costs of patients labeled as allergic to penicillin prior to age 10 years compared with those who were not allergic to penicillin.[16] They found that patients labeled as allergic to penicillin had a mean lifetime antibiotic cost of $8171 per patient, compared with $6278 for patients not allergic to penicillin. In another study, Sousa-Pinto et al identified 1718 hospitalizations corresponding to children labeled as allergic to penicillin.[25] Compared with patients without such a label, these children had longer hospital stays (mean 5 vs 4 days, $P = .03$) and a higher comorbidity index (mean 0.11 vs 0.09, $P < .001$). Hospitalization costs were also higher ($2318.04 vs $2012.47), although the difference was not significant. In addition, Macy et al found that patients labeled with penicillin allergy spent 9.9% more days (0.59 days: 95% CI 0.47-0.71) in the hospital than controls, with the consequent economic cost.[8] In another study that included 252 inpatients with penicillin allergies reported on their respective medical records and were hospitalized for reason unrelated to penicillin allergy, it was determined that the evaluation and subsequent removal of this label prevented 504 inpatient days and 648 outpatient days on alternative antibiotics.[26] Also, a cross-sectional case-control study of inpatients noted a doubling of costs for antibiotics if patients had the label of penicillin allergy on their records.[27] In the US, an antimicrobial stewardship program in a tertiary care hospital noted that evaluation of penicillin allergy, with the removal of this label from 145 of 146 charts, resulted in an annual savings of $82 000.[28]

To estimate the costs of possible further reactions if our patients had not been studied, we have also estimated the costs generated by our patients prior to our study just for attending the emergency department and/or their primary care center as a consequence of the reaction presented. Taking local public prices into account,[29] the costs derived from attending the reactions for which they consulted the allergy service outpatient clinic were estimated at $6600.43. This **Figure** corresponds to 30 visits (mean 0.75; SD 0.71) to emergency departments and 39 visits (mean 0.98; SD 0.48) to primary care centers, with an average expenditure of $165.01. Obviously, this amount was not included in the total average cost per patient in our study. All these data suggest that penicillin allergy delabeling can be cost saving and justifies that we should consider the possibility of delabeling children with suspected penicillin allergy.

We cannot forget that alternative treatments with non-β-lactam antibiotics have multiple and relevant clinical implications, such as higher incidences of *Clostridioides difficile*, vancomycin-resistant *Enterococcus*, and methicillin-resistant *Staphylococcus aureus* infections.[8] Moreover, penicillin allergy labeling has been described to directly impact on the antimicrobial choice by leading to the use of less effective and broader spectrum antimicrobials that are associated with antimicrobial resistance.[30,31] Indeed, Shaikh et al have demonstrated amoxicillin to be the most cost-effective antibiotic for treating otitis media in children.[32]

Finally, our study is not without 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 on medical procedures. In addition, it has to be taken into account that gross earnings at work are different among the different countries of the EU, which implies that the indirect costs are different in other countries. Spain ranked number 13 of the 28 countries of the EU both in hourly labor costs as in median gross hourly earnings.[23]

In summary, in this prospective and comprehensive study, in which direct and indirect healthcare costs of evaluating penicillin allergy were considered in a systematic way in an outpatient clinic in Spain, a complete study reached $308.11 (SD 184.35) per patient. We believe that this is an acceptable figure, particularly considering the consequences of labeling a patient as allergic to β-lactams. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

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Table I. Reagents and concentrations used for skin prick tests, intradermal tests, and patch tests

Reagents	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

Table II. Variables and data collected in the structured questionnaire

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

ACE, angiotensin-converting enzyme.

Table III. Raw data of the study medication consumption costs provided by the hospital pharmacy service

Active principles	Costs ($)
Amoxicillin	26.68
Benzylpenicillin	47.34
Amoxicillin/ clavulanic acid	11.61
Cefuroxime	9.30
Total:	94.93

Table V. Data of materials and infrastructures

Materials	Total amount in 2017 ($)
Repairs, maintenance, and supplies	2569.46
Ordinary office supplies including photocopying and printing materials	1049.39
Laboratory material and chemical products	30 747.89
General sanitary and generic healing material	20 665.81
Electrical and communication equipment	155.21
Other (clothing, kitchen/kitchen utensils, and cleaning)	752.93
Total costs	55 940.69

Table VI. Material and infrastructure and payroll of the personnel proportionally to the number of patient visits

	Allergy service outpatient clinic		Patients of the study	
Type of cost	Total cost ($) (y)	Visits (n)	Visits (n)	Total cost ($) (x)
Material and infrastructure*	55 940.69	25 239	117	259.33
Payroll of the allergy service personnel (Payroll + insurance)	759 684.06 (606 606.23 + 153 077.83)			3521.65
Total				3780.98

The formula 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 outpatient clinic; *N*: number of visits of all patients who were attended in the allergy service outpatient clinic; and *n*: number of visits of the patients of the study.

*More detailed in **Table V**; available at www.jpeds.com.