

The economic burden of antibiotic treatment of penicillin-allergic patients in internal medicine wards of a general tertiary care hospital

K. Sade, I. Holtzer, Y. Levo and S. Kivity

Allergy and Asthma Center and the Department of Medicine 'T', Tel Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Summary

Background Penicillin allergy poses a major problem in the management of infectious diseases.

Objective We estimated the costs and usage of antibiotic treatment of 'penicillin-allergic' patients in comparison to non-allergic patients in a tertiary care hospital.

Materials and methods The study was based on the records of 118 randomly chosen in-hospital patients labelled as being 'allergic to penicillin' and who were treated with antibiotics. The antibiotic selection and cost of the patients with alleged penicillin allergy were compared to 118 matched patients without an antibiotic allergy (controls).

Results During in-hospital treatment, the mean antibiotic cost for penicillin-allergic patients was 63% higher than the cost for the controls. In addition, there was a 38% higher cost of the recommended anti-microbial treatment regimen to be followed upon discharge by the former compared to the latter.

Conclusions Penicillin-allergic patients were more likely to receive broader spectrum antibiotics compared to the non-allergic ones. Since many of the patients who are labelled as being 'allergic to penicillin' are, in fact, not allergic to it, inaccurate reporting of penicillin allergies may have costly economic and epidemiologic repercussions in addition to more toxic effects which can occur when choosing alternative drugs in case of penicillin allergy.

Keywords allergy, antibiotic, beta-lactam, cost, drug allergy, penicillin

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Introduction

Penicillins and their semi-synthetic derivatives are the drug of choice in treating many infectious diseases and are currently the most commonly employed antibiotic because of their safety, their narrow spectra of activity and their low cost [1, 2]. The possibility of penicillin allergy is recognized as the main factor limiting its use and that of other beta-lactam drugs [3–5]. A history of allergy to penicillin is usually vague and an unreliable indicator: there are many studies demonstrating that skin tests using penicillin and its degradation products are safe, practical and useful in ruling out penicillin allergy in many of the patients who had previously been labelled as such [5–10]. In spite of their efficacy, the practice of applying skin tests has been gradually abandoned and restricted to specialized centres and cases, and the most prevalent approach to providing an acceptable pharmacotherapeutic alternative to penicillin in suspected cases of penicillin allergy has become the prescribing of different antibiotics [11, 12].

Withholding penicillin from many patients who could safely receive the drug or its derivatives could be expected to raise the

costs accrued by the unnecessary use of more expensive broad spectrum antibiotics. To date, there have been a few studies which showed that incorrectly labelling patients as being allergic to penicillin could be associated with increased healthcare costs: these studies, however, were specific to outpatient clinics, to specific diseases or situations [13–18].

We hypothesized that the label of 'penicillin allergy' would potentially affect the costs and selection of antibiotics used to treat patients for common infectious conditions in general hospitals. The current study was designed to examine the differences in cost and antibiotic usage between patients labelled as being penicillin-allergic and those who were not, in internal medicine wards of a tertiary-level teaching hospital.

Methods

This is a retrospective review of the medical records of patients who were hospitalized in the internal medicine wards of Tel Aviv Sourasky Medical Center (TASMC), a tertiary-level teaching hospital affiliated with the Sackler Faculty of Medicine, Tel Aviv University, Israel. The study period extended from 1 January 1997 to 31 December 1998. The costs of the drugs were calculated according to the prevailing prices of the pharmacies which provided the antibiotics.

Correspondence: K. Sade, Allergy and Asthma Center, Tel Aviv Sourasky Medical Center, 6 Weizman Street, Tel Aviv 64239, Israel.
E-mail: allergy@tasmc.health.gov.il

This study was reviewed and approved by the hospital human research subjects protection committee.

The computerized medical records of hospitalized patients in TASMC include a list of all their medical problems and medical procedures, coded by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) Codes. The diagnosis of infectious disease and the assignment of the label 'penicillin allergy' were determined by these codes.

We searched and reviewed all the computerized records of the patients who were hospitalized in the internal medicine wards during the study period and identified all those patients who were labelled with ICD-9-CM codes which define adverse effects to antibiotics in general and to penicillins in particular. Only those patients who were labelled as penicillin allergic by their physicians in their complete medical records were included. The codes regarding penicillin allergy which were searched included:

E930.0 Penicillins causing adverse effects in therapeutic use.

E960.0 Poisoning by penicillins.

V14.0 History of allergy to penicillin.

After identifying all the patients labelled as allergic to penicillin who were hospitalized in the internal wards during the study period (among whom approximately 10% were hospitalized due to infectious diseases), 118 allergic patients who were hospitalized due to an infectious disease were randomly chosen to comprise the study cohort. Randomization was done by generating random numbers using the random function of our database Excel® software.

The study patients were matched with 118 patients who were hospitalized due to similar causes but who were not labelled as being allergic to antibiotics (controls).

Matching was carried out on the basis of gender, age (3 years), admission diagnosis, and concurrent diseases. Patients in the study group were stratified along these four parameters and patients without allergy were randomly picked as the match for the allergic patient who fell within the same stratum. The complete inpatient medical record was reviewed for each case and control.

The study and control groups were compared according to the following parameters: mortality, transfer to other departments, length of hospitalization, number and type of anti-microbial used, the duration of anti-microbial use, method of delivering the anti-microbial drug (i.e. parenteral vs. enteral), frequency of the dose, and cost per hospitalization of each anti-microbial used. The out-of-hospital antibiotic usage and cost of the drugs which were recommended to each study participant upon discharge from the hospital were analysed as well.

Statistical analysis

Student's *t*-test was used to compare the age and costs of treatment between the two study groups. The chi-square test compared gender differences. The Fisher's exact test was applied to compare between the use of antibiotics and the prevalence of allergy. The SPSS software was used for the analysis, and significance was set at $P < 0.05$.

Results

During the two-year study period, 1384 of a total of 22 323 patients hospitalized in the internal medicine wards were

Table 1. Characteristics of the allergic and matched control non-allergic hospitalized patients

	Allergic		Non-allergic		P-value
	Average	SD	Average	SD	
Number of patients	118		118		
Age (years)	72.3	17.676	71.6	19.4	0.77
Female (%)	60		57		0.65
Urinary infections (%)	45		46		NS
Respiratory infections (%)	45		44		NS
Number of background diseases	2.31	1.2	2.39	1.4	0.31

SD, standard deviation.

found to be labelled as penicillin-allergic, with an estimated prevalence of 6.2%.

Demographics of the study patients and the matched controls are presented in Table 1. The two groups were highly similar with respect to the independent variables of age, gender, admission diagnosis and concurrent diseases.

The differences in outcome and in antibiotics administration and cost between the allergic and the non-allergic patients during hospitalization are presented in Table 2. No differences were observed in respect to the mortality, transfer to other departments, length of hospitalization, number of antibiotics which were used during the treatment, method of antibiotic delivery, frequency of drug delivery, or duration of therapy. There were significant differences in the cost of treatment and the antibiotics which were used. The mean antibiotic cost for patients labelled as being penicillin-allergic was $\$81.7 \pm 80.5$ compared with $\$52.5 \pm 53$ per day for patients without an allergy ($P = 0.0154$). This translated into a 63% greater cost for the former group. As for the instructions regarding post-hospitalization antibiotic treatment, the recommended duration of treatment was longer and the recommended antibiotics were more expensive for the penicillin-allergic patients compared to the non-allergic ones. The difference in total cost of therapy upon discharge was significant: US\$43.00 for the penicillin-allergic patients vs. US\$31.00 for the non-allergic patients ($P < 0.0005$) (Table 3). For this parameter, the cost was 38% greater for the former group.

In terms of antibiotic usage in hospital, patients who were reportedly penicillin-allergic were more likely to receive a cephalosporin, macrolide, vancomycin or a miscellaneous agent ($\chi^2 = 57.19$, $P = 0.001$) (Fig. 1).

Of the 118 patients reporting penicillin 'allergy', 111 had a history of 'allergy' only to penicillins, and seven had a history of 'allergy' to both penicillin and at least one cephalosporin. None reported intolerance to vancomycin. Only 24 (33%) of the 118 beta-lactam-allergic patients could describe the expression of their purported allergy, and most of them reported reacting with a skin rash (Fig. 2).

Discussion

The present investigation was designed to explore an association between the labelling of patients as being penicillin-allergic and healthcare costs in the setting of a tertiary-care university-affiliated general hospital. The calculations of our

Table 2. Differences in outcome and in antibiotics (Ab) administration, and cost between the allergic and the non-allergic patients during hospitalization

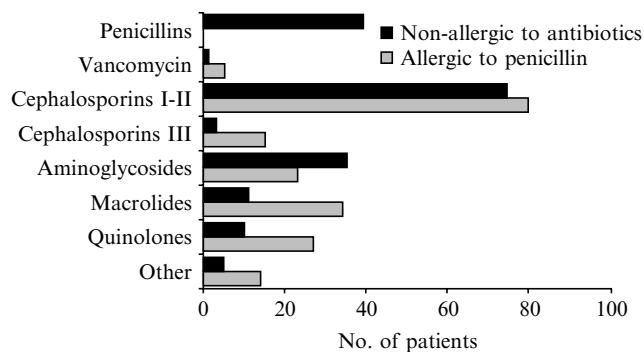
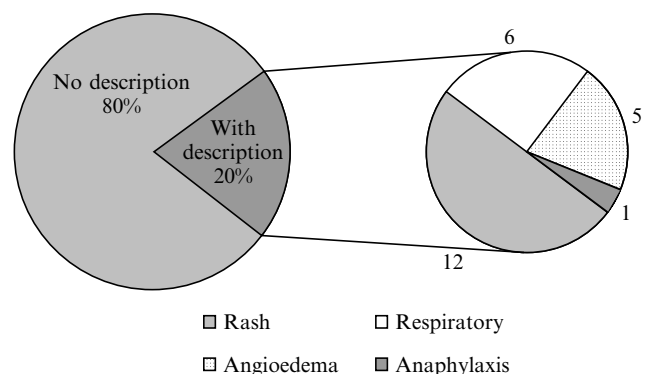
	Allergic		Non-allergic		P-value
	Average	SD	Average	SD	
Number of patients	118		118		
Hospitalization mortality	2		3		NS
Transportation to other departments	3		2		NS
Duration of hospitalization (days)	5.2	2.8	5.5	3.1	0.41
Number of Ab per hospitalization	1.67	0.71	1.43	0.65	0.40
Parental Ab (%)	65	0.47	71	0.45	0.09
Doses per day (n)	2.5	0.9	2.6	1.0	0.075
Duration of Ab treatment (days)	3.99	2.17	4.44	2.51	0.057
Price of each Ab dose (US\$)	33.9	42.7	19.9	20.2	0.0001
Price of each Ab treatment (US\$)	328.1	389.5	232.5	235.7	0.0085
Total costs of Ab during hospitalization (US\$)	546.8		334.7		0.0015
Total cost per Ab treatment per day (US\$)	136.7		75.4		0.0015

SD, standard deviation.

Table 3. Differences of costs of the antibiotics (Ab) which were recommended to the allergic and non-allergic patients before being discharged from hospital

	Allergic		Non-allergic		P-value
	Average	SD	Average	SD	
Number of patients	116		115		
Recommended Ab on discharge (n)	1.9		1.8		NS
Parental Ab (%)	0		0		NS
Doses per day (n)	2.21	0.6	2.17	0.81	0.33
Duration of recommended Ab treatment (days)	7.98	2.57	6.16	2.11	< 0.001
Price of each Ab dose (US\$)	11.33	12.8	9.25	6.17	0.0048
Total price per recommended outpatient Ab treatment (US\$)	379.6	253.4	222.5	148.7	< 0.001
Total price per Ab treatment per day (US\$)	47.6		36.1		

SD, standard deviation.

**Fig. 1.** Antibiotic usage in the allergic group and the non-allergic group. The numbers represent the total count of each antibiotic group in the allergic and the non-allergic patients. The differences between the allergic and the non-allergic groups were significant, with $P = 0.0001$, by Fisher's exact test.**Fig. 2.** Allergy description. Right pie: relative proportion of allergic manifestations of the patients described as having an allergic reaction to penicillin.

study show that the presumed diagnosis of penicillin allergy, which was based entirely upon the patient's testimony, is associated with greater costs of antibiotics and the usage of broader-spectrum antibiotics for common infections.

It was estimated that nearly 90% of patients who report a penicillin allergy have negative skin tests and are not at risk for

allergic reaction. Accordingly, it is reasonable to conclude that most of our patients who had been labelled as penicillin-allergic were actually not allergic and could tolerate penicillins or other beta-lactams [6–10]. Although many studies confirmed the usefulness of skin tests in ruling out penicillin allergy, most clinicians will skip this practice and will choose to avoid penicillins when treating patients with the label of penicillin allergy. The

main drawbacks of tests for allergy to penicillin are the accessibility of such tests, the costs of testing and the difficulties in obtaining good, convenient, commercial reagents for both the major and the minor allergen determinants of penicillin [11, 12].

In addition, most beta-lactams antibiotics, including cephalosporins, are unnecessarily avoided in patients with a history of allergy to penicillin, owing to lack of guidelines or lack of experience [19]. This practice and the high level of reported penicillin allergy often lead to the prescribing of agents which may be safely avoided in order to manage increasing antibiotics costs and resistance in hospitals [11, 12, 19–21].

Forrest et al. recently investigated the impact of a new clinical practice guideline for penicillin skin testing in patients who have a history of penicillin allergy. Although the introduction of this practice guideline did not achieve financial savings during the hospitalization period during which the guideline was introduced, the investigators estimate that its usefulness extends beyond this hospitalization to subsequent inpatient and outpatient encounters and that modification of the guideline as well as reducing the cost of skin testing can improve the cost effectiveness of this practice [22].

This is a retrospective case control study that relies on electronic data systems (discharged coding) and, as such, did not review all the medical records but rather concentrated on those patients who had definitively been labelled as allergic to penicillin by formal coding.

We found the prevalence of penicillin allergy in the internal medicine departments to be 6.14%. The true prevalence of penicillin allergy has been described as being difficult to determine, being as it is dependent on a number of variables, among them exposure history, duration of treatment, elapsed time since the last reaction, nature of the reaction, age, and concurrent diseases. Moreover, the efforts which are made by the physicians to extract a history of penicillin allergy and the level of reporting of adverse drug reaction by the department or institute can also influence the reported prevalence which ranges from 1 to 20% [6, 10, 20, 21, 23–27].

The numbers we used to arrive at the 6.14% prevalence in our study were based on the computerized database; in some cases, however, the drug allergy may not have been indicated but had been noted in the patient's written records. Therefore, we estimate that the in-hospital prevalence of presumed penicillin allergy is much higher. In a preliminary study conducted in our institute, we found that the level of reporting adult adverse drug reactions in internal medicine departments was the highest compared to other departments, such as the orthopedic and the surgical departments where the level of reporting was only 10% of that of the former departments.

As has been seen in other studies, the label of 'penicillin allergy' was vague and based entirely upon history taking with no other effort having been made by the physicians to try to rule out or to doubt the diagnosis [20, 21, 23–27]. In most of our cases, there had been no delineation of the type or severity of the drug allergy and, when there was some description, it was inevitably short and lacking details. This lack of documented descriptions of penicillin allergies is similar to that found by Preston et al. [27]. In their study, the symptoms of the allergic reaction were described in the medical record for only 34% of hospitalized patients with a reported penicillin allergy.

When a patient is hospitalized, it is usually the young intern who does the intake and collects the information for past and

present medical history. The sick patient and the individuals who accompany him are inevitably in a stressful situation, and the information regarding past events are not infrequently confused or difficult for them to recall. When the physician queries patients about a possible drug reaction, in trying to recall some warning or side-effect in the past, some patients' replies will be based upon what they know about allergic reactions to drugs, especially antibiotics, rather than on their own experience with the drug, and they are very likely to point to penicillin; the most ubiquitous and well-known antibiotic. It would be very difficult for the attending physician to rule out an alleged drug allergy and, if the drug is urgently needed (as in the case of an antibiotic), he will accept the patient's reply at face value, label the patient as 'allergic' and proceed to prescribe an alternative drug. Thus, many of the patients who are labelled as being 'allergic to penicillin' are, in fact, not allergic to it at all, and the inaccuracy of a reported penicillin allergy by the patients emerges as being a common event. Indeed, more than 50% of allergies reported by patients may not be immunologic in nature [14, 24].

Our study shows that the treatment of hospitalized patients in internal medicine wards of a general hospital is influenced by the label 'penicillin allergy'. The differences in antibiotic usage did not influence the outcome of the patients as measured by mortality rate, length of hospital stay, or rate of transfer to other departments (e.g. intensive care units or rehabilitation centres). We also found no differences regarding the method of administration or the duration of treatment. Our study did show, however, that the penicillin-allergic patients received broader-spectrum antibiotics in comparison to the non-allergic patients, and that the cost of the antibiotics which were used in the former patients was significantly higher than those administered to the matched, non-allergic patients, with an average greater cost expansion of US\$212.00 during hospitalization.

After the patients were discharged from the hospital, most of them were instructed to continue antibiotic treatment by the enteral route. We found a significant difference in the cost of these antibiotics between the two patient groups: the average cost was US\$157.00 greater for the discharged penicillin-allergic patients.

Although the costs of antibiotics can change from time to time and are influenced by many financial and administrative factors, our method of using the most recent single list of costs for the entire study cohort simplified our analyses and comparisons in the current study and served as a good marker for the significant differences in treatment costs. Notably, the costs we recorded were similar to those which had been reported in recent related studies conducted in North America [21, 22].

For the sake of simplicity, the costs we considered were limited to those of antibiotics only, a more accurate hospitalization cost would include all direct costs for services including for example measurements of serum antibiotic level.

The use of anti-bacterial agents in hospitals accounts for 20–50% of all drug costs and represents the largest expenditure for any pharmacologic class. It was estimated that up to 50% of antibiotic usage in hospitals is inappropriate, and various strategies to control antibiotic usage has been attempted [28–31].

In addition to the significant burden of antibiotic treatment on costs, there is increasing concern about emerging bacterial resistance due to the misuse of antibiotics. The use of broad-spectrum antibiotics became a major risk factor for acquiring resistant bacteria; for example, it was shown that, for most

cases, vancomycin was prescribed instead of another antibiotic because of a suspected penicillin allergy, and it was recently suggested that penicillin skin testing may be useful as part of the effort to control vancomycin and other expensive and broad-spectrum antibiotics use [16–18, 32, 33].

Optimization and control of antibiotic usage may assist the health systems in improving the quality of care. There are many reports of antibiotic management programs designed to guide their appropriate and cost-effective use however, none of these studies has addressed the potential influence of penicillin allergy on the antibiotic selection strategy [28–31, 34].

The possible influence of penicillin-allergic labelling on antibiotic usage and cost was demonstrated in several other studies. While assessing the consistency of penicillin allergy documentation, Preston et al. found differences between the allergic and non-allergic patients in respect to both toxic potentiality of the penicillin substitute and the cost of antibiotics [27]. Other studies attempted to determine if skin tests and specific penicillin allergy guidelines can improve the usage and reduce the cost of antibiotics, but most of them were limited to outpatient clinics [13, 14], subjects with rheumatic fever [16, 17], or sexually transmitted disease [15], hospitalized patients in special situations such as patients treated for endocarditis [20], admitted to an intensive care unit [18], or undergoing surgery prophylaxis [21, 32], or orthopedic patients [33]. All these studies demonstrated a significant impact of the label 'penicillin-allergic' on antibiotic usage but the cost-effectiveness of skin tests was inconclusive.

In summary, inaccurate reporting of beta-lactam allergies may have far-reaching economic and epidemiologic consequences. Further studies are warranted to determine the economic feasibility of confirming hypersensitivity by skin testing of patients who have a self-reported allergy.

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