

Treatment of Patients with a History of Penicillin Allergy in a Large Tertiary-Care Academic Hospital

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What is already known about this topic? Alleged penicillin allergy is common among hospitalized patients and leads to substantial additional costs. Practice parameters have been issued to guide primary-care physicians in the treatment of these patients.

What does this article add to our knowledge? In a hospital setting without allergists on staff, treatment of patients with a history of penicillin allergy is frequently suboptimal despite availability of practice parameters, reflecting poor knowledge about penicillin allergy.

How does this study impact current management guidelines? Efforts should be made to improve education about penicillin allergy aimed at nonallergists. Allergists on staff could help ensure optimal care of patients with a history of penicillin and contribute to guidelines dissemination.

BACKGROUND: Prescribing antibiotics to patients with a history of penicillin allergy is common in clinical practice. Opting for non-beta-lactam antibiotics has its inconveniences and is often unnecessary, because most of these patients are in fact not allergic.

OBJECTIVE: This study aimed to determine how physicians in a large Canadian tertiary-care academic hospital without allergists on staff treat patients with a history of penicillin allergy.

METHODS: A retrospective study was conducted during a 1-year period among all patients hospitalized in the intensive care unit, coronary care unit, and internal medicine wards. Files of patients with a record of penicillin allergy were reviewed to assess the need for antibiotics during their hospitalization and

the decision-making process underlying the choice of antibiotic. The additional costs of alternative antibiotics were calculated.

RESULTS: The files of 1738 patients admitted over a 1-year period were hand reviewed. A history of penicillin allergy was found in 172 patients (9.9%). The allergic reaction was described in only 30% of cases and left unmentioned in 20.7%. Beta-lactam antibiotics were used on 56 occasions despite a history of penicillin allergy. The use of alternative antibiotics in place of the beta-lactam standard of care carried an additional cost of \$15,672 Canadian.

CONCLUSION: Alleged penicillin allergy is common among hospitalized patients and leads to substantial additional costs. Poor documentation of penicillin allergy likely reflects a lack of knowledge on this issue in the medical community, which impairs optimal treatment of these patients. Increased education on this matter is needed, and allergists on staff could be part of the solution. © 2013 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol: In Practice 2013;1:252-7)

Key words: Penicillin allergy; Quality of care; Antibiotic; Cost-effectiveness; Allergist; Education; Management; Drug allergy; Intensive care unit; Internal medicine

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Patients with a history of penicillin allergy are commonly encountered in clinical practice because they represent on average 10% of the population.¹⁻³ However, only approximately 10% of these patients are found to be truly allergic on an allergologic work-up, including skin tests and/or a drug challenge.^{4,5} Despite this low reactivity, physicians often opt for alternative antibiotics, most commonly fluoroquinolones and vancomycin, to avoid the risk of provoking an allergic reaction.^{1,6-8} However, this practice is fraught with inconveniences. For one, the cost of therapy with

Abbreviations used
CAD- Canadian dollar
ICU- Intensive care unit

those antibiotics is higher than with the beta-lactam equivalent.^{2,6,9} In addition, because of their broad spectrum of antimicrobial activity, they have been shown to have a negative effect on antimicrobial resistance patterns and have been associated with serious complications such as *Clostridium difficile*-associated diarrhea.¹⁰⁻¹² Finally, they may be less efficacious and/or more toxic in some instances.³ To guide physicians in the decision-making process leading to the choice of antibiotic in those patients with a history of penicillin allergy, practice parameters from American and European authorities have been published.^{3,13} However, as suggested by prior studies, treatment of these patients seems poor in the absence of targeted interventions led by allergists.^{7,14,15}

This study took a comprehensive look at the treatment of patients with a history of penicillin allergy in a large tertiary-care academic hospital without allergists on staff to assess quality of care. More precisely, we sought to identify common flaws in their treatment, related adverse consequences, and factors hampering optimal care of these patients.

METHODS

Study design

This study was conducted at Hôpital Maisonneuve-Rosemont, a tertiary-care academic hospital in Montreal, Quebec, Canada. Files of all patients admitted to the intensive care unit (ICU), coronary care unit, and internal medicine wards during a 1-year period extending from December 1, 2008, to November 30, 2009, were manually reviewed to identify patients with a history of penicillin allergy. A history of penicillin allergy was considered present if it was mentioned in any of the following sections of the file and not negated anywhere else: (1) medical notes (emergency department consultation, admission note, medical consultations, and anesthesiology note when available), (2) penicillin allergy tag on file, or (3) emergency department triage note. Patients developing an acute allergic reaction to a beta-lactam antibiotic were not included in this study if a history of penicillin allergy was not present before the hospitalization. This was the case for only one patient, which was excluded from the studied cohort.

When a history of penicillin allergy was present, files were further reviewed to assess the following items: (1) documentation of the allergic reaction to penicillin (type of reaction and time elapsed since reaction), (2) need for antibiotics during hospitalization and if so antibiotics used, (3) documentation of the decision-making process underlying the choice of antibiotics, (4) deviation from the standard-of-care antibiotic regimen attributable to the history of penicillin allergy (see last sentence of this section), (5) allergy referral at time of discharge, and (6) presence of any of the following comorbidities that strengthened the indication for an allergy referral at time of discharge, either because of a heightened risk of needing antibiotics in the near future or because the patient was running out of options for antibiotic treatment: ≥ 2 antibiotic courses in the past 5 years, claimed allergy to another non-beta-lactam antibiotic, chronic obstructive pulmonary disease, end-stage kidney disease, diabetes

TABLE I. Costs of antibiotics used for calculation of additional costs associated with the use of alternative antibiotics

Antibiotic	Estimated daily cost (CAD)
Alternative antibiotics	
Vancomycin	\$120
Moxifloxacin	\$35
Ciprofloxacin	\$60
Clindamycin	\$4
Metronidazole	\$45
Azithromycin	\$10
Gentamycin	\$10
Aztreonam*	\$250
Tigecycline	\$140
Beta-lactam antibiotics	
Penicillin G	\$1
Piperacillin-tazobactam	\$18
Ampicillin	\$1
Amoxicillin-clavulanic acid	\$1
Cloxacillin	\$1
Cefazolin	\$24
Ceftriaxone	\$17
Meropenem	\$150

*Despite its monocyclic beta-lactam structure, aztreonam does not cross-react with penicillins and was used as an alternative to other beta-lactams because of a history of penicillin allergy.

mellitus, immunosuppression. The standard-of-care antibiotic regimen was established on the basis of type of infection or need for antibiotic prophylaxis, antimicrobial susceptibilities (when available), institutional recommendations, and/or published guidelines regardless of the history of penicillin allergy.

Cost calculation

The costs of antibiotic treatment were calculated for patients whose standard-of-care antibiotic regimen included beta-lactam antibiotics but who were treated with an alternative antibiotic regimen because of their history of penicillin allergy. The cost of the alternative antibiotic regimen was estimated according to the duration of treatment (in days) and the average daily cost of the antibiotic(s) as estimated by the hospital pharmacy (Table I). The cost of the preferred regimen was calculated with the same method and subtracted from the first figure to give the estimated additional cost.

Survey

A survey was conducted among attending physicians within the Department of Medicine of Hôpital Maisonneuve-Rosemont in May 2010 before the results of the study were known. Anonymous written questionnaires were distributed at the Department of Medicine weekly meetings. The questionnaire assessed allergy referral habits for patients with a history of penicillin allergy and reasons/obstacles for not referring a patient with a history of penicillin allergy to an allergist. This study was approved by the institutional review board.

Statistical analysis

Comparisons between groups were made for categorical variables with the use of the Fisher exact test when the variable was dichotomous and the chi-square test when the nominal variable

TABLE II. Characteristics of patients with a history of penicillin allergy

	No indication for beta-lactam antibiotic (n = 85)	Indication for beta-lactam antibiotic (n = 87)	P value
Age (y), mean (range)	66.0 (28.6-101.1)	66.5 (23.0-105.8)	.820
Female sex, no. (%)	53 (62.4)	54 (62.1)	.547
Hospitalization unit, no. (%)			<.0005
ICU	17 (20.0)	61 (70.1)	
Coronary care unit	38 (44.7)	10 (11.5)	
Internal medicine ward	30 (35.3)	16 (18.4)	
Penicillin allergy tag on file, no. (%)	53 (62.4)	66 (75.9)	.069
History of penicillin allergy mentioned in medical notes, no. (%)	70 (82.4)	69 (79.3)	.377
Allergic reaction described, no. (%)	24 (28.2)	28 (32.2)	.346
Time elapsed since allergic reaction reported in medical notes, no. (%)	2 (2.4)	5 (5.7)	.231

TABLE III. Characteristics of patients with a history of penicillin allergy treated with beta-lactam antibiotics compared with patients treated with alternative antibiotics

	Alternative antibiotics used (n = 34)	Beta-lactam antibiotics used (n = 53)		P value
		From the same group that had caused the allergic reaction* (n = 26)	From a potentially cross-reactive group† (n = 27)	
Age (y), mean (range)	65.2 (23.0-96.8)	65.9 (26.7-87.9)	68.8 (41.3-105.8)	.663
Female sex, no. (%)	20 (58.8)	15 (57.7)	18 (66.7)	.759
Hospitalization unit, no. (%)				.902
ICU	23 (67.6)	20 (76.9)	18 (66.7)	
Coronary care unit	4 (11.8)	2 (7.7)	4 (14.8)	
Internal medicine ward	7 (20.6)	4 (15.4)	5 (18.5)	
Penicillin allergy tag on file, no. (%)	26 (76.5)	19 (73.1)	21 (77.8)	.918
History of penicillin allergy mentioned in medical notes, no. (%)	28 (82.4)	19 (73.1)	22 (81.4)	.642
Type of allergic reaction (%)				
Not reported in file	26 (76.5)	18 (69.2)	15 (55.6)	.218
Intolerance	1 (2.9)	1 (3.8)	1 (3.7)	.978
Rash	6 (17.6)	4 (15.4)	9 (33.3)	.215
Angioedema	2 (5.9)	3 (11.5)	3 (11.1)	.692
Anaphylaxis	0	0	1 (3.7)	.325
Time elapsed since allergic reaction not reported in file, no. (%)	31 (91.2)	25 (96.2)	26 (96.3)	.614
Decision-making process documented, no. (%)	6 (17.6)	6 (23.1)	7 (25.9)	.727
Faulty rationale, no. (%)	N/A	3 (11.5)	2 (7.4)	.274
Error, no. (%)	N/A	0	1 (3.7)	

NA, Not applicable.

*Received a penicillin or a cephalosporin antibiotic and had a history of reacting to these drugs.

†Received either a cephalosporin or carbapenem antibiotic and did not have a history of allergic reaction to these drugs besides the history of penicillin allergy.

exceeded 2 categories. The 1-way ANOVA test was used to compare means between groups. A *P* value <.05 was considered significant. The 95% CI was calculated with the Clopper and Pearson method.

RESULTS

The prevalence of a history of penicillin allergy was 9.9% (95% CI, 8.5-11.4) in the studied cohort (172 of 1738 patients) and was more common in females than males (14.0% vs 6.7%; *P* < .0001). In addition, a history of cephalosporin allergy was present in 13 cases and a history of carbapenem allergy in one case. History of penicillin allergy was not mentioned in a consistent location in the medical file. It was most frequently mentioned in

the medical notes (at admission or at time of antibiotic prescription), reaching 80.9%. A penicillin allergy tag was absent in 29.1% of the files of patients with a penicillin allergy history documented in the medical notes. The history was poorly detailed in most cases, because only 30.2% mentioned the type of allergic reaction and 4.1% the time elapsed since the reaction.

One-half of the patients with presumed penicillin allergy (87 of 172 patients; 50.6%) had a total of 111 indications for beta-lactam antibiotics during their hospitalization (Table II). History of penicillin allergy was not found to be significantly more detailed in those patients and was left unmentioned in 20.7% of the medical notes. Most patients with an indication for beta-lactam antibiotics were hospitalized in the ICU (70.1%). This is likely explained by the frequent use of piperacillin-tazobactam in our institution for

respiratory and abdominal sepsis, among others, given established indications and local antibiotic resistance patterns.

Among 87 patients whose standard-of-care antibiotic regimen included a beta-lactam, alternative antibiotics were preferred among 34 patients and 53 patients received at least one dose of beta-lactam antibiotic (Table III). Among the latter, 25 patients were treated with a penicillin antibiotic, most commonly piperacillin-tazobactam, for a total of 28 courses, and 2 patients, one of whom also received a penicillin antibiotic, were treated with a cephalosporin antibiotic despite a history of cephalosporin allergy in addition to penicillin allergy. Twenty-seven patients received a beta-lactam antibiotic other than penicillin, and from a group they did not have a history of allergic reaction to (cephalosporins on 18 and carbapenems on 9 occasions). No factors related to the history of penicillin allergy appeared to influence the decision to prescribe a beta-lactam antibiotic, not even penicillin antibiotics, as opposed to an alternative antibiotic. Notably, a history of severe reaction (angioedema or anaphylaxis) was present in 7 patients treated with beta-lactam antibiotics, 3 of whom received penicillin antibiotics. Again, the history of penicillin allergy was not found to be more detailed in patients who received beta-lactam antibiotics and was left unmentioned in 26.9% of the medical notes of patients who received a penicillin antibiotic.

Among patients treated with beta-lactam antibiotics, the decision-making process was documented in only 13 cases and 5 (38.5%) of those cases were based on a faulty rationale, which can be exemplified by the use, in one case, of cefazolin without any precaution because the patient had had a successful desensitization to ampicillin the year before. In another case, administration of cefazolin was recognized as an error and documented as so in the medical file. In addition, skin testing, drug challenge, and drug desensitization procedures were not performed in any case. Despite administration of beta-lactam antibiotics on 56 occasions, no allergic reaction was documented. Finally, all patients treated with a penicillin antibiotic were still identified as penicillin allergic at time of discharge.

Vancomycin and fluoroquinolones were by far the most frequently used alternative antibiotics in patients with a history of penicillin allergy (Table IV). The combined estimated additional cost of the use of alternative antibiotics on 55 occasions among 48 patients compared with the standard-of-care treatment was estimated at Canadian dollar (CAD) \$15,672, averaging CAD \$326.50 per patient.

Only 2 patients were referred to an allergist on an outpatient basis for evaluation of their presumed penicillin allergy. However, among 172 patients with a history of penicillin allergy, 91 had an additional factor that reinforced the indication for such a referral and were alive at discharge (Table V).

Forty-four physicians answered the survey for a 50.6% completion rate. Only 16% had ever referred a patient to an allergist because of a history of penicillin allergy. Lack of allergists among the hospital staff was given by 66% of surveyed physicians as the reason for not referring patients. In addition, 25% said they never thought about it or did not know the indications for referral. Finally, 16% considered it useless.

DISCUSSION

A history of penicillin allergy was a common finding in our cohort, but its documentation and description in the medical file were deficient in a substantial number of patients. The decision-

TABLE IV. Choice of alternative antibiotics in patients with a history of penicillin allergy and a first-line indication for treatment with beta-lactam antibiotics and associated costs

Antibiotic	No. of patients treated*	Days of treatment (total)	Estimated costs (CAD) [†]	Estimated additional costs (CAD) [‡]
Vancomycin	27	97	\$11,640	\$10,105
Fluoroquinolones	26	168	\$7030	\$4425
Moxifloxacin	20	122	\$4270	\$1983
Ciprofloxacin	6	46	\$2760	\$2442
Others	15	84	\$2444	\$1142
Clindamycin	8	41	\$164	–\$554
Metronidazole	3	28	\$1260	\$1069
Azithromycin	1	5	\$50	\$15
Gentamycin	1	5	\$50	\$43
Aztreonam	1	2	\$500	\$200
Tigecyclin	1	3	\$420	\$369
Totals			\$21,114	\$15,672

*Number of patients could include patients that were also treated with beta-lactam antibiotics on another occasion.

[†]Estimated costs = antibiotic cost per day times days of treatment.

[‡]For each occasion on which a particular alternative antibiotic was used the cost of the preferred beta-lactam antibiotic was calculated (beta-lactam cost per day × days of treatment). The total cost of the preferred beta-lactam antibiotics was then subtracted from the total cost of a particular alternative antibiotic. The preferred beta-lactam antibiotic was established according to type of infection or need for antibiotic prophylaxis, antimicrobial susceptibilities (when available), institutional recommendations, and/or published guidelines regardless of the history of penicillin allergy.

making process underlying the choice of antibiotic therapy was infrequently mentioned and when present, was often based on a faulty rationale. Use of alternative antibiotics was associated with important additional costs, and patients were rarely referred to an allergist at time of discharge. A survey conducted among attending physicians revealed two key factors that hampered optimal treatment of these patients: lack of allergists on staff and poor knowledge on penicillin allergy.

To the best of our knowledge, this is the first study that thoroughly addresses treatment of patients with a history of penicillin allergy, from documentation of the allergic status to prescription of antibiotics, while looking at the decision-making process underlying it. In addition, it looked at referral habits of physicians about patients with penicillin allergy.

Several other studies looking at different aspects of treatment of patients with a history of penicillin allergy suggest that poor treatment of these patients is a generalized problem far from being unique to the center studied herein.^{1,2,7,9,16-19} In a study conducted in a large tertiary care academic medical center in the United States, Lee et al¹ showed that 68% of files lacked details about the nature and severity of an allergic reaction to penicillin. In a similar hospital setting, Lutomski et al¹⁶ found that the penicillin allergy description in the medical file was inaccurate in 22% of files. History taking is crucial in the decision-making process leading to the prescription of antibiotics in patients with alleged penicillin allergy. It allows identification of patients in whom re-exposure is contraindicated in all instances (eg, Stevens-Johnson syndrome) and gives a raw estimate of the probability that the patient truly has a penicillin allergy.^{3,5,20} In this light, it is concerning that in the studied cohort histories were poorly detailed in most patients with an indication for beta-lactam

TABLE V. Presence of factors strengthening the indication for a penicillin allergy evaluation

Argument	No. of patients with a history of penicillin allergy and alive at discharge (n = 134)
Two or more antibiotic courses in the past 5 years	30
Claimed allergy to another non-β-lactam antibiotic	29
Chronic diseases with an increased risk of infections*	60
Immunosuppression	10
Had an indication for treatment with a β-lactam antibiotic during hospitalization and penicillin allergy was not ruled out	82
Any of the above arguments and penicillin allergy not ruled out during hospitalization	91

*Chronic diseases considered with an increased risk of infections were end-stage chronic kidney disease treated by dialysis and chronic obstructive pulmonary disease or diabetes mellitus with any complication.

antibiotics, even in patients finally treated with these drugs, and that no factors related to the history of penicillin allergy appeared to influence this decision.

Jones and Como¹⁸ reported that the most common factor leading to an erroneous prescription of β-lactam to a patient with penicillin allergy was unawareness of the allergic status by the prescribing physician. This is certainly an important factor that explains why 53 patients were treated with β-lactams in our cohort, because 20.7% of physician's notes lacked awareness of penicillin allergy at the time of antibiotic prescription in patients with an indication for β-lactam antibiotics.

Patients with a history of penicillin allergy are commonly re-exposed to β-lactams without adequate precautions but react only rarely.^{2,17} This is especially true for cephalosporins and carbapenems in which the reaction risk is <1%.²¹⁻²⁶ Despite their low frequency, allergic reactions have the potential to be severe, and fatalities in such circumstances have been reported, emphasizing the need to take into account even a seemingly trivial history of penicillin allergy.²⁷ Therefore, practice parameters on drug allergy advise to take several precautions before exposing patients with a history of penicillin allergy to any β-lactam antibiotic. Different procedures such as skin testing, drug challenges, and desensitizations are part of the recommended treatment algorithms for those patients, but they were not used in a single patient in this study.^{3,13} Moreover, by reviewing the decision-making process in each file when a β-lactam was used in a person with penicillin allergy, we found that it was infrequently mentioned and when present commonly faulty. This situation likely reflects deficient knowledge on penicillin allergy in the medical community and the need for increased education on that matter, a conclusion also supported by a recent survey conducted by Puchner and Zacharisen.⁷

The economic and medical burdens of having on average 10% of the population reporting a history of penicillin allergy are substantial, given that they are more likely to be treated with broad-spectrum antibiotics, particularly vancomycin and fluoroquinolones.^{1,6-8} Treatment with those antibiotics leads to increased costs and could lead to increased antibiotic resistance and could promote colonization with resistant bacterial strains such as vancomycin resistant enterococcus and promote *Clostridium difficile*—associated diarrhea.^{2,6,9-12} This is partly reflected in the estimated additional cost of CAD\$15,672, which resulted from the avoidance of β-lactam antibiotics on just 55 occasions. This amount could have been considerably higher had β-lactam antibiotics been systematically avoided among all

persons with alleged penicillin allergy and if the entire hospital was considered. This finding stresses the importance of referring patients with a history of penicillin allergy for a thorough allergologic workup, because this has been shown to decrease the use of these antibiotics and hence their associated costs.^{14,15,28-32}

This study involved a single center and evaluated the care of patients hospitalized either in the ICU, coronary care unit, or internal medicine wards. Therefore, these findings may not accurately reflect the situation in other divisions of the hospital, among outpatients, and in other medical centers. However, as stated in the third paragraph of this section, similar caveats in the treatment of these patients have been reported in other studies that emerged from diverse hospital settings.^{1,2,7,9,16-19} It is thus highly likely that our findings could be reproduced in other medical centers and that poor treatment of patients with a history of penicillin allergy is a generalized problem. In addition, evidence that the presence of allergists on staff and education about penicillin allergy would lead to better care of these patients is inferred from the study results but has not been directly shown. However, previous studies have shown a positive effect on the appropriateness of antibiotic use in targeted interventions led by allergists, such as systematic referral of patients before surgery.³³⁻³⁵ A similar beneficial effect of consulting allergists has also been shown for patients with a history of penicillin allergy who were hospitalized in the ICU.^{28,30} These examples show the need for a proactive role of allergists in their institution to ensure the optimal care of patients with a history of penicillin allergy. However, availability of allergists may be problematic in some areas, especially in Canada, where there is a shortage of allergists. Actions aimed at generating interest for the field of allergy and immunology in medical students and residents could be part of the solution in the long run.

These findings clearly indicate that a history of penicillin allergy is a common clinical problem in everyday practice and that its management is often poor. Two key factors may explain this situation: lack of knowledge about penicillin allergy and absence of available allergists on staff. These issues need to be addressed to improve this highly undesirable situation, which leads to increased health care-related costs and, most importantly, could negatively affect patient outcome.

Future research should focus on large-scale interventions, rather than targeted ones, aimed at reducing the prevalence of presumed penicillin allergy in populations at increased risk of needing antibiotics. As an example, it might be proposed that allergists systematically inquire about and evaluate electively a history of penicillin allergy in any patient referred to them.

Finally, in the acute setting, different measures should be studied to ensure that patients with a history of penicillin allergy are treated in accordance with current guidelines.

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