

Elective penicillin skin testing and amoxicillin challenge: Effect on outpatient antibiotic use, cost, and clinical outcomes

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Background: Elective penicillin skin testing in advance of acute antibiotic need and amoxicillin challenge in patients with negative skin test responses have not been evaluated.

Methods: I reviewed 236 patients previously entered in a study of new penicillin reagents who received at least 1 prescription drug over a 2-year period. Antibiotic use, outpatient visit rate, and adverse reactions to antibiotics during the year before and after skin testing were evaluated.

Results: Forty (17%) of the 236 subjects had positive responses. Antibiotic courses dispensed to the 236 subjects fell 28% from 779 the year before testing to 558 the year after testing. The total cost for antibiotics dispensed fell 32% from \$17,211.88 to \$11,648.27, with a 5.5% reduction in the average cost per antibiotic. Outpatient visit rate did not change but shifted from primary to specialty departments in subjects with both positive and negative skin test responses. In 93 subjects with negative skin test responses, a total of 188 therapeutic courses of penicillin during the year after testing resulted in 3 (3.2%) unrechallenged mild adverse reactions. Optional amoxicillin challenge in 146 of the subjects with negative skin test responses resulted in complaints of an adverse reaction in 6 of these subjects. Four of these received a penicillin analogue in the next year without reaction.

Conclusions: Elective penicillin skin testing done by an allergist was associated with unexpected declines in the number and cost of antibiotics used the year after testing but only modestly lowered the average cost per antibiotic. Adverse reactions to penicillins in subjects with negative skin test responses were infrequent, and amoxicillin challenge did not affect outcomes. (*J Allergy Clin Immunol* 1998;102:•••.)

Key words: Adverse reaction, allergy, amoxicillin, antibiotic use, cephalosporin, challenge, cost, health care use, penicillin, skin test

The effect of elective penicillin skin tests (PenSTs) on oral outpatient antibiotic use has not been prospectively evaluated in routine clinical practice. Hospitalized patients¹ and restricted groups, such as subjects with rheumatic fever^{2,3} or sexually transmitted disease,⁴ have been studied.

There has been concern that if patients have PenSTs in advance of therapeutic need for penicillin class anti-

Abbreviations used

AC: Amoxicillin challenge
PCA: Penicillin class antibiotic
PenST: Penicillin skin test

otics (PCAs), they could become resensitized and have increased rates of drug allergy.⁵ Elective PenSTs in children are not associated with significant resensitization.⁶ The use of parenteral antibiotics after a negative PenST response in a small ($n = 18$) inpatient-based trial showed a 20% PenST conversion rate (3 of 15) among subjects given PCA, cephalosporins, or both.⁷ The clinical significance of these findings are unclear as they apply to the majority of outpatients who receive oral antibiotics.

The first article in this series described a method for the production of penilloate and penicilloate and their use in elective PenSTs in 348 subjects.⁸ This report provides additional clinical data on a subgroup of these patients. The goal of this article is to evaluate the effect of PenSTs on subsequent adverse drug reactions and to determine if there were changes in antibiotic use and costs.

METHODS

Study design and patient selection

A natural history study on 255 patients who underwent PenSTs between November 16, 1994 and November 15, 1995 was performed. A subgroup of 237 patients (92.9%) who were health plan members during the full year before and after PenSTs and who obtained at least 1 prescription medication from a health plan pharmacy were identified. One outlier with a mycobacterium lung infection, who accounted for 4.2% of all antibiotic courses and 18.4% of antibiotic costs for the 2-year duration of the study, was excluded, leaving 236 subjects.

PenSTs with or without amoxicillin challenge (AC) results were placed in the patient's medical record. If allergy follow-up care was indicated by the allergist providing the consultation, it was provided, but it was not influenced by this study. Outcome data was collected by chart and electronic medical record review.

The primary allergy department (San Diego) involved in this study enrolled 165 (69.9%) subjects, and the remaining 71 subjects were enrolled by 7 other allergy departments in the Kaiser Permanente Southern California Region.

PenST and AC

Penicillin, Pre-Pen, amoxicillin, penilloate, penicilloate, and histamine were prepared and used as previously described.⁸

AC consisted of a 250-mg oral dose of amoxicillin with a 1-hour observation period, and 146 of the 196 subjects with nega-

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TABLE I. Patient demographics

	Negative PenST responses (n = 196)	Positive PenST responses (n = 40)	P value
Age (yrs)	40.0 ± 22.4	28.8 ± 23.1	.0045
Female	133 (67.9%)	31 (77.5%)	NS
Time since reaction (yrs)	15.75 ± 16.23	7.43 ± 13.27	.003
Dispensed penicillin (yr before PenST)	40 (20.4%)*	13 (32.5%)*	NS
Dispensed penicillin (yr after PenST)	93 (47.4%)	1† (2.5%)	.001
Total outpatient visits/subject (yr before PenST)	14.30 ± 10.98	15.03 ± 13.70	NS
Total outpatient visits/subject (yr after PenST)	13.55 ± 12.89	15.30 ± 24.07	NS

Statistics: Ordinal data, Wilcoxon test; categorical data, chi-squared test; values = mean ± SD, number of subjects (%).

NS, Not significant.

*All of these patients had their index adverse reaction within 1 year of PenST.

†Patient dispensed PCA but may not have taken it.

tive PenST responses (74.5%) agreed to undergo the procedure. Subjects were able to opt out of the AC for any reason.

Protection of human subjects

This protocol was approved by the Kaiser Permanente Southern California Institutional Review Board. Written informed consent was obtained from all individuals. No patients "allergic" to PCAs were intentionally rechallenged with a PCA unless they had a negative PenST response. PenSTs, including the minor determinants, have been available in our health plan for more than 10 years. Individuals allergic to PCAs are commonly prescribed cephalosporins if they have no history of adverse reaction to the cephalosporin, and if it is clinically indicated.

Pharmacy and medical record review

Computerized pharmacy records were condensed to include only oral antibiotic data. Average use data was collected on 1.5 (68.2%) of the 2 million total health plan members who received at least 1 prescription medication from a health plan pharmacy during 1995. The average member who received at least 1 prescription from a health plan pharmacy received 1.1 prescriptions for antibiotics. PCA accounted for 870,610 (51.2%) of 1,699,074 total antibiotic prescriptions. Amoxicillin and amoxicillin combination antibiotics accounted for 81.6% of all PCAs and 41.8% of all antibiotics dispensed. Adverse reaction complaints after antibiotic therapy were collected by chart review of outpatient medical records.

Computerized outpatient visit data were collected. Primary care visits were defined as pediatric, family practice, primary care, internal medicine, urgent care, and emergency department visits. Specialty care visits were defined as total outpatient visits minus primary care visits. Data on all health plan outpatient visits in 1995, independent of pharmacy use, were used to calculate average visit rates. There were 12,011,032 total outpatient visits made by 2,022,958 total health plan members (mean, 5.9 ± 7.1). The median number of outpatient visits was 4, with an interquartile range of 5. There were 6,651,671 (55.4%) visits to primary care departments with family practice (24.5%), pediatrics (14.5%), internal medicine (10.9%), and emergency medicine (5.6%) the most visited.

Drug costs

The cost presented reflects the acquisition cost of the antibiotic along with a fixed pharmacy dispensing cost. This can be considered the cost to the health plan of providing the antibiotic. The average cost for PCAs was \$12.67 and that for non-PCAs was \$24.09 in 1995. The overall average was \$18.24 per antibiotic prescription.

Statistics

The chi-square test was used for categorical data comparisons between patients with positive PenST responses and patients with negative PenST responses and for comparisons between patients who did and patients who did not undergo AC. The McNemar test was used to compare changes in the number of subjects receiving PCAs before and after PenSTs. The Stuart-Maxwell test was used to compare outpatient care use for each department before and after PenSTs. The paired *t* test was used to compare outpatient care use, antibiotic use, and cost before and after PenSTs. The *t* test was used to compare outpatient care use between study patients and region-wide patients. The Fisher exact test was used to compare adverse reaction rates with therapeutic courses of PCAs after a negative PenST response. The Wilcoxon test was used for the rest of the non-normal data analyses, including comparing outpatient care use, antibiotic use, and cost between patients with positive PenST responses and patients with negative PenST responses, as well as patients who did and did not undergo AC.

RESULTS

Demographics of the study subjects

The demographics of the 236 subjects in this study are displayed in Table I. The clinical histories of the study subjects, including the type of index adverse reaction, time to onset of adverse reaction after initiation of antibiotic therapy, and treatment of the index adverse reaction, are not significantly different from the whole population as reported previously.⁸

AC

The demographics of the 146 subjects who self selected AC are displayed in Table II and compared with those of subjects who refused AC. Among the 93 subjects with negative PenST responses who were dispensed at least 1 therapeutic course of PCA during the year after testing, 69 (74.2%) had undergone AC, which was not significantly different from the 74.5% overall rate. Subjects who underwent AC were no more likely to be dispensed subsequent PCAs during the year after PenSTs than individuals who failed to undergo AC. Subjects who failed to undergo AC were significantly older than subjects willing to undergo AC.

Four of the 6 subjects who complained of adverse

TABLE II. Amoxicillin challenge

	AC (n = 146)	No AC (n = 50)	P value
Age (yrs)	37.4 ± 22.4	47.7 ± 21.0	.0072
Female	99 (67.8%)	34 (68.0%)	NS
Time since reaction (yrs)	15.58 ± 16.23	16.23 ± 16.55	NS
Dispensed penicillin (yr before PenST)	27 (18.4%)	13 (26.0%)	NS
Dispensed penicillin (yr after PenST)	69 (47.3%)	24 (48.0%)	NS
Reported adverse reaction with AC or therapeutic course of penicillin (yr after PenST)	8* (5.5%)	3 (12.5%)	NS
Unrechallenged adverse reaction with therapeutic course of penicillin (yr after PenST)	1 (1.4%)	2 (8.3%)	NS

Statistics: Ordinal data, Wilcoxon test; categorical data, chi-squared test; Adverse Reaction Rates, Fisher Exact test; values = mean ± SD, number of subjects (%).

NS, Not significant.

*Six of these reactions were to the AC.

reactions during AC subsequently received a total of 12 courses of PCA during the year after testing without further adverse reactions.

Antibiotic use of the study subjects

There were significant changes in the classes of antibiotics dispensed during the year after PenSTs in both patients with positive PenST responses and patients with negative PenST responses, indicating that PenSTs influenced antibiotic choice ($P = .001$, data not shown). The use of PCAs increased from 13.7% to 39.8% of all antibiotics prescribed to subjects with negative PenST responses, but was still less than the health plan average of 51.2%.

Antibiotic use data is presented in Table III. There were 779 courses dispensed to 191 (80.9%) subjects during the year before the PenSTs, and 558 courses used by 169 (71.6%) subjects during the year after the PenSTs. The average study subject received 3.30 ± 3.41 antibiotics during the year before the PenSTs and 2.36 ± 2.58 antibiotics ($P = .0001$) during the year after the PenSTs. Both rates were higher than the health plan average of 1.1 antibiotics per year.

Among the 196 patients who had negative PenST responses, 142 (72.4%) received at least 1 antibiotic in the year after the PenSTs, and 93 (47.4%) received at least 1 PCA. This was a significant increase from the 40 (20.4%) subjects with negative PenST responses who received at least 1 PCA during the year before the PenSTs ($P = .001$).

Among the 40 patients with positive PenST responses, 27 (67.5%) received at least 1 antibiotic in the year after the PenSTs. There were 15 patients with positive PenST responses who received a total of 33 prescriptions for cephalosporins during the year after the PenSTs.

Antibiotic costs of the study subjects

The average annual cost for antibiotics per study subject is presented in Table III. The total cost for the 236 patients in the study fell 32% during the year after the PenSTs. The average cost fell 5.5% from \$22.09 during the year before the PenSTs to \$20.88 during the year after the PenSTs for all subjects. The average cost rose 3.3% from \$21.61 to \$22.34 if the subject had a positive

PenST response. The average cost fell 7.2% from \$22.21 to \$20.61 if the subject had a negative PenST response. The overall average cost for study subjects was 15.5% higher (\$21.59 compared with \$18.24) than the health plan average.

Outpatient health care use by study subjects

Outpatient annual visit rates are given in Table I. Study subjects had significantly more outpatient visits than average health plan members (15.9 ± 12.9 vs 5.9 ± 7.1 , $P = .001$). Total outpatient visits after PenST were unchanged, but there was a shift away from primary care to specialty care visits. Before PenSTs, 51.9% of study subjects' outpatient visits were to primary care departments, and this fell to 39.1% after the PenSTs ($P = .0001$).

Cephalosporin use in subjects with positive penicillin skin test responses

There were 15 subjects with positive PenST responses who received at least 1 posttest cephalosporin. There were 33 prescriptions for oral cephalosporins dispensed to this group during the year after the PenSTs, and only 1 delayed reaction occurred. The reaction occurred in a 1-year-old female who had a positive PenST response on February 14, 1995. On December 23, 1995, 2 days after completion of a 10-day course of cefaclor started on December 11, 1995, the patient had a fixed rash that was believed to be a serum sickness reaction by the treating physician. No treatment was needed.

Adverse reactions to antibiotics in subjects with negative penicillin skin test responses

There were 93 patients who had negative PenST responses and subsequently received at least 1 PCA. There were 354 total antibiotic prescriptions dispensed to this group, of which 188 (53%) were PCAs. There were 5 (5.4%) subjects who reported an adverse reaction associated with PCA use, all occurring after a course of amoxicillin (Table IV). Two of the patients who noted adverse reactions subsequently tolerated 5 additional courses of PCAs, including at least 1 more course of amoxicillin each. One patient only reacted after her

TABLE III. Annual antibiotic use and cost for subjects during the year before and after the PenSTs

		Year before PenST	Year after PenST	P value*
Positive PenST response (n = 40)	Antibiotics/subject	3.78 ± 3.68	2.15 ± 2.51	.0009
	Cost/subject	\$81.58	\$48.03	.03
	(95% CI)	(\$67.99, \$95.17)	(\$37.20, \$58.86)	
Negative PenST responses (n = 196)	Antibiotics/subject	3.20 ± 3.35	2.41 ± 2.60	.0007
	Cost/subject	\$71.17	\$49.63	.01
	(95% CI)	(\$53.59, \$88.84)	(\$38.04, \$61.22)	
Total (n = 236)	Antibiotics/subject†	3.30 ± 3.41	2.36 ± 2.58	.0001
	Cost/subject*	\$72.93	\$49.36	.0015
	(95% CI)	(\$57.41, \$88.45)	(\$38.93, \$59.79)	
	Total cost	\$17,211.88	\$11,648.27	

*P values determined by paired *t* test.

†Health plan averages were 1.1 therapeutic courses of antibiotics at a cost of \$23.74 per patient per year in 1995.

fourth course of PCA. Two subjects had single exposures to PCA. All of the PCA-associated reactions started after at least 7 days of treatment. The overall nonrechallenged adverse reaction rate to therapeutic courses of PCAs during the year after a negative PenST response was 3.2% (3 of 93). The adverse reaction rate to non-PCAs in these same 93 patients was 5.4% (data not shown), and no patients were rechallenged with the same non-PCA.

DISCUSSION

Up to 10% of outpatients will report histories of PCA "allergy."⁸⁻¹⁰ The specifics of the clinical history of the adverse reaction have been shown to be inadequate to safely determine true allergy as defined by the presence of specific IgE directed against penicillin determinants.^{8,11} Thus physicians must avoid PCAs in any patient claiming penicillin allergy unless the allergy can be disproven. PenSTs have been previously shown to identify those individuals at highest risk for serious IgE-mediated reactions.¹¹⁻¹³

This article provides evidence that elective PenSTs are safe and will convince physicians to once again prescribe PCAs in individuals with negative PenST responses. There were significant changes in the types of antibiotics prescribed during the year after a negative PenST response. Even when multiple courses of PCAs are used in individuals with negative PenST responses, there are low rates of subsequent adverse reactions.

Patients "allergic" to PCAs may be treated with more expensive non-PCAs.⁹ Although patients allergic to PCAs in this study received antibiotics costing an average of 15.5% more per course compared with the health plan average (\$21.59 vs \$18.24), this was not a dramatic difference. What was more impressive was that study subjects received 3 times more total courses of antibiotics (3.3 vs 1.1) per year during the year before PenSTs compared with average health plan members. Antibiotic use dropped by approximately one third in both subjects with positive PenST responses and subjects with negative PenST responses after the PenSTs.

This decrease in antibiotic use may have occurred because of spontaneous resolution of the condition which resulted in recurrent "infections." Alternatively, because

PenSTs were coupled to an evaluation by an allergist, the appropriate diagnosis, treatment, and/or prevention of common conditions (eg, rhinitis, sinusitis, vascular headaches, and asthma) may have reduced the clinical symptoms (eg, cough, postnasal drip, and headaches) that drove the patient to receive multiple and possibly inappropriate antibiotic prescriptions.

There was no change seen in overall outpatient visit rate despite the fall in antibiotic use. There was a shift toward receiving care from specialty departments and away from primary care departments. Specialty physicians may have been more conservative in their use of antibiotics, though I have no data to support this.

AC was included as part of the testing protocol initially to see whether PenSTs were missing a significant number of truly allergic individuals. There was also the theoretic concern that AC could resensitize subjects. It was found that AC had no effect on the frequency of patients receiving PCAs during the year after a PenST. The reported adverse reaction rate in the group undergoing AC trended lower with subsequent PCAs compared with the group not undergoing AC, arguing against resensitization. This was biased in that older individuals were more likely to refuse AC. The types of adverse reactions noted secondary to the AC were, in general, not convincingly attributable to PCA-specific IgE, and 4 of 6 of the individuals with positive AC responses were prescribed and tolerated multiple PCAs during the year after PenSTs. The AC more than doubled the time the patient needed to be in the allergy department for the initial PenST. For these reasons, AC has been discontinued as a part of our PenST protocol.

This study should help reduce the theoretic concern of resensitization in adults after negative PenST responses and therapeutic PCA administration.⁵ The observed, unrechallenged, adverse reaction rate of 3.2% (3 of 93) is much less than the 20% (3 of 15) PenST reconversion rate reported by Parker et al.⁷ Repeat PenSTs were not performed in my study, and therefore resensitization rates cannot be reported. The clinical outcomes would suggest that if significant resensitization does occur after oral PCA use, it must be rare.

Data presented in this paper also lends support to the widespread clinical practice of oral cephalosporin use in

TABLE IV. Clinical courses of the 5 patients with adverse reactions to penicillins of the 93 patients who received a total of 188 courses of PCAs during the year after a negative PenST response

Age (yrs)	Sex	AC	Reaction	Treatment	Comments
45	F	No	Itch, no rash 14 days after first course of amoxicillin started	None	Tolerated 4 additional courses of amoxicillin
58	F	Yes	Rash 7 days after second course of amoxicillin started	Oral steroids	Tolerated 1 additional course of dicloxacillin
48	F	No	Hives 1 day after finishing fourth course of amoxicillin	None	No further penicillin over the 1 year follow-up
13	M	Yes	Rash 2 days after finishing first course of amoxicillin	None	No further penicillin over the 1 year follow-up
2	M	No	Rash isolated to neck 11 days after first course of amoxicillin	None	No further penicillin over the 1 year follow-up; rash also reported after erythromycin

patients who have positive PenST responses.¹⁴ To further add to this important penicillin-cephalosporin cross-reaction data base, the pharmacy records of 13 additional patients who had positive PenST responses between March 16, 1993 and April 15, 1994, and who had been previously reported on in abstract form only, were reviewed.¹⁵ This group represents all individuals with positive PenST responses seen during this period who received at least 1 course of an oral cephalosporin during the year after the PenSTs. These patients received a total of 30 courses of oral cephalosporins without any adverse reactions noted. In summary, 28 previously unreported individuals with positive PenST responses tolerated 63 courses of oral cephalosporins during the year after the PenSTs, and only one patient experienced a delayed adverse reaction that did not appear to be IgE mediated.

The nonrandomized observational cohort design of this study resulted in significant differences in the demographics, specifically age, between the subjects with positive PenST responses and the subjects with negative PenST responses. The constant fraction of women and the consistently high use of antibiotics and outpatient care in both groups argues against significant bias. The initial PenST study,⁸ out of which this cohort was obtained, enrolled mostly individuals referred to an allergy department for other problems who were incidentally noted to have a history of PCA allergy. The high levels of antibiotic and outpatient medical care use seen may be a characteristic of patients referred to allergy departments more than random health plan members allergic to PCAs. A prospective randomized trial is planned to help answer these questions.

Elective PenSTs in the context of an allergy consultation were associated with unexpected significant reductions in antibiotic use and overall antibiotic cost. It allows over 75% of patients who thought they were allergic to PCAs to be safely prescribed oral PCAs in the outpatient setting if indicated.

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