Introduction of a Practice Guideline for Penicillin Skin Testing Improves the Appropriateness of Antibiotic Therapy

David M. Forrest,1 R. Robert Schellenberg,2 Vincent V. S. Thien,2 Serena King,3 Aslam H. Anis,3 and Peter M. Dodek4

Divisions of 1Infectious Diseases and 2Allergy and Immunology, Department of Medicine, 3Center for Health Evaluation and Outcome Sciences, and 4Program of Critical Care Medicine, St. Paul’s Hospital, University of British Columbia, Vancouver, British Columbia, Canada

We hypothesized that the introduction of a practice guideline for penicillin skin testing would increase the appropriateness of skin testing and reduce antibiotic costs for patients with a history of penicillin allergy who have infections caused by penicillin-susceptible pathogens. We measured the appropriateness of skin testing and daily antibiotic costs before and after the introduction of a guideline for penicillin skin testing. For patients who had negative results of skin testing and were subsequently treated with a penicillin instead of an alternative antibiotic, we calculated the difference between the actual costs and the projected costs of continuing alternative antibiotics without skin testing. After the guideline was introduced, appropriateness of skin testing increased from 17% to 64%, but daily antibiotic costs did not change. For patients who had negative results of skin testing and who were subsequently treated with a penicillin, there was no difference between actual costs and the projected costs if they had not been skin tested. We conclude that introduction of a guideline for penicillin skin testing increases the percentage of eligible patients who have a skin test, and it does so without increasing costs.

The percentage of the population who report a history of penicillin allergy is estimated to be 0.7%–10% [1]. However, only ~10%–30% of patients who report this history have documented IgE-mediated allergy, as proven by a positive penicillin skin test result [1, 2]. A patient with a history of penicillin allergy whose condition would otherwise be treated with penicillin usually is given an alternative antibiotic. Although many effective alternative antibiotics are available, these antibiotics may be associated with significant toxic effects, including the development of antibiotic resistance. In addition, these alternative antibiotics are usually more expensive than are penicillins.

Penicillin skin testing can accurately and safely distinguish between patients who have IgE-mediated allergy and those who do not. The negative predictive value of a penicillin skin test for IgE-mediated allergy is >99% [1–7]. Therefore, patients who have a history that is suggestive of IgE-mediated allergy to penicillins but who have a negative skin test result can be treated safely with a penicillin. Reactions to penicillins that are not IgE-mediated are not predicted by penicillin skin tests. Therefore, we hypothesized that introduction of a clinical practice guideline for penicillin skin testing would increase appropriateness of skin testing and use of penicillins, thus reducing antibiotic costs for patients who have a history of penicillin allergy and have infections that should be treated with penicillin or penicillin-like drugs.

METHODS

Guideline development. On the basis of a systematic literature search and critical appraisal of articles on penicillin skin testing, including a decision analysis [8], a multidisciplinary team (2 allergists, 2 infectious disease
physicians, 2 pharmacists, 1 research fellow, and 1 intensivist-epidemiologist team leader) developed a clinical practice guideline. The guideline recommended penicillin skin testing for inpatients who had a history of penicillin allergy, who had infections for which a penicillin was the drug of choice, and who would require treatment with iv antibiotics for at least 7 days. Use of this guideline was limited to patients who would require treatment with iv antibiotics for at least 7 days, because the cost of the skin test (including the consultation and reagents) was approximately equal to the difference in cost between a 7-day course of vancomycin and an equivalent course of a penicillin (including the costs of drug administration). We did not expect to see any cost savings for patients who received only a few doses of antibiotics or for those who received predominantly orally administered antibiotics. Furthermore, the additional work required to test every eligible patient who was receiving any course of antibiotics was not possible in our current system.

A protocol for penicillin skin testing was also developed. The draft guideline and skin testing protocol were circulated to all infectious disease and allergy specialists in British Columbia and to the directors of pharmacy at 2 tertiary-care hospitals in Vancouver, and their suggestions were incorporated into the final version of the guideline (figure 1) and skin testing protocol.

**Guideline implementation.** In May 1996, this guideline was introduced at St. Paul’s Hospital, a 440-bed hospital in the urban center of Vancouver. Strategies to facilitate implementation included holding seminars about the guideline as part of the orientation for all medical and general surgical housestaff, making presentations at residents’ morning report and to clinical pharmacists who worked on the medical and surgical wards, and disseminating posters and pocket cards. Only inpatients at St. Paul’s Hospital were identified during this phase of implementation. All skin tests were performed by consultant allergists.

**Guideline evaluation.** Using a before-after cohort design, we compared measurements from the period 3.5 years before (January 1993–May 1996) with the period 2 years after (May 1996–May 1998) introduction of the guideline. This evaluation
was approved by the Clinical Research Ethics Board of the University of British Columbia.

Patients who were eligible for this evaluation were identified using sequential record linkage. First, we obtained from the pharmacy database at St. Paul’s Hospital the hospital record numbers of all patients admitted during the study period who had received any antibiotics and who had a history of penicillin allergy or had received a penicillin skin test during hospitalization. At the same time, we obtained 2 additional lists of hospital record numbers for (1) all inpatients who were seen by the allergists at St. Paul’s Hospital for penicillin skin testing during the study period, and (2) all individuals who were inpatients during the study period and whose discharge diagnoses (from their medical records) included any of the diagnoses listed on the guideline document (figure 1). Duplicate records in any of these lists were removed.

Data on the list obtained from the pharmacy was checked against records in the database of the microbiology department to select only those patients whose specimens yielded a bacterial pathogen on culture. This list was then narrowed to include only those patients for whom it was determined that the bacterial pathogen isolated was susceptible to a penicillin. Next, these records were checked against the medical records database to select only those patients who had a hospital stay of at least 7 days. Finally, these records and the unique records created from the original allergists’ list and the original medical records list were reviewed manually to verify that the patient actually had a history of penicillin allergy reported at admission, that the patient had one of the diagnoses listed in the guideline, and that the patient had been treated with iv antibiotics for at least 7 days.

We measured appropriateness of penicillin skin testing as the percentage of eligible inpatients (according to the guideline) who underwent skin testing. We also measured both the interval from the time when a patient was eligible to have a skin test performed to the time when the skin test was performed and the interval from the time when a negative skin test result was obtained to the time when treatment was changed from an alternative antibiotic to a penicillin.

To monitor the impact of the guideline on resource use, we measured costs of iv antibiotics (including all material and labor costs), costs of vancomycin, and costs of skin tests (including the costs of allergy consultation and all reagents used) in the eligible population. Average cost per patient per day was expressed in 2 ways. First, costs of iv antibiotics alone (including materials and labor) were averaged over the duration of their administration for each patient. Second, costs of antibiotics plus the cost of vancomycin and the cost of the skin test were averaged over the duration of the administration of the antibiotics. We did not measure effectiveness in terms of clinical outcome, because it has already been established that alternatives to penicillins are usually clinically equivalent to penicillins with regard to effectiveness. The perspective that was adopted for the economic analysis was that of the third-party payer in British Columbia, the Ministry of Health. All costs were actual costs (in Canadian dollars) that were incurred at the time of service and were adjusted, by means of the consumer price index, to reflect the value of the Canadian dollar in 1997.

To calculate potential savings in the best-case scenario of this study, we analyzed costs for the subset of patients who had negative skin test results and whose treatment regimen had been changed from an alternative antibiotic to a penicillin after the skin test was done. Potential savings were defined as the difference between actual total cost incurred for antibiotics (with or without the added costs of skin testing and vancomycin) and projected cost if treatment with the alternative antibiotic was continued for the same total duration in each of these patients.

**Statistical analysis.** Differences in appropriateness of skin tests were analyzed by use of a z test for proportions [9]. Differences in time intervals and in costs per patient per day were analyzed by use of the Mann-Whitney test after determining that each data set was not normally distributed according to a Lilliefors test (Systat). Significance of potential savings was analyzed by comparing this value with 0 in a 1-sample Student’s t test [10]. P ≤ .05 was accepted as significant. All grouped data are expressed as mean ± SD.

**RESULTS**

Using the record linkage to identify patients who might have been eligible for penicillin skin testing during January 1993–May 1998, we identified a total of 573 patients. From this total, 64 patients from the period before introduction of the guideline (January 1993–May 1996) and 95 patients from the period after introduction of the guideline (May 1996–May 1998) were found to be truly eligible after manual chart review. These 159 patients comprise the total population for the subsequent analysis. Patient characteristics (data not shown) and distributions of infections diagnosed in the 2 groups (table 1) were similar.

Before introduction of the guideline, penicillin skin tests were performed on 11 (17%) of 64 eligible patients (95% CI, 8%–26%) during their hospitalization. After introduction of the guideline, this proportion increased to 61 (64%) of 95 eligible patients (95% CI, 54%–74%; P < .001). Before introduction of the guideline, 1 patient had a positive skin test result and 10 patients had negative skin test results. In 7 of these 10 patients, antibiotic treatment was changed to use of a penicillin. After introduction of the guideline, 3 patients had positive skin test results (1 of these was false positive, as determined by the inadvertent use of a penicillin after a positive skin test result
was obtained), and 58 patients had negative skin test results. In 54 (93%) of these 58 patients, the antibiotic used for treatment was changed (P > .05 compared with proportion of patients who had negative skin test results and were switched to treatment with a penicillin before introduction of the guideline). There was 1 false-negative result, but the patient’s reaction to penicillin was only a minor skin rash. None of the patients who had positive results were desensitized. There were no significant differences between the 2 groups with regard to either the interval between the time when the patient became eligible for a skin test and the time when the skin test was performed (2.64 ± 6.14 days, before introduction of the guideline, vs. 1.82 ± 3.26 days, after introduction of the guideline) or the interval from the time when a negative skin test result was found to the time when antibiotics were changed (0.29 ± 0.76 days, before introduction of the guideline, vs. 0.46 ± 0.93 days, after introduction of the guideline).

Average daily costs of antibiotics alone were $37.24 ± $27.14 before and $30.00 ± $17.95 after introduction of the guideline. Average daily costs, including the cost of antibiotics, skin tests, and vancomycin, were $39.84 ± $28.18 before and $38.27 ± $20.56 after introduction of the guideline. In neither analysis was there a significant difference between the 2 groups. Potential savings in those patients who had negative skin test results and whose treatment was shifted to use of another antibiotic on the basis of this result were $80.07 ± $207.11 when only the costs of antibiotics were considered and $80.12 ± $207.31 when the costs of antibiotics, vancomycin, and the skin test were considered. Neither of these values was significantly different from 0. Therefore, there were no potential savings or losses for these patients.

### Table 1. Infections diagnosed in eligible patients before and after introduction of the clinical practice guideline.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Before introduction of guideline (n = 64)</th>
<th>After introduction of guideline (n = 95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteremia</td>
<td>16 (25)</td>
<td>19 (20)</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>7 (11)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Respiratory infection</td>
<td>12 (19)</td>
<td>24 (25)</td>
</tr>
<tr>
<td>Abscess/wound infection</td>
<td>3 (4)</td>
<td>15 (16)</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>12 (19)</td>
<td>14 (15)</td>
</tr>
<tr>
<td>Septic arthritis</td>
<td>5 (8)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>5 (8)</td>
<td>7 (8)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (8)</td>
<td>5 (5)</td>
</tr>
</tbody>
</table>

DISCUSSION

We found that introduction of a practice guideline for penicillin skin testing was associated with a significant increase in the percentage of eligible patients who underwent skin testing. For >90% of the patients, test results were negative, and antibiotic treatment was altered to reflect this finding. Although we found that proportionately more patients underwent skin testing after introduction of the guideline, there were no differences in the time that it took to obtain the skin test or to respond to the results of the skin test between groups. Furthermore, we found no significant differences in antibiotic costs per patient per day and no potential savings or losses in those patients who were treated with different antibiotics in response to negative skin test results.

The implications of our findings are best considered in the context of the problem of IgE-mediated allergy. Among all patients who receive penicillin, the risk of IgE-mediated anaphylaxis is ~5 cases per 10,000 patients [3], and the risk of death due to anaphylaxis is ~1–2 deaths per 100,000 patients [3]. Because of these risks, it is recommended that patients who are allergic to penicillin not be given penicillin or penicillin-like drugs. Fortunately, a broad spectrum of alternative antibiotics is available. Although the risk of cross-reactivity of penicillins with nonpenicillin β-lactam antibiotics is not clear [2, 11], because of shared antigenic determinants [12], many clinicians avoid administering these antibiotics to patients who have a history of penicillin allergy.

However, up to 90% of patients who claim to be allergic to penicillin do not have IgE-mediated allergy according to skin test results [1]. These tests have a high predictive value for a negative result. For example, among >2000 patients who said they were allergic to penicillin but who had negative skin test results and received penicillin, no life-threatening immediate reactions occurred [4]. Other series have corroborated this low incidence of reactions to penicillin treatment in patients who have negative skin test results [1–3, 5–7]. Decision analysis has also supported the usefulness of this test [8], except when the patient has a convincing history of a severe allergic reaction to penicillin [13]. In this case, skin testing is probably unnecessary.

For the treatment of some diseases, such as syphilis and infective endocarditis, alternative antibiotics are not as effective as penicillins [14]. Considering the excellent safety profile of penicillins compared with that of other antibiotics, the morbidity and mortality rates associated with eliminating penicillin as a treatment option on the basis of a history of allergy in the patient are underestimated [11]. In addition, penicillins are usually less toxic and may be considerably less expensive than alternative antibiotics.

In light of the overdiagnosis of penicillin allergy, the relative expense and toxicity of alternative antibiotics, the utility of
Penicillin skin tests, and the equal or superior effectiveness of penicillins, we believed that there was an opportunity to improve current practice by developing and implementing an evidence-based practice guideline to help clinicians manage the treatment of patients who should receive penicillins. Related work by Harris et al. [15] supports the introduction of penicillin skin testing as a strategy to reduce antibiotic use.

Our observation that there were no financial savings after implementation of this guideline is consistent with a decision-analysis model of this change in practice [16]. There are several possible explanations for the lack of change in daily antibiotic costs per patient and the absence of net savings, despite unit costs for penicillins being lower than those for alternative antibiotics. First, the data used for the calculation of average cost per patient per day included all individuals in each group, not just those who were tested. Therefore, savings due to changes in antibiotic use that were based on the results of skin tests were diluted by the costs associated with treatment of patients who did not have skin tests. Second, although the unit cost of penicillins is less than that of vancomycin, penicillins are generally administered more frequently than is vancomycin. Therefore, much of the difference in unit cost is made up by a difference in cost of administration (e.g., iv tubing, medication bags, and labor). Third, during the study period, the unit cost of vancomycin decreased by 62%, from $31.80 per gram in 1993 to $12.15 per gram in 1998. During the same time, the unit cost of cloxacillin decreased by only 11%, from $1.27 per gram to $1.13 per gram. Finally, when the overall costs that were determined in this study are considered, it is important to note that most of the cost of skin testing is the cost of a consultation with an allergist. If skin testing was done by another trained health professional (such as a resident or a nurse), it is likely that this cost would be considerably lower.

Although introduction of this practice guideline for penicillin skin testing did not achieve financial savings during the hospitalization in which the guideline was introduced, we believe that its usefulness extends beyond this hospitalization. The knowledge that a patient does not have IgE-mediated allergy to penicillins should obviate the need for successive skin testing or use of alternative antibiotics during subsequent clinical encounters. In addition, it is known that patients who have a history of an adverse reaction to β-lactam antibiotics but who have negative skin test results can safely receive single or multiple courses of β-lactam antibiotics [17]. Furthermore, the use of penicillins rather than vancomycin will likely decrease the incidence of infections caused by vancomycin-resistant strains of bacteria. Therefore, the ongoing costs of education (which were trivial in this study) would easily be offset by the avoidance of costs of successive skin tests, more-expensive alternatives to penicillins, and treatment of infections caused by antibiotic-resistant bacteria.

It is important to note that this guideline applies only to IgE-mediated reactions to penicillins. Determining that a patient does not have an immediate reaction to major and minor determinants of penicillin does not preclude a delayed reaction, such as Stevens-Johnson syndrome, or other reactions that are not mediated by IgE. Similarly, because we did not test for a wide variety of penicillin side-chain reactions, we can only draw conclusions about reactions caused by the major and minor determinants of penicillin. However, there is considerable cross-reactivity between ampicillin and these determinants [18].

In summary, we conclude that introduction of a clinical practice guideline for penicillin skin testing in patients who have a history of penicillin allergy is associated with an increase in appropriate use of skin testing and a change in antibiotics for those patients found to have negative reactions. These changes in practice were not associated with any changes in daily antibiotic costs or in potential savings, compared with the use of alternative antibiotics during a single course of treatment. However, savings may be accrued by avoidance of successive skin tests and the use of alternative antibiotics during subsequent inpatient and outpatient encounters. If compliance with this guideline increases the use of more-appropriate antibiotics that have a narrower spectrum of activity, emergence of resistant microbes may also decrease.

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References


