Questionable History of Immediate-Type Hypersensitivity to Penicillin in Staphylococcal Endocarditis: Treatment Based on Skin-Test Results Versus Empirical Alternative Treatment—A Decision Analysis

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Approximately 10% of the population claim to be allergic to penicillins, but only ~10%–30% of these have IgE-mediated reactions to penicillin skin tests. Alternatives to penicillins may be less effective, more toxic, and more expensive. Therefore, we used decision analysis to calculate maximum expected utility and minimum cost for skin-testing or not skin-testing patients who have endocarditis due to Staphylococcus aureus that is susceptible to cloxacillin and who have a questionable history of immediate-type hypersensitivity to penicillin. We used known probabilities of intermediate outcomes, actual costs, and measured utilities and included one-way sensitivity analysis. Whether utility, cost, or average cost-utility was the outcome of interest, skin-testing was preferred to no skin-testing in most conditions. Patients who have endocarditis due to S. aureus that is susceptible to cloxacillin and who also have a questionable history of immediate-type hypersensitivity to penicillin should be skin-tested before starting antibiotic therapy.

Infective endocarditis occurs in 10,000–15,000 individuals each year in the United States [1]. Staphylococcus aureus is the cause of endocarditis in an increasing proportion of patients who have this disease. Current estimates are that this organism is the cause in 20%–30% of cases [1, 2]. Mortality due to this condition ranges from 5% to nearly 90%, depending on the patient population studied [1, 3, 4]. Although nearly 90% of S. aureus isolates are resistant to penicillin, most are susceptible to β-lactamase-resistant penicillins such as cloxacillin.

Treatment of staphylococcal endocarditis usually consists of administration of a β-lactamase–resistant penicillin such as cloxacillin for 4–6 weeks, with optional addition of an aminoglycoside such as gentamicin for the first 3–5 days [2, 4–7]. Although combination therapy does not improve mortality compared to cloxacillin alone, in patients who have left-sided endocarditis combination therapy shortens the time to clearance of bacteremia [8]. For selected injection drug users who have right-sided endocarditis, a 2-week course of a β-lactamase–resistant penicillin plus an aminoglycoside may be adequate [9].

In patients who are allergic to penicillins, several alternatives are available. First, cephalothin or cefazolin may be used [2, 5–7]. However, there may be some cross-reactivity between penicillins and cephalosporins, and this alternative is not recommended, especially in the setting of immediate-type hypersensitivity to penicillin [2, 4, 7, 10]. A second alternative is vancomycin [2, 3, 5–7]. Vancomycin is widely used in this setting, but it may not be as effective and is more expensive than cloxacillin [11–13]. For example, Small and Chambers found that 5 of 13 patients treated with vancomycin had unsatisfactory or complicated clinical courses [11]. Other less commonly used alternatives include administration of rifampin or ciprofloxacin and desensitization to penicillin [6].

One problem in treating patients who have a history of penicillin allergy is determining whether they are truly allergic. The proportion of the population who report a history of penicillin allergy is estimated to be between 0.7% and 10% [14]. However, only ~10%–30% of patients who report such a history actually have documented immediate-type hypersensitivity as proven by a positive skin test [14, 15].

The risk of IgE-mediated anaphylaxis among all patients who receive penicillins is about 5 in 10,000 [16]. About one-half of these reactions occur in patients who have a history of allergy to penicillin [17]. Mortality due to anaphylaxis occurs in ~1–2 per 100,000 patients who receive penicillin. In the United States, this incidence translates to ~300–1000 deaths per year [15].

Should patients who have a history of penicillin allergy be skin-tested, or should they simply be given an alternative agent such as vancomycin? Redelmeier and Sox recently used a threshold model of decision analysis to calculate the range of probabilities in which a skin test will help to discern whether a patient who has viridans streptococcal endocarditis is truly allergic or not [18]. They calculated the threshold probability of a severe allergic reaction that would dictate changing.
from penicillin to vancomycin on the basis of the expected utilities of these 2 options.

On the basis of a median threshold probability of 0.00013 and the sensitivity (89%–96%) and specificity (89%–96%) of skin-testing for penicillin allergy, these authors found that skin-testing was helpful when the prior probability of a severe allergic reaction was between 0.00001 and 0.001. This range of probabilities corresponds to a weak or questionable history of penicillin allergy.

Given that there is a range of prior probabilities of penicillin allergy that should prompt a skin test, do all patients who have these prior probabilities of severe reactions undergo skin-testing? Unfortunately, there are no data available to accurately answer this question. However, clinical impressions are that many patients are simply given an alternative antibiotic if they give any history of penicillin allergy. Skin-testing may be underused in these circumstances.

Although skin-testing adds additional cost and time to a consultation with a patient, it is possible that the costs and risks of vancomycin may exceed the cost of the skin test. The purpose of this study was to calculate maximum expected utility and minimum cost for skin-testing or not skin-testing patients who have endocarditis due to *S. aureus* that is susceptible to cloxacillin and who have a questionable history of immediate-type hypersensitivity to penicillin. In addition, average cost-effectiveness for the 2 strategies was calculated.

**Methods**

**Comparative strategies.** Given the population of patients who have endocarditis due to *S. aureus* that is susceptible to cloxacillin and who have a questionable history of penicillin allergy, we used a decision analysis approach to compare the strategy of antibiotic treatment based on results of penicillin skin-testing with the strategy of not skin-testing and treating with vancomycin (figure 1). These 2 strategies were chosen because they are the most common choices in this setting. Although it may seem obvious that skin-testing is always the dominant choice because cloxacillin appears to be more effective than vancomycin (against methicillin-susceptible *S. aureus*) and is much cheaper, there is still some controversy because the inconvenience and cost of a skin test may dissuade some clinicians and patients from ordering it.

We used Decision Maker 6.0 software (Pratt Medical Group, Boston, MA) to construct the decision tree and to do all calculations.

**Outcomes.** In the “skin test” strategy, the patient is tested with major and minor determinants of penicillin according to a standard protocol [14]. If the test is positive, the patient is treated with vancomycin (30 mg/kg/day in 2 divided doses) for 4 weeks. Most of these patients experience no toxic effects from this drug. Some patients develop toxic side-effects caused by vancomycin and require adjustments in dosage or infusion rate. The outcome for patients in both groups is either cure or microbiological failure, defined by persistent positivity of blood cultures after 7 days of treatment. Microbiological failures necessitate additional treatment that includes administration of antibiotics, with or without surgery.

If the skin test is negative, the patient is treated with cloxacillin. Most of these patients experience no toxic effects, but such effects sometimes occur, usually in the form of an immediate hypersensitivity reaction (IgE-mediated hypersensitivity). After a toxic reaction the patient either lives or dies. For the patients who live, cloxacillin is switched to vancomycin [7] for a total treatment course of 4 weeks. The outcome for all of these patients is either cure or microbiological failure, as defined above.

In the “no skin test” strategy, patients receive vancomycin (30 mg/kg/day), and the outcomes are the same as those in the group that received vancomycin because of a positive skin test (see above).

**Probability values.** The probability of a positive skin test in this patient population (0.1–0.3) was estimated based on ranges calculated in other populations of patients who have a history of penicillin allergy [14, 15]. The probability of a toxic reaction to vancomycin, including “red man syndrome,” hypotension associated with infusion, and nephrotoxicity, ranges between 0.09 and 0.24 [19, 20]. A point estimate of 0.15 was used in the initial case. The probability of microbiological cure with a vancomycin-based regimen ranges from 0.62 to 0.79 [6, 11]. A point estimate of 0.7 was used in the initial case.

The probability of a toxic reaction (mainly IgE-mediated hypersensitivity) to penicillin in a patient who has a negative skin test ranges from 0 to 0.04 [21]. A point estimate of 0.02 was used in the initial case. The probability of a severe hypersensitivity reaction in a patient who has a history of penicillin allergy is estimated at 0.002 [18]. If we estimate the probability of a negative skin test in a patient who has a questionable history of penicillin allergy to be 0.8 and we estimate the probability of death due to a severe hypersensitivity reaction to be 0.1 [18], then the probability of a severe hypersensitivity reaction in this setting is 0.0016 and the probability of death, given a severe hypersensitivity reaction to penicillin, is 0.00016. The probability of microbiological cure with a cloxacillin-based regimen is estimated at 0.95 [11].

**Utility values.** To determine patient preferences regarding management, a description of this project, including each of the 13 possible outcomes (figure 1), was provided to a patient who had endocarditis due to *S. aureus*. Unfortunately, the patient was unable to cooperate with an assessment of utilities. Therefore, the same outcomes were provided to a head nurse who cares for inpatients who are treated for *S. aureus* endocarditis. To estimate utilities associated with each outcome, the standard gamble technique was used. Specifically, the nurse was asked, “Would you rather have this outcome for certain or an x chance of normal life?” By “ping-ponging” the value of x, the point of indifference was eventually identified, and the probability of normal life at that point was the utility value for that outcome. Utilities of outcomes for this nurse were used to determine maximum utility in the decision analysis.

**Economic perspective and assumptions.** The analysis was done from the perspective of the third-party payer. In particular, the main benefit of therapy was assumed to be microbiological cure and the costs (in Canadian dollars) were those of cloxacillin ($1.25 per 2-g dose), vancomycin ($21.00 per 1-g dose), rifampin ($0.65 per 300-mg dose), measurements of serum vancomycin concentration ($31.51 per assay), penicillin skin tests ($123.15 each, including the consultation by an allergist and materials), and hospitalization costs ($3151 per hospitalization) for a course of 4 weeks.
Figure 1. Decision tree for choice between skin-testing and not skin-testing patients who have infective endocarditis due to *Staphylococcus aureus* that is susceptible to cloxacillin and who have a questionable history of immediate-type hypersensitivity to penicillin. Each numbered outcome includes percentage of patients (from either skin-tested or nonskin-tested group) who would likely have indicated outcome, based on point estimates of probabilities, point estimates of cost (including costs of antibiotics, measurements of serum vancomycin concentration, penicillin skin tests, and hospital stay), and point estimates of utility ($u$).

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assumed to be the same in all groups; therefore, these common costs were not considered in the analysis. Figures for all costs were obtained from the laboratory and pharmacy of St. Paul’s Hospital in Vancouver.

For the vancomycin groups that did not have toxic reactions and were microbiologically cured, we assumed a 4-week course of daily intravenous (iv) vancomycin (1 g iv every 12 h) and 2 measurements of serum vancomycin concentration. (One measurement includes 2 assays, 1 before and 1 after the dosing.) For the vancomycin groups that did not have toxic reactions and for whom the outcome was microbiological failure, we assumed a 1-week course of vancomycin alone and a 4-week course of vancomycin and oral rifampin (300 mg po every 12 h), plus 2 measurements of serum vancomycin concentration.

For the vancomycin groups that had toxic reactions and were microbiologically cured, we assumed a 4-week course of vancomycin at a longer dosing interval (1 g iv every 24 h) and 4 measurements of serum vancomycin concentration. For the vancomycin groups that had toxic reactions and for whom microbiological failure was the outcome, we assumed a 5-week course of reduced-dose vancomycin (1 g iv every 24 h) and a 4-week course of rifampin, plus 4 measurements of serum vancomycin concentration.

For the cloxacillin group that did not have any toxic reactions and was microbiologically cured, we assumed 4 weeks of iv cloxacillin (2 g iv every 4 hours). For the cloxacillin group that did not have any toxic reactions and in which bacteriologic failure was the outcome, we assumed 5 weeks of iv cloxacillin and 4 weeks of oral rifampin (same dosage as above). For the cloxacillin group that had a nonfatal toxic (IgE-mediated) reaction to cloxacillin and was microbiologically cured, we assumed 1 dose of iv cloxacillin plus 4 weeks of iv vancomycin and 2 measurements of serum vancomycin concentration.

For the cloxacillin group that had a nonfatal toxic reaction and microbiological failure, we assumed 1 dose of iv cloxacillin plus 5 weeks of iv vancomycin, 4 weeks of oral rifampin, and 2 measurements of serum vancomycin concentration. For the cloxacillin group that had a fatal IgE-mediated reaction, we assumed 1 dose of cloxacillin and 2 hospital days (approximate cost of 1 day in intensive care unit or services required for attempted resuscitation from cardiac arrest) were assumed.

Discounting was not done in this analysis because costs and benefits accrued over a short time. Therefore, no adjustment of future costs and benefits to their present values was necessary.

**Analysis.** First, the decision tree was folded back to calculate maximum expected utility and minimum expected cost, based on the initial estimates of probabilities, costs, and utilities. Then sensitivity analysis was done to test the robustness of conclusions drawn. Specifically, one-way sensitivity analysis was done in 3 ways: with expected utility as the outcome, while each probability and utility was allowed to vary individually; with total cost as the outcome, while each cost and probability was allowed to vary individually; and with average cost-utility as the outcome, while each cost, probability, and utility was allowed to vary individually.

**Results**

Maximum expected utility, based on the initial estimates of probabilities and utilities, was 0.965 in favor of skin-testing. Expected utility for no skin-testing was 0.936. Minimum cost, based on the initial estimates of probabilities and costs, was $14,927.26, in favor of skin-testing. Cost for no skin-testing was $16,375.25. Average cost-utility was $15,468.69 for skin-testing and $17,494.46 for no skin-testing.

One-way sensitivity analysis for expected utility as the outcome showed that skin-testing was preferable in most circumstances. For example, the threshold above which one would choose no skin-testing for the probability of a positive skin test was 0.62; this value is much higher than any in the literature [14, 15]. Sensitivity analysis for the probability of a toxic reaction to cloxacillin showed that the threshold above which one would choose no skin-testing was 0.57; this value is much higher than any in the literature [21].

Sensitivity analysis for the probability of a toxic reaction to vancomycin showed no threshold; skin testing was always preferable. With respect to treatment, sensitivity analysis for the probability of microbiological cure in skin test-negative patients who have no adverse reactions to cloxacillin showed that skin-testing was preferable below a threshold of 0.59; this value is much lower than any in the literature [11]. In contrast, there was no threshold for the probability of microbiological cure after receipt of vancomycin; skin-testing was always preferable. Similarly, sensitivity analysis for the probability of survival in patients who are skin test-negative, receive cloxacillin, and have an allergic reaction showed that skin-testing was always preferable.

With respect to utilities, thresholds to change the decision from skin-testing to no skin-testing were as follows: utility of microbiological cure in skin test-negative patients who receive cloxacillin and do not have any allergic reaction (outcome 5, figure 1), <0.95; utility of microbiological failure in skin test-negative patients who receive cloxacillin and do not have any allergic reaction (outcome 6, figure 1), <0.16; utility of microbiological cure in skin test-positive patients who receive vancomycin and have no adverse reactions (outcome 1, figure 1), <0.71; utility of microbiological failure in skin test-positive patients who receive vancomycin and have no adverse reactions (outcome 2, figure 1), <0.28; utility of microbiological failure in patients who are not skin-tested and who receive vancomycin without adverse reactions (outcome 11, figure 1), >0.99. For all other utilities, skin testing was always preferred; there were no thresholds.

One-way sensitivity analysis for cost as the outcome variable showed that cost was less in the skin-test group as long as any of the following factors were true: the cost of a dose of cloxacillin was <$12.11, the cost of the penicillin skin test was <$1571, the probability of a positive skin test was <0.94, or the probability of a microbiological cure in skin-test negative pa-
tients who receive cloxacillin without allergic reactions was >0.45.

One-way sensitivity analysis for average cost-utility showed that this ratio favored skin-testing below a threshold of 0.8 for the probability of a positive skin test, above a threshold of 0.5 for the probability of a microbiological cure in skin test–negative patients who receive cloxacillin without allergic reactions, and below a threshold of $16 for the cost of a dose of cloxacillin. There was no threshold for average cost-utility for the cost of the penicillin skin test; skin-testing was preferred over the full range of costs.

For utilities, the threshold above which average cost-utility favored skin-testing is 0.85 for utility of microbiological cure in skin test–negative patients who receive cloxacillin without allergic reactions (outcome 5, figure 1) and 0.05 for utility of microbiological cure in skin test–positive patients who receive vancomycin without adverse reactions (outcome 1, figure 1). For all other utilities, skin-testing had a lower average cost-effectiveness ratio than not skin-testing over the entire range.

**Discussion**

The major finding of this study is that patients who have endocarditis due to *S. aureus* that is susceptible to cloxacillin and who also have a questionable history of immediate-type hypersensitivity to penicillin should be skin-tested before starting antibiotic therapy. This choice is associated with both a higher expected utility and a lower cost in most circumstances. Sensitivity analysis for probabilities of intermediate outcomes shows that either thresholds for changing the preferred choice are unrealistic or there are no thresholds for changing the preferred choice, on the basis of expected utility. Sensitivity analysis for utilities is similar, except for the utility of microbiological cure in skin test–negative patients who have no toxic reactions to cloxacillin, in which the preferred choice changes below a value of 0.95, and for the utility of microbiological failure in nontested patients who receive vancomycin and who have no toxic reactions, in which the preferred choice changes above a value of 0.99.

Sensitivity analysis based on cost as the outcome of interest shows that skin tests are nearly always a cheaper choice, except when the cost of either cloxacillin or a skin test becomes unrealistically high. Similarly, skin-testing is cheaper for various probabilities of intermediate outcomes, except when the probability of microbiological cure in skin test–negative patients who receive cloxacillin and who have no toxic reactions is <0.45 or when the probability of having a positive skin test is >0.94. These probabilities are unrealistic. Sensitivity analysis based on average cost-effectiveness shows that skin-testing has a lower cost-effectiveness ratio (preferred) and is generally dominant.

Penicillin skin-testing in patients who give an uncertain history of penicillin allergy is supported by other studies [22, 23]. In a cohort study of children and adolescents who had a history of an adverse reaction to a β-lactam sufficient to lead to a recommendation by a physician to avoid further use, only 34% were found to have an IgE-mediated reaction to skin-testing with major, minor, and other determinants [22]. Similarly, in a rudimentary decision analysis involving patients who had an equivocal history of penicillin allergy and who were being treated for an active infection, skin-testing was associated with potential cost-avoidance of $30.68 per course of treatment [23]. However, skin-testing was associated with an increased cost of $25.29 per course for patients who were receiving prophylactic antibiotics [23].

There are several limitations in this study. First, only 2 strategies were considered. Other strategies in this setting include using a first-generation cephalosporin as an alternative to vancomycin. This alternative was not considered because it appears to be used less commonly than vancomycin and because there are limited data about toxicity and cure rates for these treatments. Furthermore, cephalosporins are not recommended for patients who have IgE-mediated hypersensitivity to penicillin [7]. In addition, best estimates for usual and reduced doses of vancomycin were used.

The strategy of desensitization for patients who have positive skin tests was also not considered because these patients are usually given another agent, such as vancomycin, that is effective against methicillin-susceptible staphylococci.

A second limitation is that these analyses are based on 4 weeks of antimicrobial therapy. If therapy had continued for 6 weeks, the difference in favor of skin-testing would have been amplified. In addition, empirical therapy (before knowledge of culture and sensitivity results) was not considered. The time frame for this analysis begins when the organism and its susceptibility to antibiotics are known. The cost of empirical vancomycin, for example, for 2–3 days would be common to both strategies and was therefore not included. Relapses after initial microbiological cure were also not considered in this analysis.

A third limitation is that the fact that treatment failure was limited to microbiological failure. Hemodynamic failure was not considered. The clearest indication for valve replacement in the setting of endocarditis is refractory congestive heart failure. This event was not considered.

A fourth limitation in this study is the economic perspective. For the sake of simplicity, costs were limited to those of antibiotics, measurements of serum antibiotic levels, penicillin skin tests, and hospitalization (estimated). A more accurate hospitalization cost would include all direct costs for services plus capital and allocated overhead costs. In addition, indirect costs such as those incurred by lost time for the patients and their families were not considered. It was assumed these costs would be the same for each outcome group.

A fifth limitation is that there is no commercially available preparation of minor determinants for penicillin skin-testing.
Therefore, there may be some variability in the proportion of positive skin tests, depending on the local preparation of minor determinants.

In summary, this decision analysis shows that penicillin skin-testing is a favored strategy compared with no skin-testing for patients who have infective endocarditis due to *Staphylococcus aureus* that is susceptible to cloxacillin and who have a questionable history of immediate-type hypersensitivity to penicillin.

References
