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Complications - Infection

Preoperative Allergy Testing for Patients Reporting Penicillin and Cephalosporin Allergies is Cost-Effective in Preventing Infection after Total Knee and Hip Arthroplasty

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ABSTRACT

Background: Routine preoperative allergy testing in patients reporting penicillin and cephalosporin allergies increases the number able to receive cefazolin, which should reduce the risk of infection after total knee and hip arthroplasty (TKA/THA), but it remains unclear whether this practice is cost-effective. Using a break-even analysis, we calculated the cost-effectiveness of routine preoperative allergy testing for infection prevention in total joint arthroplasty patients reporting penicillin and cephalosporin allergies.

Methods: The cost of a penicillin allergy evaluation, the cost of revision arthroplasty for prosthetic joint infection (PJI), and baseline rates of PJI in patients receiving a noncefazolin antibiotic in the perioperative period were derived from existing literature. A break-even economic model using these variables was constructed to calculate the absolute risk reduction (ARR) in infection rate needed for preoperative allergy testing to be cost-effective. The number needed to treat (NNT) was calculated from the ARR.

Results: Preoperative allergy testing before TKA and THA in patients reporting penicillin and cephalosporin allergies was cost-effective if the initial infection rate decreased by an ARR of 0.810% (NNT = 123) and 0.655% (NNT = 153) for TKA and THA, respectively. Cost-effectiveness was maintained with varying allergy consultation costs, infection rates, and costs associated with PJI treatment.

Conclusion: Routine preoperative allergy testing and clearance are cost-effective infection prevention strategies among patients reporting penicillin and cephalosporin allergies in the setting of elective joint arthroplasty. Widespread adoption of this practice may considerably reduce the economic and societal burden associated with prosthetic infections.

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The most recent International Consensus Meeting on Musculoskeletal Infection (2018) concluded that the preferred perioperative prophylactic antibiotic in patients undergoing primary total joint arthroplasty (total knee [TKA] and hip [THA] arthroplasty) is a first-generation or second-generation cephalosporin such as cefazolin [1]. These first-line antibiotics are favored due to their minimal side effect profile, effectiveness against the bacteria causing most

prosthetic joint infections (PJIs), and synergy with the innate immune system [2–4]. However, many patients undergoing primary total joint arthroplasty (TJA) receive perioperative antibiotics other than cefazolin owing to concerns for serious allergic reactions to penicillin and cephalosporins [5,6].

Emerging evidence has demonstrated that the administration of noncefazolin antibiotics is associated with significantly higher rates of surgical site infections after various surgical procedures, including TJA [6]. Interestingly, while 10% of the US population reports an allergy to penicillin antibiotics [7,8], the majority are deemed nonallergic following allergy evaluation [7,9,10]. As such, the administration of second-line or third-line antibiotics may be placing these patients at an unnecessary increased risk of healthcare-associated infections and overall suboptimal outcomes [11–14]. In fact, these concerns have led to recommendations by

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the American Academy of Allergy, Asthma, and Immunology for formal allergy consultation and testing for all patients with unconfirmed penicillin allergies [15].

In light of this, Wyles et al published a recent landmark study examining the rates of PJI after TJA in patients who received either cefazolin or alternative antibiotics in the perioperative period [5]. The rate of PJI was 32% lower in patients administered perioperative cefazolin after adjusting for confounders. Furthermore, a preoperative allergy consultation for patients reporting penicillin and cephalosporin allergies cleared 97% of tested patients for perioperative cephalosporins and increased the proportion of patients receiving cefazolin by 27%.

Despite recent evidence in favor of routine preoperative allergy testing in the TJA setting, no formal analysis has been performed to assess its economic feasibility. As such, we used a break-even economic model to determine whether routine allergy consultation and testing in patients presenting with penicillin and cephalosporin allergies before TJA is a cost-effective intervention.

Methods

We utilized a break-even analysis to determine the cost-effectiveness of routine preoperative allergy testing in patients presenting with penicillin and cephalosporin allergies. Break-even economic modeling, first described by Hatch et al (Figure 1), establishes the effectiveness that an infection prevention intervention must have in order to offset the costs of its routine use [16]. The variables utilized in the equation are the initial infection rate, the total cost of treating an infection, and the cost of the intervention. When solved for IR_f (the final break-even infection rate with routine penicillin allergy testing), a percentage is obtained. If the intervention can reduce the infection rate to or below this threshold, then its use is economically justified. Calculating the difference between the initial and final infection rate yields the absolute risk reduction (ARR), which then can be used to calculate the number needed to treat (NNT). Furthermore, by holding certain variables constant, while changing others, the model has the power to show the economic viability of the intervention over a range of costs and infection rates.

The values used for the break-even variables were obtained from the literature. As this study did not involve protected health information, institutional review board approval was not required.

The initial infection rate used was 3.04%. This represents the rate of PJI in patients who did not receive cefazolin as prophylaxis before TKA or THA as reported by Wyles et al [5]. The most common antibiotics used for patients who did not receive preoperative cefazolin in their study were clindamycin and vancomycin. However, because of the potential variability in infection rates, we also performed a sensitivity analysis to study a broad range of initial infection rates (1%–10%).

The costs associated with treating a PJI after TKA and THA used in our analysis were \$27,870 and \$34,445, respectively. These costs were adjusted for inflation to reflect 2020 costs (USD) and were derived from the costs reported by Kamath et al [17] who reported the average hospitalization costs for revision knee and hip arthroplasty to treat PJI. We chose these costs as they were among the

most recently reported data and likely an underestimation of the total cost of treating a PJI because they did not include the cost of both stages of a 2-stage treatment (the most commonly performed method of treatment in the United States) or the antibiotic administration between stage 1 and stage 2, because we did not want to overestimate the cost-effectiveness of our intervention. However, studies have shown significant variability in costs associated with treating PJIs, leading us to consider a wide range of potential costs (\$10,000–\$400,000). Our upper limit (\$400,000) was chosen based on the report by Parisi et al who used a Markov analysis to determine the long-term costs associated with treating a PJI after THA [18].

Standard penicillin allergy skin testing in the United States uses the major antigenic determinant benzylpenicilloyl with dilutions of penicillin G, providing a negative predictive value of 95% [7,19]. Standard practice involves administering an observed test dose challenge of amoxicillin to patients with a negative penicillin skin test, increasing the negative predictive value to nearly 100% [19,20]. A board-certified allergist/immunologist typically performs this evaluation. The cost of penicillin allergy evaluation (penicillin skin testing plus one-step amoxicillin drug challenge performed by an allergist/immunologist) used in our analysis was \$225.71. We derived this cost from a report by Blumenthal et al who estimated the cost associated with a penicillin allergy evaluation using time-driven activity-based costing to be \$220 [19]. The components of this cost include estimated personnel costs (\$98), consumables costs (\$119), and space costs (\$3) [19]. We adjusted this cost for inflation to represent 2020 costs (USD) and performed a sensitivity analysis across a large spectrum of costs to account for variability between institutions.

Results

At a cost of \$225.71 and a cost of \$27,870 for treating PJI after TKA, routine preoperative allergy consultations for patients with reported penicillin and cephalosporin allergies would be cost-effective if the initial infection rate decreased by an ARR of 0.810%, from 3.04% to 2.23% (Table 1). At the same cost of \$225.71 and a cost of \$34,445 for treating PJI after THA, routine preoperative allergy consultation in the same population would be cost-effective if the initial infection rate decreased by an ARR of 0.655%, from 3.04% to 2.385%. In other words, routine allergy consultation is economically substantiated if it prevents at least 1 infection out of 123 TKA or 1 infection out of 153 THA (NNT). When considering

Table 1
Cost-Effectiveness of Penicillin Allergy Testing for Infection Prevention in Total Knee and Hip Arthroplasty.^a

Cost of Penicillin Allergy Evaluation, \$ (USD)	Initial Infection Rate, %	Break-Even Infection Rate, %	ARR, %
Total Knee Arthroplasty			
100.00	3.04	2.681	0.359
175.00	3.04	2.412	0.628
225.71	3.04	2.230	0.810
500.00	3.04	1.246	1.794
750.00	3.04	0.349	2.691
Total Hip Arthroplasty			
100.00	3.04	2.750	0.290
175.00	3.04	2.532	0.508
225.71	3.04	2.385	0.655
500.00	3.04	1.588	1.452
750.00	3.04	0.863	2.177

Bolded values denote actual cost.

ARR, absolute risk reduction; USD, United States Dollar.

^a Presumes a baseline infection rate (cohort not receiving cefazolin) of 3.04% and treatment cost of \$27,870 (TKA) and \$34,445 (THA).

$$S_t \times C_t \times IR_i = (S_t \times C_d) + (S_t \times C_t \times IR_f)$$

$$IR_f = \frac{(IR_i \times C_t) - C_d}{C_t}$$

Fig. 1. Calculating break-even infection rate using the initial infection rate, cost of treatment, and cost of intervention [16]. S_t , total annual suspected-allergy surgeries; C_t , total cost of treating infection; C_d , cost of allergy consultation and testing; IR_i , initial infection rate; IR_f , break-even infection rate.

Lastly, our study found that baseline PJI rate does not impact cost-effectiveness. PJI rates may vary considerably based on a number of institution-related and patients-specific factors [18,30–40]. Here we demonstrate that the ARR needed for cost-effectiveness remained constant at 0.810% for TKA and 0.655% for THA for initial infection rates between 1% and 10%.

Given our findings, we believe that the implementation of routine preoperative allergy testing in patients presenting with penicillin and cephalosporin allergies before TJA is a cost-effective infection prevention strategy. As institutions begin to implement preoperative allergy testing protocols, it is important to understand how to best interpret potential results. Penicillin allergy testing has a negative predictive value above 99%, indicating that surgeons can have a very high degree of confidence in the safe administration of cefazolin to patients who ultimately test negative [15,41]. In patients who have a positive test, penicillin desensitization is a safe, efficient, and effective option that may be considered [42–44]. Some institutions alternatively administer a test dose of cefazolin to patients with reported penicillin and cephalosporin allergies on the day of surgery. If, however, the patient shows cephalosporin sensitivity, a change to vancomycin can significantly delay the operation, which is not cost-effective or efficient. However, the current standard of care is to have patients undergo a formal evaluation with an allergist. Using this approach, the patient's ability to tolerate cefazolin is known before the day of surgery and situations where a test dose is unable to be administered are avoided. Finally, a number of patients receive vancomycin as their sole perioperative antibiotic on the basis of methicillin-resistant *Staphylococcus aureus* (MRSA) colonization. However, multiple prior investigations have demonstrated that cefazolin and vancomycin work in synergy against MRSA [5,45,46]. Furthermore, vancomycin has relatively poor coverage for the numerous other bacteria responsible for PJI. Given this, patients with known MRSA colonization and reported penicillin allergies should still undergo formal preoperative allergy evaluation and receive cefazolin in addition to vancomycin if appropriate.

The major strength of this study involves the use of an economic model to determine cost-effectiveness in a scenario where the low baseline infection rate precludes a randomized controlled trial. Prospective studies investigating PJI are often unrealistic given the large sample size needed to achieve statistical power. Furthermore, a randomized controlled trial examining cost and antibiotic choice in patients with reported penicillin allergies would not be ethically justified given the mounting evidence indicating the superiority of cefazolin. For these reasons, our break-even model is especially valuable.

A number of limitations to our study should be acknowledged. First, PJI rates likely vary widely based on host factors and practice setting. To address this, we performed our calculations across a broad range of baseline infection rates. Second, the cost of treating PJI used here represents a national average and may actually underestimate that cost at distinct institutions. However, the cost-effectiveness of preoperative penicillin allergy testing for infection prophylaxis is actually strengthened as the true cost of PJI treatment increases. In addition, we did not consider the role of penicillin desensitization in suspected-allergy patients ultimately determined to have IgE-mediated reactions to penicillin. This would require a complex contingency analysis beyond the scope of our economic model. Furthermore, accurate cost analyses of modern penicillin desensitization protocols are not available. The implications of penicillin desensitization in TJA remain an avenue for future study. Finally, this model is unable to account for barriers individual institutions may face in attempting to implement a preoperative penicillin allergy-testing program.

Conclusion

In this study, we used a break-even economic model to demonstrate that routine preoperative allergy consultation and testing in patients reporting penicillin and cephalosporin allergies is a highly cost-effective intervention for preventing PJI after TJA. This practice remains cost-effective at a range of testing costs, treatment costs, and initial infection rates. The model utilized here provides a valuable resource for individual institutions to evaluate the economic impact of implementing such a preoperative allergy testing protocol into their own practice. Widespread adoption of allergy testing for antibiotic prophylaxis may considerably reduce the economic and societal burden associated with prosthetic infections.

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