



ELSEVIER

Contents lists available at ScienceDirect

## The Journal of Arthroplasty

journal homepage: [www.arthroplastyjournal.org](http://www.arthroplastyjournal.org)

# Economic Burden of Patient-Reported Penicillin Allergy on Total Hip and Total Knee Arthroplasty

Olivia C. Lee, MD <sup>a, b</sup>, Darren C. Cheng, MS, BSM <sup>b</sup>, Jonathan L. Paul, BS <sup>b</sup>,  
Bailey J. Ross, BA <sup>b</sup>, Barrett J. Hawkins, MD <sup>b</sup>, William F. Sherman, MD, MBA <sup>b, \*</sup>

<sup>a</sup> Department of Orthopaedic Surgery, Louisiana State University Health Sciences Center and Southeast Louisiana Veterans Healthcare System, New Orleans, LA

<sup>b</sup> Department of Orthopaedic Surgery, Tulane University School of Medicine, New Orleans, LA

## ARTICLE INFO

## Article history:

Received 16 March 2021

Received in revised form

15 April 2021

Accepted 26 April 2021

Available online xxx

## Keywords:

total joint arthroplasty

economic burden

penicillin allergy

penicillin allergy testing

cost savings

prosthetic joint infection

## ABSTRACT

**Introduction:** Self-reported penicillin allergies in patients undergoing total joint arthroplasty often results in the use of second-line prophylactic antibiotics. A higher risk of prosthetic joint infection (PJI) is associated with suboptimal antibiotics vs first generation cephalosporins, which have historically been grouped with other beta-lactam antibiotics such as penicillin for potential allergic reactions. This study evaluates the economic burden of self-reported penicillin allergies in total joint arthroplasty (TJA).

**Methods:** Data from studies reporting true incidence of IgE-mediated penicillin allergies, infection-free survivorship of TJA, and cost of PJI attributed to use of second-line antibiotics were obtained. Projected cost of preoperative penicillin allergy testing and potentially avoidable PJI associated with second-line antibiotic usage were calculated. This was compared with projected cost of PJI in the current state to estimate cost savings.

**Results:** Implementation of preoperative penicillin allergy testing leads to a potential savings of nearly \$37 million to payors in the first year based on 1-year survivorship. This savings increases to \$411.6 million over a 10-year span and \$1.18 billion over a 20-year span.

**Conclusion:** Preoperative penicillin allergy testing or risk stratification via thorough history should be implemented as standard of care for patients with self-reported penicillin allergies before TJA and would result in decreased cost of PJI.

© 2021 Elsevier Inc. All rights reserved.

The standard perioperative antibiotics for total joint arthroplasty (TJA) are first-generation cephalosporins due to their broad-spectrum coverage and limited side effect profile [1]. However, penicillin allergy is a common self-reported allergy in the United States, with over 10% of patients indicating a previous adverse reaction [2]. History of a penicillin allergy will often result in treatment modification to avoid serious adverse reactions, such as precluding the usage of cephalosporins secondary to potential cross-reactivity between these two classes of antibiotics [3]. Blumenthal et al. demonstrated patients with self-reported penicillin allergies were administered clindamycin (49%) and vancomycin (35%) at a much higher rate than cefazolin (12%) to avoid adverse

allergic reactions [4]. However, with second-line antibiotics, prosthetic joint infections (PJIs) become more prevalent and can be between 32%–50% more likely [1,4]. In addition, a study evaluating cefazolin use in non-IgE-mediated penicillin allergies reported no adverse reactions to cefazolin. Although most self-reported penicillin allergies are non-IgE mediated, fewer patients still receive cefazolin (27%) regardless of documentation of adverse reaction to beta-lactam antibiotics in contrast to 93% of patients who receive cefazolin when there is no history of adverse reaction to penicillin antibiotics [5].

PJIs are not only a health burden to the patient, but also a significant financial burden to payors. TJA complicated by PJI and subsequent revision can cost up to \$93,000 with an average cost of \$43,900 per infection, including up to three additional surgeries [6,7]. PJI can also extend the average length of hospital stay by 4.9 to 5.2 days [8,9].

Preoperative allergy testing for penicillin allergy is not routinely performed, and there is no currently available test for cephalosporin allergy in the United States. For patients who self-report

No author associated with this paper has disclosed any potential or pertinent conflicts which may be perceived to have impending conflict with this work. For full disclosure statements refer to [doi:10.1016/j.arth.2021.04.032](https://doi.org/10.1016/j.arth.2021.04.032).

\* Address correspondence to: William F. Sherman, MD, MBA, 1430 Tulane Avenue, New Orleans, LA 70112.

**Table 1**

Summary of Studies Used to Identify Costs of Total Knee and Total Hip Arthroplasty, Including Associated Complication Costs.

| Paper                      | Primary (\$) | PJI Complication (\$) |
|----------------------------|--------------|-----------------------|
| Chin et al [6]             | THA: 29,987  | THA: 44,025           |
| Kurtz et al [14]           | THA: 30,300  | THA: 93,600           |
|                            | TKA: 24,200  | TKA: 74,900           |
| Lethbridge et al [15]      | TKA: 3685    | TKA: 29,965           |
| Maradit Kremers et al [16] | TKA: 17,662  | TKA: 24,314           |
| Stambough et al [7]        | TJA: 9500    | TJA: 43,900           |

penicillin allergies, surgeons typically rely on second-line antibiotics to mitigate the risk of potential anaphylactic reactions. Pagani recently demonstrated that routine penicillin allergy testing is cost-effective in a break-even model, however, the economic impact of self-reported penicillin allergies on TJA is not well-studied [10]. This study aims to identify the economic impact of a self-reported penicillin allergy in TJA by determining the potential savings generated from preoperative penicillin allergy testing and subsequent increased usage of cephalosporins.

## Methods

Three databases were used (PubMed, EBSCO, and Embase) to search for studies reporting the incidence of true IgE-mediated penicillin allergies [2,11,12], PJIs resulting from perioperative antibiotics used in TJA [1,4,5,13], and cost of both uninfected and infected TJA using the current 2020 nominal dollar value [6,7,14–16]. Twelve studies met the inclusion criteria for at least one of the above parameters and were incorporated into this review. The potential cost savings in TJA was estimated by modeling the cost of care for patients to be clinically cleared of penicillin allergy via preoperative allergy testing and subsequently administered cephalosporins against the estimated cost of PJI associated with second-line antibiotics in patients with a self-reported penicillin allergy. No funding was obtained for this study from the commercial, government, or nonprofit sectors.

The cost of a primary TJA and the cost of a TJA with PJI complication were calculated by averaging the data across studies.6, 7, 14–16 This resulted in a \$13,762 average cost of an uninfected TKA vs \$43,270 for a TKA with a PJI. Similarly, this resulted in a \$23,262 average cost of an uninfected THA vs \$60,508 for a THA with a PJI (Tables 1 and 2). The average cost of PJI ( $\bar{P}PJI$ ) in total joint arthroplasty was calculated by taking the weighted average of infected TKA and infected THA in a 2:1 ratio (2 TKA:1 THA) due to the ratio estimation by Singh et al demonstrating twice as many TKAs projected in years 2020–2040 (Tables 2 and 3).16, 17 The rate of self-reported PCN allergy was set at 10%, and the rate of true PCN allergy was established as 1% (Table 4).2, 11, 12 Using infection-free survivorship percentages established by Wyles et al, the expected infection rate for both 1- and 10-year survivorship

**Table 2**

Analysis of Average Cost of Uninfected Versus Infected Total Joint Arthroplasty [6,7,14–16].

| Infection Status                                   | TKA Average Cost | THA Average Cost | TJA Average Cost <sup>a</sup> |
|----------------------------------------------------|------------------|------------------|-------------------------------|
| Total joint arthroplasty: uninfected [ $P_0$ ]     | \$13,762         | \$23,262         | \$18,512                      |
| Total joint arthroplasty: infected (PJI) [ $P_1$ ] | \$43,270         | \$60,508         | \$49,016                      |

<sup>a</sup> TJA = 2\*TKA average cost + THA average cost accounting for double the frequency of TKA procedures versus THA procedures.

**Table 3**

Polynomial Regression Adjusted for Overdispersion to Predict Number of Total Joint Arthroplasties 2020–2040<sup>a</sup>.

| Year | Predicted Number TKA (% Increase) | Predicted Number THA (% Increase) | Total Predicted Number of TJA |
|------|-----------------------------------|-----------------------------------|-------------------------------|
| 2020 | 1,065,000 (56%)                   | 498,000 (34%)                     | 1,563,000                     |
| 2025 | 1,272,000 (110%)                  | 652,000 (75%)                     | 1,924,000                     |
| 2030 | 1,921,000 (182%)                  | 850,000 (129%)                    | 2,771,000                     |
| 2040 | 3,416,000 (401%)                  | 1,429,000 (284%)                  | 4,845,000                     |

<sup>a</sup> Adapted from Singh et al (2019) [17].

cohorts was calculated for patients who were administered cefazolin, and those who were not by subtracting the infection-free survivorship percentages from 100 percent. The 10-year rates were divided by 10 to obtain an annual infection rate for 10-year survivorship (Table 5). Finally, although specific infection rates were chosen and held constant throughout the projections, these infection rates were validated with average infection rates for both TKA and THA across multiple studies to ensure they fell within commonly accepted parameters (Table 6) [13,18–25].

## Preoperative Penicillin Allergy Test

The skin pinprick test (b-\*SPT) was selected as the least invasive and most cost-effective modality of penicillin allergy testing posited by Souza-Pinto et al, ranging from \$33 to \$58 [26]. A range exists due to variations in cost of materials, personnel, and reimbursement by study. The low-end cost of \$33 was chosen as many self-reported penicillin allergies can be ruled out by taking a more extensive history alone [27]. The cost of SPT was multiplied by 10 percent of the projected number of TKA and THA patients, yielding the total cost of penicillin allergy testing per year. The total cost of SPT allergy testing ( $\bar{C}_{SPT}$ ) for the years 2020, 2025, 2030, and 2040 can be found in Table 7.

## Potential Annual Cost Savings 1-Year Survivorship Cohort

The total number of TJA projected by Singh et al for the year 2020 was multiplied by a 10% self-reported penicillin allergy rate to yield the number of patients with self-reported penicillin allergies in TJA for 2020 (Table 8, Item B). Ten percent of the self-reported penicillin allergy patients were presumed to have a true allergy, matching the reported 1% true penicillin allergy rate in the population. This number of patients was then multiplied by the 1.78% infection rate for noncefazolin use in the 1-year survivorship cohort to derive the number of patients with true penicillin allergy who develop PJI (Table 8, Item C) [1]. The remaining 90% of self-reported penicillin allergy patients was presumed to be cleared of penicillin allergy through testing and subsequently given cefazolin. This number of patients was multiplied by the 1.17% cefazolin infection rate to derive the number of patients cleared of penicillin allergy who still develop PJI in the 1-year survivorship cohort (Table 8, Item D) [1]. The total number of patients who self-report a penicillin allergy and develop a PJI, regardless of cefazolin or noncefazolin administration, was the sum of Items C and D (Table 8, Item E) and that number was multiplied by the average cost of PJI ( $\bar{P}PJI$ ) to

**Table 4**

Summary of Studies Used to Identify Percentage of True Penicillin Allergy.

| Paper               | PCN-Reported Allergy | Rate of True Allergy |
|---------------------|----------------------|----------------------|
| Kufel et al [2]     | 10%                  | 1%                   |
| Stone et al [11]    | 10%–20%              | 1%–3%                |
| Trubiano et al [12] | 10%                  | <1%                  |

**Table 5**

Infection-Free Survivorship and Expected Infection Rate by Perioperative Antibiotics in Total Joint Arthroplasty.

| Perioperative Antibiotic | Infection-Free Survival (%) <sup>a</sup> |       | Expected Infection Rate (%) |       | Expected Infection Rate Per Year for 10-Y Survivorship (%) |
|--------------------------|------------------------------------------|-------|-----------------------------|-------|------------------------------------------------------------|
|                          | 1 y.                                     | 10 y. | 1 y.                        | 10 y. |                                                            |
| Cefazolin                | 98.83                                    | 98.15 | 1.17                        | 1.85  | 0.185 ( $r_1$ )                                            |
| Noncefazolin             | 98.22                                    | 96.96 | 1.78                        | 3.04  | 0.304 ( $r_2$ )                                            |

<sup>a</sup> Infection-free survivorship rates as reported by Wyles et al. [1].

obtain the total cost of PJI in patients after implementation of SPT (Table 7, Item F). Subsequently, this number was added to the total cost of SPT for this group ( $\bar{C}_{SPT}$ ) (Table 8, Item G) based on testing all patients undergoing TJA who self-report a penicillin allergy (Table 8, Item H). The cost of PJI without SPT of the self-reported penicillin allergy population was obtained by multiplying the total predicted number of TJA patients who self-report a penicillin allergy with the 1.78% noncefazolin infection rate and then multiplying by the average cost of PJI ( $\bar{P}_{PJI}$ ) (Table 8, Item I). Total cost of SPT for all self-reporting patients and their PJIs after implementing testing (Item H) was subtracted from total cost of PJIs in self-reporting patients without testing (Table 8, Item I) to calculate the cost savings generated by implementing SPT ( $\bar{S}$ ) (Table 8, Item J). This same calculation was used for the 1-year survivorship cohorts of years 2025, 2030, and 2040 to calculate the potential cost savings with the administration of the SPT allergy test using each year's respective predicted volume of TJA (Table 8).

#### Potential Cost Savings 10-Year Survivorship Cohort, 2020-2030

The 10-year survivorship infection rates were applied to a 10-year population of all TJA patients from 2020 to 2030. For the 2020 cohort of TJA patients, there is no way to predict their infection rate past 10 years when using a 10-year survivorship rate. The 1-year potential cost savings calculation (Table 8) was repeated for the 10-year survivorship cohorts using projected numbers of TJAs in 2020, 2025, and 2030 (Table 9). The infection rate applied was derived from the 10-year survivorship rate yielding an annual rate of 0.185% ( $r_1$ ) and 0.304% ( $r_2$ ) for cefazolin and noncefazolin usage from Table 5.

Starting with the 2020 cohort and following through to the 2030 cohort, the calculation method described for Table 9 was used to calculate savings each year. Each individual year's TJA population was followed annually through 2030. For the years 2020-2024, the 2020 total predicted number of TJA was used. For the years 2025-2029, the 2025 total predicted number of TJA was used. For the 2020 group of patients, the number of patients who developed PJI

**Table 6**

Summary of Studies to Validate Average Infection Rate in Total Joint Arthroplasty.

| Published Study       | Reported Infection Rate in TJA |
|-----------------------|--------------------------------|
| Kapadia et al [18]    | 0.9%-2.5% (THA)                |
| Kurtz et al [14]      | 0.92% (TKA)                    |
|                       | 0.88% (THA)                    |
| Inabathula et al [19] | 1.0% (TKA)                     |
|                       | 2.2% (THA)                     |
| Dobson et al [20]     | 0.2%-2.2% (THA)                |
|                       | 0.3%-1.9% (TKA)                |
| Blanco et al [21]     | 0.72% (TKA) [22]               |
|                       | 0.26%-0.65% (TKA) [23]         |
|                       | 0.76% (TKA) [24]               |
| Phillips et al [25]   | 0.57% (THA)                    |
|                       | 0.85% (TKA)                    |

**Table 7**Total Cost of SPT Allergy Testing ( $\bar{C}_{SPT}$ ) Based on Predicted TJA Volume per Year.

| Cohort/Year | Total Cost of SPT Allergy Testing ( $\bar{C}_{SPT}$ ) |
|-------------|-------------------------------------------------------|
| 2020        | \$5,157,900                                           |
| 2025        | \$6,349,200                                           |
| 2030        | \$9,144,300                                           |
| 2040        | \$15,988,500                                          |

that year was subtracted from the number of 2020 patients to calculate the 2020 cohort's population size for 2021. The annual rates of infection were then applied to derive the annual savings for 2021. This was repeated for 2022 and so forth until 2030. The cost of SPT was applied in the first year of each cohort, ie, SPT calculated as an expense only in 2020 for the 2020 cohort of patients. The cost of PJI with implementing SPT was subtracted from the cost of PJI without implementing SPT to yield the annual cost savings of that individual year. For the 2020 cohort, the annual cost savings for

**Table 8**

Cost Savings for 1-Y Survivorship Rates.

| Variable                                                                                                                   | 2020          | 2025          | 2030          | 2040          |
|----------------------------------------------------------------------------------------------------------------------------|---------------|---------------|---------------|---------------|
| Total predicted number of TJA [A]                                                                                          | 1,563,000     | 1,924,000     | 2,771,000     | 4,845,000     |
| Total predicted number of TJA with self-reported penicillin allergy [10% * A] = B                                          | 156,300       | 192,400       | 277,100       | 484,500       |
| Number of self-reported penicillin allergy patients with true penicillin allergy who develop PJI [10% * B] * 1.78% = C     | 279           | 343           | 494           | 863           |
| Number of self-reported penicillin allergy patients cleared by allergy testing who still develop PJI [90% * B] * 1.17% = D | 1646          | 2026          | 2918          | 5102          |
| Total number of patients who develop PJI with penicillin allergy testing C + D = E                                         | 1925          | 2369          | 3412          | 5965          |
| Cost of PJI regardless of cefazolin or noncefazolin administration [E * $\bar{P}_{PJI}$ ] = F                              | \$94,309,382  | \$116,091,651 | \$9,144,300   | \$15,988,500  |
| Cost of SPT allergy testing ( $\bar{C}_{SPT}$ ) * B = G                                                                    | \$5,157,900   | \$6,349,200   | \$9,144,300   | \$15,988,500  |
| Total cost of PJI in patients who self-report penicillin allergy and SPT testing F + G = H                                 | \$99,461,282  | \$122,440,851 | \$176,342,827 | \$308,329,482 |
| Expected cost of PJI in self-reported penicillin allergy patients without SPTB * 1.78% * $\bar{P}_{PJI}$ = I               | \$136,369,375 | \$167,866,076 | \$241,765,538 | \$422,718,886 |
| Cost savings with SPT allergy testing implementation ( $\bar{S}$ ) I - H = J                                               | \$36,902,092  | \$45,425,224  | \$65,422,711  | \$114,389,403 |

**Table 9**  
Cost Savings for 10-Y Survivorship Rates.

| Variable                                                                                                                     | 2020         | 2025         | 2030         |
|------------------------------------------------------------------------------------------------------------------------------|--------------|--------------|--------------|
| Total predicted number of TJA with self-reported penicillin allergy [B]                                                      | 156,300      | 192,400      | 277,100      |
| Number of self-reported penicillin allergy patients with true penicillin allergy who develop PJI [10% *B]<br>* $r_2 = K$     | 48           | 59           | 85           |
| Number of self-reported penicillin allergy patients cleared by allergy testing who still develop PJI [90% *B]<br>* $r_1 = L$ | 261          | 320          | 461          |
| Total number of patients who develop PJI with penicillin allergy testing K + L = M                                           | 309          | 379          | 546          |
| Cost of PJI regardless of cefazolin or noncefazolin administration M * $\bar{P}_{PJI} = N$                                   | \$15,084,904 | \$18,547,094 | \$26,716,643 |
| Cost of SPT allergy testing ( $\bar{C}_{SPT}$ ) [G]                                                                          | \$5,157,900  | \$6,349,200  | \$9,144,300  |
| Total cost of PJI in patients who self-report penicillin allergy and SPT testing N + G = O                                   | \$20,242,804 | \$24,891,226 | \$35,861,814 |
| Number of patients who self-report penicillin allergy and develop PJI without SPT allergy testing [B * $r_2$ ] = P           | 476          | 584          | 841          |
| Expected cost of PJI in self-reported penicillin allergy patients without SPT P * $\bar{P}_{PJI} = Q$                        | \$23,290,050 | \$28,598,675 | \$41,203,404 |

2020–2030 were summed to derive the total cost savings for this cohort. The 2021 cohort savings was calculated the same way by summing 2021–2030 annual savings. The 2030 cohort savings were calculated for that year only. The total cost savings for each individual cohort from 2020 to 2030 were then summed (Table 10).

#### 10-Year Analysis of Administration of Preoperative Penicillin Allergy Testing in TJA

The total cost savings from 2020 to 2030 due to implementation of SPT based on 1-year survivorship was calculated using the following formula:

$$5 * (\hat{S})_{2020} + 5 * (\hat{S})_{2025}$$

The total cost savings from 2020 to 2030 due to implementation of SPT based on 10-year survivorship were calculated by adding the total cost savings for each individual cohort over the span of 10 years.

$$(\hat{S})_{2020} + (\hat{S})_{2021} + (\hat{S})_{2022} + \dots + (\hat{S})_{2030}$$

#### 20-Year Analysis of Administration of Preoperative Penicillin Allergy Testing in TKA and THA

The total cost savings from 2020 to 2040 due to implementation of SPT based on 1-year survivorship was calculated using the following formula:

$$5 * (\hat{S}_{2020}) + 5 * (\hat{S}_{2025}) + 10 * (\hat{S}_{2030}) + (\hat{S})_{2040}$$

**Table 10**  
Aggregate Cost Savings Over 10 Year-Span Using 10-Y Survivorship Rates.

| Cohort | Year Range | Cost Savings  |
|--------|------------|---------------|
| 2020   | 2020–2030  | \$100,369,768 |
| 2021   | 2021–2030  | \$92,166,745  |
| 2022   | 2022–2030  | \$84,011,162  |
| 2023   | 2023–2030  | \$75,854,692  |
| 2024   | 2024–2030  | \$67,698,222  |
| 2025   | 2025–2030  | \$58,350,452  |
| 2026   | 2026–2030  | \$48,298,871  |
| 2027   | 2027–2030  | \$38,258,575  |
| 2028   | 2028–2030  | \$28,218,237  |
| 2029   | 2029–2030  | \$18,177,899  |
| 2030   | 2030       | \$5,341,589   |
|        |            | \$616,746,211 |

## Results

The total cost of SPT over a 20-year period (2020–2040) was estimated at \$165 million, or approximately \$8.2 million per year. An annual cost savings of nearly \$37.0 million in 2020, \$45.4 million in 2025, \$65.4 million in year 2030, and \$114.4 million in year 2040 were projected with implementation of preoperative penicillin allergy testing before TJA using 1-year infection-free survivorship rates. Based on the 1-year survivorship rates, the summative cost savings over a 10-year span (2020–2030) amounts to \$411.6 million, whereas the cost savings over a 20-year span (2020–2040) exceeds \$1.18 billion. Using the 10-year infection-free survivorship rates, it is not possible to calculate the summative cost savings beyond a 10-year span. Based on 10-year survivorship rates, the summative cost savings for 2020–2030 amount to \$616.7 million. As the 10-year survivorship data are more accurate as it includes patients who become infected after 1 year, this implies the 20-year cost savings (\$1.18 billion) is an underestimate. These totals are summarized in Table 11.

## Discussion

The health care cost of a single PJI was calculated to be \$30,500 and does not take into account the patient's lost wages or productivity [6–8,16]. Although up to 10% of patients self-report a penicillin allergy, clinically significant IgE-mediated or T lymphocyte-mediated penicillin hypersensitivity is uncommon (1 to <5%) [28]. Of the penicillin allergy testing modalities available, SPT has been shown to allow patients to receive cefazolin with minimal severe adverse effects [2,12]. Furthermore, Trubiano suggests as the immune system matures over a 10-year period, penicillin sensitivity may no longer be present with many previously penicillin-sensitive patients displaying a negative SPT [12]. In addition, other studies suggest IgE-mediated penicillin allergy wanes over time, with 80% of patients becoming tolerant after a decade [12,28]. Therefore, patients with self-reported penicillin allergy should participate in preoperative allergy testing or thorough history taking to verify accuracy and continued existence of the diagnosis and to ensure usage of preferred antibiotics when possible [12,28]. Pagani et al found that testing 123 TKA and 153 THA patients would make preoperative penicillin allergy testing a cost-effective infection prevention strategy [10].

Without preoperative allergy testing, the increased PJI in a 1-year survivorship cohort correlates with an additional expenditure of \$36.9 million in 2020 alone. Using the same 1-year survivorship rate, cost savings of \$411.6 million are projected over the 10-year period of 2020–2030. The cost savings nearly triples to

**Table 11**

Summary Table of Total Cost Savings Over 10-Y and 20-Y Span.

|                                                                           |                 |
|---------------------------------------------------------------------------|-----------------|
| Total cost savings in 2020 based on 1-y survivorship rates                | \$36,902,093    |
| Total cost savings over 10 y (2020–2030) based on 1-y survivorship rates  | \$411,636,584   |
| Total cost savings over 10 y (2020–2030) based on 10-y survivorship rates | \$616,746,211   |
| Total cost savings over 20 y (2020–2040) based on 1-y survivorship rates  | \$1,180,253,102 |

\$1.18 billion over the 20-year period of 2020–2040 due to the increasing volume of TJA. The 10-year survivorship rate takes into account the additional patients who are diagnosed with PJI after year one until year 10, thus that rate is more accurate for longer term projections. Using the 10-year survivorship rate, cost savings of \$616.7 million are projected for 2020–2030. Although it is not possible to calculate a 20-year savings from a 10-year survivorship rate, the discrepancy between the 10-year cost savings using 1-year and 10-year survivorship rates implies that the 20-year cost savings of \$1.18 billion using 1-year survivorship rates are likely a notable underestimate.

Furthermore, Helwig et al. demonstrated patients developing infection after TJA suffer from significantly reduced quality of life regardless of the successful treatment or revision of the prosthetic joint [29]. Noncefazolin use in TJA correlates with 4.9 to 5.2 more days in the hospital [8] and potential multiple revision surgeries for the infected joint [7]. Beyond the financial burden alleviated from the health care system by preoperative allergy testing, the potential of improved quality of life by reduction of infections is also supported by this analysis.

The modeling projections for this study have several limitations. First, the data and presumptions used to calculate savings were based on research and information from the United States and cannot be directly applied to other countries given variation in prophylactic antibiotic usage, surgical volume, and costs. Second, the extrapolation of data is reliant on the trends for TJA volume after the polynomial regression statistical prediction for the increase in total procedures from 2020 to 2040. In addition, penicillin-specific testing is not cephalosporin-specific, and therefore not directly for the preferred antibiotic used in TJA. A more precise allergy test for cephalosporin sensitivity would allow for more accurate calculation of subsequent cefazolin tolerance and usage [30]. In some instances, clinical history is sufficient to negate the need for SPT and therefore the \$33 cost per self-reporting patient used in this calculation may be an overestimate of allergy testing cost [31]. The SPT was chosen as the testing modality because of its lower cost and high clearance rate (97%), as well as obviating a formal allergist consultation as it can be administered and read in a preoperative setting. While Sousa-Pinto et al. reference a minimum cost of \$33 for SPT, it can vary depending on cost of personnel as well as access to testing material [4]. Another limitation is that several values were held constant over the projected 10- and 20-year spans. Cost of TJA, PJI, and SPT was all held at the currently available averages or estimates throughout the calculations. In addition, patients with true penicillin allergy were assumed to be entirely contained within the self-reporting allergy patient group. Patients with a true penicillin allergy who were unaware until the time of surgery and the cost of any PJI arising from that population is not included. Although this model used Wyles et al.'s survivorship rates, there are mixed data regarding the true increase in risk attributed to alternate use antibiotics as prophylaxis [11] and potential intrinsic increase in infection rate seen with a self-reported penicillin allergy [32]. Finally, although it was assumed the discrepancy of PJI rates after TJA between patients given cefazolin vs those not given cefazolin could be completely

eliminated by switching to cefazolin usage, the variable PJI risk at the individual patient level and other unknown factors could be present [15].

The direct economic impact of PJI in the self-reporting penicillin allergy population was examined as a health care cost. The economic impact of lost wages, quality-adjusted life years, inflation, and discount rates was not included. These variable costs warrant further exploration into the potential impact of optimizing perioperative antibiotics in TJA. Although there is a trend to encourage delabeling of penicillin allergy, it can remain challenging to do so [33]. Perhaps instead, labeling patients who complete a thorough history and/or SPT and tolerate the subsequent index surgical exposure to a cephalosporin as “cephalosporin tolerant” would be beneficial for future health care needs and cost.

## Conclusion

These projections suggest preoperative allergy testing or thorough history taking should be implemented as a standard of care for patients with self-reported penicillin allergies to ensure the best and most cost-effective care available. Without implementation of these strategies, conservative modeling suggests the economic impact is \$616.7 million increased expenditure over the next decade and upward of \$1.18 billion increased expenditure over the next 20 years.

## References

- [1] Wyles CC, Hevesi M, Osmon DR. 2019 John Charnley Award: increased risk of prosthetic joint infection following primary total knee and hip arthroplasty with the use of alternative antibiotics to cefazolin: the value of allergy testing for antibiotic prophylaxis. *Bone Joint J* 2019;101-B:9–15. <https://doi.org/10.1302/0301-620X.101B6.BJJ-2018-1407.R1>.
- [2] Kufel WD, Justo JA, Bookstaver PB. Penicillin allergy assessment and skin testing in the outpatient setting. *Pharmacy (Basel)* 2019;7. <https://doi.org/10.3390/pharmacy7030136>.
- [3] Miranda A, Blanca M, Vega JM. Cross-reactivity between a penicillin and a cephalosporin with the same side chain. *J Allergy Clin Immunol* 1996;98: 671–7. [https://doi.org/10.1016/s0091-6749\(96\)70101-x](https://doi.org/10.1016/s0091-6749(96)70101-x).
- [4] Blumenthal KG, Li Y, Banerji A. The cost of penicillin allergy evaluation. *J Allergy Clin Immunol Pract* 2018;6:1019–27. <https://doi.org/10.1016/j.jaip.2017.08.006>.
- [5] Haslam S, Yen D, Dvirnik N. Cefazolin use in patients who report a non-IgE mediated penicillin allergy: a retrospective look at adverse reactions in arthroplasty. *Iowa Orthop J* 2012;32:100–3.
- [6] Chin G, Wright DJ, Snir N. Primary vs conversion total hip arthroplasty: a cost analysis. *J Arthroplasty* 2016;31:362–7. <https://doi.org/10.1016/j.arth.2015.08.014>.
- [7] Stambough JB, Nam D, Warren DK. Corrigendum to “decreased hospital costs and surgical site infection incidence with a universal decolonization protocol in primary total joint arthroplasty. *J Arthroplasty* 2017;32:728–34. <https://doi.org/10.1016/j.arth.2017.04.008>.
- [8] Adeyemi A, Trueman P. Economic burden of surgical site infections within the episode of care following joint replacement. *J Orthop Surg Res* 2019;14:196. <https://doi.org/10.1186/s13018-019-1224-8>.
- [9] Macy E. Elective penicillin skin testing and amoxicillin challenge: effect on outpatient antibiotic use, cost, and clinical outcomes. *J Allergy Clin Immunol* 1998;102:281–5. [https://doi.org/10.1016/s0091-6749\(98\)70097-1](https://doi.org/10.1016/s0091-6749(98)70097-1).
- [10] Pagani NR, Moverman MA, Puzitiello RN. Preoperative allergy testing for patients reporting penicillin and cephalosporin allergies is cost-effective in preventing infection after total knee and hip arthroplasty. *J Arthroplasty* 2021;36:700–4. <https://doi.org/10.1016/j.arth.2020.08.045>.
- [11] Stone AH, Kelmer G, MacDonald JH. The impact of patient-reported penicillin allergy on risk for surgical site infection in total joint arthroplasty. *J Am Acad Orthop Surg* 2019;27:854–60. <https://doi.org/10.5435/JAAOS-D-18-00709>.
- [12] Trubiano JA, Adkinson NF, Phillips EJ. Penicillin allergy is not necessarily forever. *JAMA* 2017;318:82–3. <https://doi.org/10.1001/jama.2017.6510>.
- [13] Blumenthal KG, Shenoy ES, Huang M. The impact of reporting a prior penicillin allergy on the treatment of methicillin-sensitive *Staphylococcus aureus* bacteremia. *PLoS One* 2016;11:e0159406. <https://doi.org/10.1371/journal.pone.0159406>.
- [14] Kurtz SM, Lau E, Watson H. Economic burden of periprosthetic joint infection in the United States. *J Arthroplasty* 2012;27:61–5. <https://doi.org/10.1016/j.arth.2012.02.022>.

- [15] Lethbridge LN, Richardson CG, Dunbar MJ. Total cost of surgical site infection in the two years following primary knee replacement surgery. *Infect Control Hosp Epidemiol* 2020;41:938–42. <https://doi.org/10.1017/ice.2020.198>.
- [16] Maradit Kremers H, Visscher SL, Moriarty JP. Determinants of direct medical costs in primary and revision total knee arthroplasty. *Clin Orthop Relat Res* 2013;471:206–14. <https://doi.org/10.1007/s11999-012-2508-z>.
- [17] Singh JA, Yu S, Chen L. Rates of total joint replacement in the United States: future projections to 2020–2040 using the national inpatient sample. *J Rheumatol* 2019;46:1134–40. <https://doi.org/10.3899/jrheum.170990>.
- [18] Kapadia BH, Banerjee S, Cherian JJ. The economic impact of periprosthetic infections after total hip arthroplasty at a specialized tertiary-care center. *J Arthroplasty* 2016;31:1422–6. <https://doi.org/10.1016/j.arth.2016.01.021>.
- [19] Inabathula A, Dilley JE, Ziemba-Davis M. Extended oral antibiotic prophylaxis in high-risk patients substantially reduces primary total hip and knee arthroplasty 90-day infection rate. *J Bone Joint Surg Am* 2018;100:2103–9. <https://doi.org/10.2106/JBJS.17.01485>.
- [20] Dobson PF, Reed MR. Prevention of infection in primary THA and TKA. *EFORT Open Rev* 2020;5:604–13. <https://doi.org/10.1302/2058-5241.5.200004>.
- [21] Blanco JF, Diaz A, Melchor FR. Risk factors for periprosthetic joint infection after total knee arthroplasty. *Arch Orthop Trauma Surg* 2020;140:239–45. <https://doi.org/10.1007/s00402-019-03304-6>.
- [22] Namba RS, Inacio MC, Paxton EW. Risk factors associated with deep surgical site infections after primary total knee arthroplasty: an analysis of 56,216 knees. *J Bone Joint Surg Am* 2013;95:775–82. <https://doi.org/10.2106/JBJS.L.00211>.
- [23] Poultsides LA, Triantafyllopoulos GK, Sakellariou VI. Infection risk assessment in patients undergoing primary total knee arthroplasty. *Int Orthop* 2018;42: 87–94. <https://doi.org/10.1007/s00264-017-3675-z>.
- [24] Crowe B, Payne A, Evangelista PJ. Risk factors for infection following total knee arthroplasty: a series of 3836 cases from one institution. *J Arthroplasty* 2015;30:2275–8. <https://doi.org/10.1016/j.arth.2015.06.058>.
- [25] Phillips JE, Crane TP, Noy M. The incidence of deep prosthetic infections in a specialist orthopaedic hospital: a 15-year prospective survey. *J Bone Joint Surg Br* 2006;88:943–8. <https://doi.org/10.1302/0301-620x.88b7.17150>.
- [26] Sousa-Pinto B, Blumenthal KG, Macy E. Diagnostic testing for penicillin allergy: a survey of practices and cost perceptions. *Allergy* 2020;75:436–41. <https://doi.org/10.1111/all.13951>.
- [27] Wada KJ, Calhoun KH. US antibiotic stewardship and penicillin allergy. *Curr Opin Otolaryngol Head Neck Surg* 2017;25:252–4. <https://doi.org/10.1097/moo.0000000000000364>.
- [28] Shenoy ES, Macy E, Rowe T. Evaluation and management of penicillin allergy: a review. *JAMA* 2019;321:188–99. <https://doi.org/10.1001/jama.2018.19283>.
- [29] Helwig P, Morlock J, Oberst M. Periprosthetic joint infection—effect on quality of life. *Int Orthop* 2014;38:1077–81. <https://doi.org/10.1007/s00264-013-2265-y>.
- [30] Romano A, Gaeta F, Valluzzi RL. IgE-mediated hypersensitivity to cephalosporins: cross-reactivity and tolerability of alternative cephalosporins. *J Allergy Clin Immunol* 2015;136:685–91. <https://doi.org/10.1016/j.jaci.2015.03.012>.
- [31] Banks TA, Tucker M, Macy E. Evaluating penicillin allergies without skin testing. *Curr Allergy Asthma Rep* 2019;19:27. <https://doi.org/10.1007/s11882-019-0854-6>.
- [32] Wu VJ, Iloanya MC, Sanchez FL. Is patient-reported penicillin allergy independently associated with increased risk of prosthetic joint infection after total joint arthroplasty of the hip, knee, and shoulder? *Clin Orthop Relat Res* 2020;478:2699–709. <https://doi.org/10.1097/corr.0000000000001497>.
- [33] Stone Jr CA, Trubiano J, Coleman DT. The challenge of de-labeling penicillin allergy. *Allergy* 2020;75:273–88. <https://doi.org/10.1111/all.13848>.