Cost-effectiveness of dental antibiotic prophylaxis in total knee arthroplasty recipients with type II diabetes mellitus

Elizabeth E. Stanley, Taylor P. Trentadue, Karen C. Smith, James K. Sullivan, Thomas S. Thornhill, Jeffrey Lange, Jeffrey N. Katz, Elena Losina

ABSTRACT

Objective: Type II diabetes mellitus (T2DM) is prevalent in knee osteoarthritis (OA) patients undergoing total knee arthroplasty (TKA) and increases risk for prosthetic joint infection (PJI). We examined the cost-effectiveness of antibiotic prophylaxis (AP) before dental procedures to reduce PJI in TKA recipients with T2DM.

Design: We used the Osteoarthritis Policy Model, a validated computer simulation of knee OA, to compare two strategies among TKA recipients with T2DM (mean age 68 years, mean BMI 35.4 kg/m²): 1) AP before dental procedures and 2) no AP. Outcomes included quality-adjusted life expectancy (QALE) and lifetime medical costs. We used published efficacy of AP. We report incremental cost-effectiveness ratios (ICERs) and considered strategies with ICERs below well-accepted willingness-to-pay (WTP) thresholds cost-effective. We conducted sensitivity analyses to examine the robustness of findings to uncertainty in model input parameters. We used a lifetime horizon and healthcare sector perspective.

Results: We found that AP added 1.0 quality-adjusted life-year (QALY) and $66,000 for every 1000 TKA recipients with T2DM, resulting in an ICER of $66,000/QALY. In sensitivity analyses, reduction of the probability of PJI, T2DM-associated risk of infection, or attribution of infections to dental procedures by 50% resulted in ICERs exceeding $100,000/QALY. Probabilistic sensitivity analyses showed that AP was cost-effective in 32% and 58% of scenarios at WTP of $50,000/QALY and $100,000/QALY, respectively.

Conclusions: AP prior to dental procedures is cost-effective for TKA recipients with T2DM. However, the cost-effectiveness of AP depends on the risk of PJI and efficacy of AP in this population.

1. Introduction

Prosthetic joint infection (PJI) following total knee arthroplasty (TKA) is costly and carries high risks of morbidity and mortality [1–4]. PJIs may develop at various timepoints following TKA [1,4–7]. While early PJIs are often caused by perioperatively-seeded bacteria, late-onset PJIs are commonly attributed to hematogenous seeding [1,5–7]. Dental procedures create transient bacteremia, which can lead to hematogenous bacterial seeding and PJIs in TKA recipients [8–11]. To reduce the prevalence of PJIs, both the American Academy of Orthopaedic Surgeons (AAOS) and American Dental Association (ADA) previously recommended that all TKA recipients use antibiotic prophylaxis prior to dental procedures for two years post-surgery [12]. However, this practice remains controversial, as its efficacy is inconclusive [10,13–16]. The AAOS currently recommends antibiotic prophylaxis prior to invasive dental procedures, including those requiring the manipulation of gingival tissue or perforation of oral mucosa, for certain patients, including some with diabetes [17]. Diabetes mellitus increases likelihood of infections [1,
is considered a risk factor for PJIs [18,22], and is present in 10%-20% of TKA recipients [23,24]. Among total joint arthroplasty recipients, 92% of diabetic patients have type II diabetes [25]; as such, understanding the value of antibiotic prophylaxis for TKA recipients with type II diabetes has broad clinical implications. As dental-related PJI is an infrequent outcome of TKA, evaluating this question using a trial would be infeasible [26]; thus, computer simulation-based analysis can provide insight by using existing data to predict long-term outcomes.

Computer simulation has been used to evaluate pre-dental antibiotic prophylaxis among the general population of TKAs, to determine the incremental cost-effectiveness ratio (ICER) of dental antibiotic prophylaxis before invasive dental procedures was higher [27]. To our knowledge, there is no cost-effectiveness analysis of pre-dental antibiotic prophylaxis focused on TKA patients at increased risk of PJI, including those with type II diabetes. Therefore, we evaluated the cost-effectiveness of antibiotic prophylaxis before invasive dental procedures in TKA recipients with type II diabetes.

2. Materials and methods

2.1. Analytic overview

We used the validated Osteoarthritis Policy (OAPol) Model [28–33], a computer microsimulation of knee osteoarthritis (OA) natural history and treatments, to assess the cost-effectiveness of antibiotic prophylaxis before dental procedures in TKA recipients with type II diabetes. The primary outcome was the incremental cost-effectiveness ratio (ICER), the ratio of difference in costs to the difference in quality-adjusted life-years (QALYs) between strategies with and without pre-dental antibiotic prophylaxis. As there is no universally accepted threshold of willingness-to-pay for one QALY (i.e., the maximum expenditure to gain one QALY that represents good value), we considered a range of willingness-to-pay thresholds ($50,000 to $200,000), as recommended by the Second Panel on Cost-Effectiveness in Health and Medicine [34]. This range encompasses the historically-used threshold ($50,000/QALY), other thresholds recommended for the evaluation of treatment strategies by payors in the US healthcare system ($150,000/QALY and $200,000/QALY) [35]. We defined pre-dental antibiotic prophylaxis as cost-effective if the ICER was at or below a willingness-to-pay threshold and as cost-saving if costs were reduced and QALYs were increased compared to no pre-dental antibiotic use. Antibiotic prophylaxis was considered dominated if it increased costs and decreased QALYs. We discounted the costs, reported in 2017 US dollars (USD), and QALYs at 3% annually. We conducted analyses from the healthcare perspective and considered only the direct cost of medical care [34].

2.2. OAPol Model

The OAPol Model is a validated state-transition microsimulation model [28–33]. It uses Monte Carlo simulation to generate cohorts of hypothetical subjects with user-defined characteristics including demographics (age, sex, body mass index (BMI)) and clinical features, including comorbidities. The model tracks the annual progress of each hypothetical subject through transitions among different health states. Health states are defined based on the success or failure of primary or revision TKA, complications of TKA (including PJI), and antibiotic-related toxicities. Each state is associated with a cost and quality of life (QoL) utility, a value ranging from 0.0 (death) to 1.0 (perfect health) [36].

In the analysis, all subjects underwent primary TKA, which reduced subjects’ knee pain (Technical Appendix (TA), Section 2.2), at the beginning of the simulation. Subjects continued in the post-TKA state until they either died or received a revision TKA due to either prosthetic failure or PJI. Non-fatal PJIs were treated with a two-stage revision TKA, the procedure with the highest rate of long-term success in treating PJI [1]. Depending on the strategy, subjects either received or did not receive antibiotic prophylaxis prior to invasive dental procedures throughout their lifetime after TKA. Fig. 1 outlines patient flow in the model. Primary TKA, revision TKA, and pre-dental antibiotic prophylaxis were associated with the risk of adverse events; each of which carried event-specific costs, QoL decrements, and risk of mortality. In the perioperative period, TKA was associated with reduction in QoL due to post-surgical recovery and risks of myocardial infarction, pulmonary embolism, pneumonia, early PJI, or death.

2.3. Strategies

We considered two strategies following TKA: 1) no antibiotics prior to dental procedures and 2) lifetime antibiotic prophylaxis prior to all dental invasive procedures, such as those involving manipulation of gingival tissue or perforation of the oral mucosa. Following recommendations from the AAOS, pre-dental antibiotic prophylaxis was 2 g of generic amoxicillin [17]. Following administration of amoxicillin, subjects could experience minor reactions to antibiotics, non-fatal anaphylaxis, or fatal anaphylaxis (Fig. 1). If subjects experienced an antibiotic-related adverse event, they accumulated associated costs and decrements in QoL.

2.4. Model inputs

2.4.1. Cohort characteristics

All subjects were initialized at the time of TKA; demographic characteristics are presented in Table 1. As 92% of total joint arthroplasty recipients with diabetes have type II diabetes [25], we focused on type II diabetes in this analysis. We determined the age at TKA among patients with diabetes (mean (SD): 68.2 (9.5) years) from Partners HealthCare Research Patient Data Repository, a large database of patient records from a healthcare network in Massachusetts. We determined the BMI distribution among patients with type II diabetes from the literature (mean (SD): 35.4 (8.5) kg/m²) [37]. We assumed that subjects’ type II diabetes was treated with metformin. Based on prior literature, we estimated that those with type II diabetes had a 65.8% chance of visiting a dentist annually [38] and were 3.72 times more likely to develop PJIs than those without type II diabetes [18].

2.4.2. Quality of life

In the simulation, subjects were annually assigned a QoL utility based on age, obesity, knee pain, and number of comorbidities. We derived utilities from the Osteoarthritis Initiative (OAI) as described in previously published work [28–33,39].

2.4.3. PJI-related parameters

We assumed PJIs to fall into two categories: non-hematogenous infections caused by perioperatively-seeded bacteria, which only occurred in the first postoperative year, and hematogenous infections, which could occur in any year, including the year of surgery [1]. Using published data on the rate of PJI following TKA, as well as the prevalence of and odds (odds ratio, type II diabetes = 3.72 [18]) of PJI among those with comorbid conditions increasing PJI risk, we estimated the distribution of PJIs following TKA among those with type II diabetes (Table 1; TA Section 4.1.2). We estimated the attribution of hematogenous PJI to dental procedures (17%) using the percentage of late infections related to invasive dental procedures (11.3%) [40] and the annual probability of any dental visit (65.7%) [41] as a proxy for determining the probability...
of being at risk for dental infections (TA Section 4.1.2). We estimated that 0.82%, 0.024%, and 0.19% of TKA recipients with type II diabetes developed PJIs resulting from perioperatively-seeded bacteria, dental procedure, and other hematogenous sources, respectively (Table 1; TA Section 4.1.2). In the model, all PJIs were treated with a two-stage revision TKA because the two-stage revision TKA process delivers the highest possible infection cure rate [42].

2.4.4. Antibiotic efficacy

We estimated that amoxicillin prevents 63% of infections due to bacteremia introduced during dental procedures [43]. We varied this value in sensitivity analyses.

2.4.5. Adverse events

The risk of perioperative complication (myocardial infarction, pulmonary embolism, pneumonia, PJI, or death) following TKA ranged from 0.62% to 1.36% [44]. We assumed death due to surgery occurred 6 months postoperatively. These events carried costs between $10,322 and $48,928 [45–50]; subjects’ QoL in the year of complication (prior to death) was reduced between 9.7% and 14.6% compared to QoL in years without complications (Table 1) [39,51–55]. The derivation of complication-related QoL reductions for the OAPol Model are published elsewhere [31].

Antibiotic prophylaxis carried risks of minor gastrointestinal toxicities (nausea, vomiting, diarrhea), cutaneous reactions (angioedema, urticaria), nonfatal anaphylactic shock requiring hospitalization, and fatal anaphylaxis (Table 1) [27,56]. We estimated amoxicillin to carry a 2% chance of minor reaction (gastrointestinal, cutaneous) and a 0.006% chance of anaphylactic shock (fatal in 0.002% of case) [43,57–61]. We assumed that all subjects experiencing a minor antibiotic toxicity visited a healthcare practitioner and were treated for their symptoms. Table 1 outlines the treatment, cost (range: $39 to $13,212) and QoL reduction prior to death (range: 0.01%–9.3%) associated with each antibiotic-related toxicity. We assumed that subjects, while alive, would continue taking antibiotics, regardless of toxicity experienced. Following an antibiotic-related toxicity, we assumed that be prescribed another antibiotic, such as cephalexin, azithromycin, or clarithromycin [17]. We modeled that in this scenario, subjects would continue to experience similar reduced risk of PJI [62], risk of antibiotic-related adverse events, and cost of antibiotics, as experienced during amoxicillin use.

2.4.6. Treatment costs

The annual costs of metformin, amoxicillin, and treatments for minor antibiotic toxicities were derived from Red Book (Table 1; TA Sections 3, 5.3) [63,64].

Costs of primary TKA, revision due to prosthetic failure, and PJI treatment (hospital costs, physician fees, post-discharge rehabilitation), as well as postoperative follow-up (provider visits and radiographs) were $17,855, $24,992, $48,928, and $111, respectively (Table 1; TA Section 3) [45–50,65]. Although one-stage prosthesis exchange is a less-costly procedure, PJIs were treated with two-stage exchange, which carries a higher cure rate [1,42,66]. The cost of non-knee OA related care was stratified by age and number of comorbidities and has been detailed previously [32].

2.5. Sensitivity analyses

We performed deterministic sensitivity analyses to evaluate how variation in key parameters from base case values, described above, influenced results. We varied the following parameters from 50% to 200% of their base case values: underlying risk of PJI in the general population, increase in risk of developing infection due to type II
diabetes, percent of hematogenous infections attributable to dental procedures, and antibiotic efficacy. We created a tornado diagram depicting the range of ICERs generated by varying each one of these parameters.

We conducted a probabilistic sensitivity analysis to evaluate the impact of uncertainty in key parameters on results. We determined the ICER for 500 scenarios wherein the underlying risk of PJI in the general population, relative risk of infection due to diabetes, percent of hematogenous infections attributable to dental procedures, and antibiotic efficacy were independently drawn from distributions representing their uncertainty (TA, Section 6.2) and created a cost-effectiveness acceptability curve depicting the percent of scenarios in which each intervention was cost-effective over a range of willingness-to-pay thresholds.

3. Results
3.1. Base case

In the model simulations, antibiotic prophylaxis prior to dental
procedures prevented 293 infections over the lifetime of the 126,000 persons with type II diabetes that receive TKA annually in the US [24, 25, 45]. The prevention of infections resulted in a 1.0 quality-adjusted life-year increase per 1000 TKA recipients with DM. Pre-dental antibiotic prophylaxis was accompanied by an increase in lifetime medical costs, $66,000 per 1000 TKA recipients, leading to an incremental cost-effectiveness ratio (ICER) of $66,000/QALY (Table 2).

3.2. Sensitivity analyses

3.2.1. One-way sensitivity analyses

Fig. 2 depicts the results of varying key input parameters between 50% and 200% of base case values: each bar represents the range of ICERS corresponding to the range indicated on the vertical axis over which each parameter was varied.

A 50% decrease in the underlying risk of PJI in the general population resulted in an ICER of $890,200/QALY. A 50% decrease in the risk of PJI due to diabetes resulted in an ICER of $403,800/QALY. In these scenarios, no pre-dental antibiotic use was the preferred strategy from a cost-effectiveness perspective at all willingness-to-pay thresholds considered. A 50% decrease in the percent of hematogenous infections attributable to dental procedures resulted in an ICER of $116,200/QALY. In this scenario, pre-dental antibiotic prophylaxis was the preferred strategy at willingness-to-pay thresholds of $150,000/QALY or above. A 50% decrease in the efficacy of antibiotics resulted in an ICER of $75,100/QALY. In this scenario, pre-dental antibiotic prophylaxis was the preferred strategy from a cost-effectiveness perspective at willingness-to-pay thresholds of $100,000/QALY or above.

Doubling the risk of PJI in the general population resulted in an ICER of $6700/QALY for the pre-dental antibiotic prophylaxis strategy. Doubling the risk of PJI due to diabetes resulted in an ICER of $18,300/QALY for pre-dental antibiotic use. Increasing the efficacy of antibiotics by 50% resulted in an ICER of $30,900/QALY for pre-dental antibiotic use. Doubling the percent of hematogenous infections attributable to dental procedures resulted in an ICER of $6800/QALY for pre-dental antibiotic use. In these scenarios, pre-dental antibiotic prophylaxis was the preferred strategy at all willingness-to-pay thresholds considered.

3.2.2. Probabilistic sensitivity analysis

Results from the probabilistic sensitivity analysis—wherein we simultaneously varied the underlying risk of PJI in the general population, risk of PJI associated with diabetes, efficacy of antibiotics, and percent of hematogenous infections attributable to dental procedures—are presented in Fig. 3. At WTP thresholds of $50,000/QALY, $100,000/QALY, $150,000/QALY, and $200,000/QALY, pre-dental antibiotic prophylaxis was the cost-effective strategy in 32%, 58%, 69%, and 75% of scenarios, respectively. We found that 5% of scenarios were cost-savings, having ICERS below $0/QALY.

4. Discussion

We used the OApol Model to determine the cost-effectiveness of antibiotic prophylaxis prior to dental procedures among total knee arthroplasty recipients with type II diabetes. Under base-case assumptions, we found that antibiotic prophylaxis prior to invasive dental procedures was cost-effective if willingness to pay is greater than $66,000/QALY, which is below several willingness-to-pay thresholds well-accepted for the evaluation of treatment strategies by payors and policymakers in the US. These results fall within the range of previously reported cost-effectiveness ratios for pre-dental antibiotic use to prevent bacterial endocarditis or PJI (Table 3). As the efficacy of antibiotics for preventing dental-related PJI and risk of dental-related PJI among TKA recipients with type II diabetes remains uncertain, we simultaneously varied these parameters in a probabilistic sensitivity analysis. We found that at willingness-to-pay thresholds of $50,000/QALY, $100,000/QALY, $150,000/QALY, and $200,000/QALY, pre-dental antibiotic use was the cost-effective strategy in 32%, 58%, 69%, and 75% of scenarios, respectively.

In the context of the United States simultaneously outstanding peer countries on healthcare and achieving worse health outcomes [57], it is important for policymakers to consider the economic factors of treatment options in setting recommendations. While Canada, Australia, and many countries in Europe consider on cost-effectiveness in determining treatment coverage, the concept of healthcare rationing has been considered unsavory in the US [68]. Further, the lack of a fixed healthcare budget or single payor complicates understanding willingness-to-pay in the US [35]. Nevertheless, cost-effectiveness analyses can elucidate the opportunity cost of a resource allocation strategy and aid policymakers in determining the most efficient allocation of resources for promoting a population’s health [69,70]. Cost-effectiveness analyses allow policymakers to consider treatment value—the outcomes that can be achieved for a given cost—along with clinical and ethical considerations in creating guidelines.

There have been several studies that evaluate the cost-effectiveness of pre-dental antibiotic prophylaxis in total joint arthroplasty (TJA) recipients. Prior cost-effectiveness analyses of prophylactic penicillin and amoxicillin administration prior to dental appointments among the general population of TJA recipients, with an average risk of infection, reported that lifetime pre-dental antibiotic prophylaxis was not cost-effective compared to no antibiotic use at any willingness-to-pay threshold (ICERs: $256,700 and Dominated) [27,71,72]. Pre-dental antibiotic use was cost-effective in scenarios reflecting a higher probability of PJI after a dental visit [27,57], indicating that pre-dental antibiotic prophylaxis may provide benefit in patient populations at higher underlying risks of infection. Our results are consistent with these findings, providing evidence that antibiotic use prior to dental procedures is cost-effective at willingness-to-pay thresholds greater than $66,000/QALY for reducing risk of PJI in patients with type II diabetes, a population at increased susceptibility for infection. Further, our results support current AAOS guidelines for pre-dental antibiotic prophylaxis, which indicate that pre-dental antibiotic use may be appropriate in certain patients at increased risk, but not the general TJA-recipient population [17]. While we focused on one population considered to be at high-risk for PJI, our study may provide limited insight into other such populations at similar PJI risk. Future analyses may focus on other high-risk groups, including TKA recipients who smoke [73], receive immunosuppressive treatment [17], or have higher BMI [18].

The findings from this analysis should be interpreted in the context of its limitations. As our input data were specific to TKA recipients with type II diabetes mellitus, our results are not generalizable beyond this population. Further, our cost data were derived from data collected in the United States healthcare system and so our results should be interpreted cautiously in settings outside of the United States. We assumed that all patients with type II diabetes would be treated with metformin. We assumed the probabilities of optimal implant positioning and non-infectious implant failure following revision TKA were equivalent to the probabilities following primary TKA. We estimated the rate of PJIs among TKA recipients from a study including both total hip and knee arthroplasties [74] and assumed that the increased risk of PJI among TKA
recipients was the same for all types of diabetes. One-stage prosthesis exchange is less costly than two stage revision and has lower mortality and morbidity [1,66]. We modeled a two-stage revision because the one stage approach is associated with higher rate of reinfection, especially in a population with high infection risk [42]. As the proportion of early-onset PJIs from hematogenous origins remains uncertain, we assumed that the probability of developing a hematogenous PJI is constant in all years and that all late-onset infections are hematogenous [75, 76]. Thus, we assume that the majority of early PJIs are seeded perioperatively, in an attempt to ensure a conservative assessment of the value of antibiotic prophylaxis. As there are no longitudinal, prospective studies on the attribution of PJIs to dental origins, we determined the proportion of hematogenous infections attributable to dental procedures from a retrospective medical review of TKA recipients [40], and assume that this proportion would be constant in all years. As a randomized controlled trial evaluating the efficacy of pre-dental antibiotic prophylaxis is infeasible [26], we used reduction in the risk of bacteremia following oral amoxicillin administration [43] as a proxy for the efficacy of antibiotics in preventing hematogenous infection [76]. In clinical practice, subjects who experience an antibiotic-related adverse event would subsequently be prescribed a different antibiotic such as cephalexin, azithromycin, or clarithromycin [17]; we modeled that subjects in this scenario would continue to experience the same cost, efficacy, and adverse event risk as estimated for amoxicillin. We estimated the QoL decrement associated with minor antibiotic-related complications as the disutility of a rash caused by penicillin [71], as data for these amoxicillin-related toxicities have not been reported [27,57,58]. A better understanding of the risk of PJI following TKA, especially among those with type II diabetes; the risk of PJIs following dental procedures; and antibiotic efficacy would reduce uncertainty of results. Future analyses may also incorporate lost productivity due to toxicity, the impact of antibiotic resistance following recurring exposure to amoxicillin, and alternative antibiotic regimens.

Current AAOS clinical practice guidelines indicate that prophylactic administration of antibiotics prior to invasive dental procedures may be useful for certain patient populations, including patients with diabetes

Fig. 2. One-way sensitivity analysis of antibiotic prophylaxis prior to dental procedures. This figure shows the incremental cost-effectiveness ratios (ICERs) estimated for various scenarios of antibiotic prophylaxis use prior to dental procedures. In each analysis, all parameters were held at base case values except the parameter listed on the vertical axis, which was varied using the range of multiplicative factors noted (reported: most favorable – least favorable). The leftmost side of the bar represents the ICER in the scenario wherein the parameter had the most favorable value, and the rightmost side represents the ICER in the scenario for which the parameter had the least favorable value. The bars for probability of PJI in the general population and increased risk of PJI from diabetes extend beyond the range on the x-axis, to values of $890,200/QALY and $403,800, respectively. The orange line represents the base-case ICER ($66,000/QALY), as reported in Table 2. Costs are reported in 2017 USD.

Fig. 3. Cost-effectiveness acceptability curve. These curves show the percentage of simulations, out of 500, for which antibiotic prophylaxis use (solid blue) or no antibiotic use (dashed yellow) was the cost-effective treatment option at a given willingness-to-pay (WTP) threshold. Each of the 500 simulations independently sampled model input parameters from the distributions of number of prosthetic joint infections (PJIs), odds ratio of infection given diabetes, relative risk of infection with antibiotic use, and percent of hematogenous infections attributable to dental procedures as specified in Technical Appendix, Table XII.
Our results indicate that for patients with type II diabetes, who are at increased susceptibility to infection compared to the general population, pre-dental antibiotic use is cost-effective in context of the current understanding of dental-related PJI risks. With 870,000 individuals in the US currently living with TKAs and type II diabetes [24,25,77], increasing prevalence of type II diabetes [78], and increasing prevalence and incidence of TKA [79,80], it is important to consider this evidence in determining the most appropriate post-surgical care for TKA recipients with type II diabetes.

Author contributions

Dr. Losina had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Obtaining of funding: Losina.
Conception and design: Trentadue, Stanley, Thornhill, Smith, Sullivan, Katz, Losina.
Collection and assembly of data: Trentadue, Stanley, Losina.
Analysis and interpretation of the data: Stanley, Trentadue, Thornhill, Lange, Smith, Sullivan, Katz, Losina.
Statistical expertise: Losina.
Drafting of the article: Stanley, Trentadue, Losina.
Critical revision of the article for important intellectual content: Stanley, Trentadue, Thornhill, Lange, Smith, Sullivan, Katz, Losina.
Final approval of the article: Stanley, Trentadue, Thornhill, Lange, Smith, Sullivan, Katz, Losina.

Declaration of funding and role of the funding source

This project was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health grants R01-AR-074290, K24-AR-057827, P30-AR-072577 and the Thornhill Strategic Initiative Fund. These funding sources did not play any role in the design or reporting of the study.

Declaration of Competing Interest

The authors do not report any competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ocarto.2020.100084.

References

[1] A.J. Tande, R. Patel, Prosthetic joint infection, Clin. Microbiol. Rev. 27 (2) (2014 Apr) 302–345.
[2] R. Kasch, S. Merk, G. Assmann, A. Lahm, M. Nupp, H. Merk, et al., Comparative analysis of direct hospital care costs between aseptic and two-stage septic knee revision, PLoS One 12 (1) (2017), e0169558.
[3] P.C. Matthews, A.R. Berendt, M.A. McNally, I. Byren, Diagnosis and management of prosthetic joint infection, BMJ 338 (2009 May 29) b1773.
[4] A.D. Toms, D. Davidson, B.A. Masri, C.P. Duncan, The management of peri-prosthetic infection in total joint arthroplasty, J Bone Joint Surg Br 88 (2) (2006 Feb) 149–155.
[5] R.H. Fitzgerald Jr., D.R. Nolan, D.M. Bstrup, R.E. Van Scy, J.A. Washington 2nd, M.B. Coventry. Deep wound sepsis following total hip arthroplasty, J Bone Joint Surg Am 59 (7) (1977 Oct) 847–855.
[6] W. Zimmerli, A. Trampuz, P.E. Ochsner, Prosthetic-joint infections, N. Engl. J. Med. 351 (16) (2004 Oct 14) 1645–1654.
[7] E.G. Maderazo, S. Judson, H. Pasternak, Late infections of total joint prostheses. A review and recommendations for prevention, Clin. Orthop. Relat. Res. (229) (1988 Feb) 131–142.
[8] P. Sendi, F. Banderet, P. Graber, W. Zimmerli, Periprosthetic joint infection following Staphylococcus aureus bacteremia, J. Infect. Dis. 63 (1) (2011 Jul) 17–22.
[9] A. Chen, F. Haddad, P. Lachiewicz, M. Bolognesi, L.E. Cortes, M. Franceschini, et al., Prevention of late PJI, J. Orthop. Res. 32 (Suppl 1) (2014 Jan) S158–S171.
[10] P.B. Lockhart, An analysis of bacteremias during dental extractions. A double-blind, placebo-controlled study of chlorhexidine, Arch. Intern. Med. 156 (5) (1996 Mar 11) 513–520.
[11] P.B. Lockhart, M.T. Brennan, H.C. Sauser, P.C. Fox, B.J. Fatter, F.K. Brahimi-Mougeot, Bacteremia associated with toothbrushing and dental extraction, Circulation 117 (24) (2008 Jun 17) 3118–3125.
[12] Advisory statement. Antibiotic prophylaxis for dental patients with total joint replacements. American Dental Association; American Academy of Orthopaedic Surgeons, J Am Dent Assoc 128 (7) (1997 Jul) 1004–1008.
[13] S.P. DeFroda, E. Lamin, J.A. Gil, K. Sindhu, S. Ritterman, Antibiotic prophylaxis for patients with a history of total joint replacement, J. Am. Board Fam. Med. 29 (4) (2016 Jul-Aug) 500–507.
[14] W. Watters 3rd, M.P. Rothman, N.B. Hanson, E. Aft, P.A. Anderson, K.C. Carroll, et al., Prevention of orthopaedic implant infection in patients undergoing dental procedures, J. Am. Acad. Orthop. Surg. 21 (3) (2013 Mar) 180–189.
[15] T.P. Sollecito, E. Aft, P.B. Lockhart, E. Truelove, T.M. Paumier, S.L. Tracy, et al., The use of prophylactic antibiotics prior to dental procedures in patients with prosthetic joints: evidence-based clinical practice guideline for dental practitioners. A report of the American Dental Association Council on Scientific Affairs, J. Am. Dent. Assoc. 146 (1) (2015 Jan), 11-6 ef.

Table 3: Cost-effectiveness of antibiotic prophylaxis prior to dental procedures for the prevention of endocarditis and prosthetic joint infection.

| Cohort         | Antibiotic prophylaxis (AP) strategy                  | Cost-effectiveness ratio, $ (2017)/QALY | Source       |
|----------------|-----------------------------------------------------|---------------------------------------|--------------|
| Moderate and high-risk | Oral amoxicillin use prior to invasive dental procedures | $-2814       | Franklin 2016 [87] |
| High-risk       | Oral amoxicillin use prior to invasive dental procedures | $-4989       |             |
| Moderate and high-risk | Oral clarithromycin prior to invasive dental procedures | $19,518       | Agba 2005 [58] |
| High-risk (prosthetic valve) | Oral clarithromycin prior to invasive dental procedures | $22,840       |             |
| Diabetic TKA recipients | Lifetime oral amoxicillin use prior to all dental appointments | $66,000       | Present study |
| TKA recipients | Lifetime oral amoxicillin use prior to dental visits | $256,667      | Skaar 2019 [27] |
| THA recipients | Lifetime oral amoxicillin use prior to dental visits | $95,100       |             |
| TJF recipients | Oral penicillin prior to dental visits | $35,150       |             |

* Relative to no antibiotic prophylaxis; QALYs: quality-adjusted life-years.

1 Underlying cardiac complications.
2 Total knee arthroplasty.
3 Total hip arthroplasty.
4 Dominated strategies reduce quality-adjusted life expectancy (QALE) and increase costs.
5 Total joint arthroplasty.
[68] P.J. Neumann, A.B. Rosen, M.C. Weinstein, Medicare and cost-effectiveness analysis, N. Engl. J. Med. 353 (14) (2005 Oct 6) 1516–1522.

[69] M.C. Weinstein, J.A. Skinner, Comparative effectiveness and health care spending–implications for reform, N. Engl. J. Med. 362 (5) (2010 Feb 4) 460–465.

[70] D.W. Brock, N. Daniels, P.J. Neumann, J.E. Siegel, Ethical and Distributive Considerations. Cost-Effectiveness in Health and Medicine, Oxford University Press, New York, NY, 2016.

[71] J. Tsevat, I. Durand-Zaleski, S.G. Pauker, Cost-effectiveness of antibiotic prophylaxis for dental procedures in patients with artificial joints, Am. J. Publ. Health 79 (6) (1989 Jun) 739–743.

[72] J.J. Jacobson, S.O. Schweitzer, C.J. Kovalski, Chemoprophylaxis of prosthetic joint patients during dental treatment: a decision-utility analysis, Oral Surg. Oral Med. Oral Pathol. 72 (2) (1991 Aug) 167–177.

[73] C. Pangaud, M. Ollivier, J.N. Argenson, Outcome of single-stage versus two-stage exchange for revision knee arthroplasty for chronic periprosthetic infection, EFORT Open Rev. 4 (8) (2019 Aug) 495–502.

[74] L. Pulido, E. Ghanem, A. Joshi, J.J. Purtill, J. Parvizi, Periprosthetic joint infection: the incidence, timing, and predisposing factors, Clin. Orthop. Relat. Res. 466 (7) (2008 Jul) 1710–1715.

[75] H. Hamilton, J. Jamieson, Deep infection in total hip arthroplasty, Can. J. Surg. 51 (2) (2008 Apr) 111–117.

[76] W.M.H. Rademacher, G. Walenkamp, D.J.F. Moojen, J.G.E. Hendriks, T.A. Goedendorp, F.R. Rozema, Antibiotic prophylaxis is not indicated prior to dental procedures for prevention of periprosthetic joint infections, Acta Orthop. 88 (5) (2017 Oct) 568–574.

[77] H. Maradit Kremers, D.R. Larson, C.S. Crowson, W.K. Kremers, R.E. Washington, C.A. Steiner, et al., Prevalence of total hip and knee replacement in the United States, J. Bone Joint Surg. Am. 97 (17) (2015 Sep 2) 1386–1397.

[78] W.R. Rowley, C. Bezold, Y. Arikan, E. Byrne, S. Krohe, Diabetes 2030: insights from yesterday, today, and future trends, Popul. Health Manag. 20 (1) (2017 Feb) 6–12.

[79] National Health Interview Survey (NHIS), Centers for Disease Control and Prevention, National Center for Health Statistics, 2012.

[80] E. Losina, T.S. Thorburn, B.N. Rome, J. Wright, J.N. Katz, The dramatic increase in total knee replacement utilization rates in the United States cannot be fully explained by growth in population size and the obesity epidemic, J. Bone Joint Surg. Am. 94 (3) (2012 Feb 1) 201–207.

[81] S.M. Goodman, B. Johnson, M. Zhang, W.T. Huang, R. Zhu, M. Figgie, et al., Patients with rheumatoid arthritis have similar excellent outcomes after total knee replacement compared with patients with osteoarthritis, J. Rheumatol. 43 (1) (2016 Jan) 46–53.

[82] J.D. Greenberg, G. Reed, J.M. Kremer, E. Tindall, A. Kavanaugh, C. Zheng, et al., Association of methotrexate and tumour necrosis factor antagonists with risk of infectious outcomes including opportunistic infections in the CORRONA registry, Ann. Rheum. Dis. 69 (2) (2010 Feb) 380–386.

[83] J.A. Singh, C. Cameron, S. Noorbaboochi, T. Cullis, M. Tucker, R. Christensen, et al., Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis, Lancet 386 (9990) (2015 Jul 18) 258–265.

[84] S. Bengtson, K. Knutson, The infected knee arthroplasty. A 6-year follow-up of 357 cases, Acta Orthop. Scand. 62 (4) (1991 Aug) 301–311.

[85] A. Banerji, A.A. Long, C.A. Camargo Jr., Diphenhydramine versus nonsedating antihistamines for acute allergic reactions: a literature review, Allergy Asthma Proc. 28 (4) (2007 Jul-Aug) 418–426.

[86] J. Aranda-Michel, R.A. Giannella, Acute diarrhea: a practical review, Am. J. Med. 106 (6) (1999 Jun) 670–676.

[87] M. Franklin, A. Wailoo, M.J. Dayer, S. Jones, B. Prendergast, L.M. Baddour, et al., The cost-effectiveness of antibiotic prophylaxis for patients at risk of infective endocarditis, Circulation 134 (20) (2016 Nov 15) 1568–1578.