ADA CE Program ARTICLE 1

COVER STORY

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

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In 2012, a panel of experts representing the American Academy of Orthopaedic Surgeons (AAOS) and the American Dental Association (ADA) (the 2012 Panel) published a systematic review and accompanying clinical practice guideline (CPG) entitled "Prevention of Orthopaedic

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ABSTRACT

Background. A panel of experts (the 2014 Panel) convened by the American Dental Association Council on Scientific Affairs developed an evidence-based clinical practice guideline (CPG) on the use of prophylactic antibiotics in patients with prosthetic joints who are undergoing dental procedures. This CPG is intended to clarify the "Prevention of Orthopaedic Implant Infection in Patients Undergoing Dental Procedures: Evidence-based Guideline and Evidence Report," which was developed and published by the American Academy of Orthopaedic Surgeons and the American Dental Association (the 2012 Panel).

Types of Studies Reviewed. The 2014 Panel based the current CPG on literature search results and direct evidence contained in the comprehensive systematic review published by the 2012 Panel, as well as the results from an updated literature search. The 2014 Panel identified 4 case-control studies.

Results. The 2014 Panel judged that the current best evidence failed to demonstrate an association between dental procedures and prosthetic joint infection (PJI). The 2014 Panel also presented information about antibiotic resistance, adverse drug reactions, and costs associated with prescribing antibiotics for PJI prophylaxis.

Practical Implications and Conclusions. The 2014 Panel made the following clinical recommendation: In general, for patients with prosthetic joint implants, prophylactic antibiotics are not recommended prior to dental procedures to prevent prosthetic joint infection. The practitioner and patient should consider possible clinical circumstances that may suggest the presence of a significant medical risk in providing dental care without antibiotic prophylaxis, as well as the known risks of frequent or widespread antibiotic use. As part of the evidence-based approach to care, this clinical recommendation should be integrated with the practitioner's professional judgment and the patient's needs and preferences.

Key Words. Antibiotic prophylaxis; evidence-based dentistry; practice guidelines; prostheses; joint replacement.

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Implant Infection in Patients Undergoing Dental Procedures: Evidence-based Guideline and Evidence Report."[1-3] The 2012 Panel initially considered 222 questions concerning the relationship between dental procedures, bacteremia (as an intermediate outcome), and the risk of developing a prosthetic joint infection (PJI) as a clinical end point. The 2012 Panel published a comprehensive evidence-based guideline. The release of this guideline was followed by calls to the ADA Member Service Center hotline requesting additional clarification, which indicated that this guideline was 1 of the top 2 issues of concern to dental practitioners. Therefore, the ADA's Council on Scientific Affairs convened a panel of experts (the 2014 Panel) to provide dental professionals with a more specific and practical set of guidelines, the results of which are included in this article.

Supplemental material is available online.

The 2014 Panel considered the direct evidence linking a PJI with a dental procedure but did not reevaluate intermediate outcomes, including bacteremia[4] from manipulation of oral mucosa. The full report of the 2012 Panel, which includes intermediate outcomes, is available online.[1] The 2014 Panel addressed the following clinical question: For patients with prosthetic joints, is there an association between dental procedures and PJI, and, therefore, should systemic antibiotics be prescribed before patients with prosthetic joint implants undergo dental procedures? In this article, we present the evidence to answer this question and provide clinical recommendations.

EVIDENCE REVIEW

Because the 2012 Panel[1] conducted a comprehensive search of the biomedical literature and screened the results of the search according to defined inclusion and exclusion criteria, the 2014 Panel chose to use the literature selected by the 2012 Panel as the foundation of this CPG. In addition, the 2014 Panel updated the literature search and screening process to identify additional evidence. The methods are presented in Appendix 1 (available online at the end of this article). The 2014 Panel assessed each identified study according to the Critical Appraisal Skills Programme case-control critical appraisal tool[5] and then summarized the body of evidence to determine the level of certainty in the effect estimate and corresponding strength of the recommendation. Details about the process for generating clinical recommendations are in Appendix 2 (available online at the end of this article). The 2014 Panel did not conduct a meta-analysis because a meta-analysis of observational studies can produce precise, but possibly spurious, estimates of risk owing to the effects of confounding.[6]

In their systematic review,[1] the 2012 Panel identified 1 study that provided direct evidence about dental procedures as risk factors for developing prosthetic hip and knee implant infections. The study by Berbari and colleagues[7] was a case-control study of 339 patients with infected hip or knee prostheses (cases), and the authors matched them with 339 patients who did not have infected hip or knee prostheses (controls) and who were hospitalized in an orthopedic service at the Mayo Clinic Care Network (Rochester, MN) from December 2001 through May 2006. The authors reviewed and abstracted information from dental records to determine the association between the dental procedures (exposure) and hip and knee infections. Exposure was measured within the previous 6 months and 2 years before hospital admission and classified as low-risk dental procedures (fluoride treatment, restorative dentistry, and endodontic treatment) and high-risk dental procedures (periodontal treatment, extractions, treatment of a dental abscess, oral surgery, and dental hygiene), as defined by Berbari and colleagues.[7]

The authors controlled for confounding variables by matching control patients to case patients on the basis of joint arthroplasty location, resulting in exactly the same number of prosthetic hip (n = 164) and knee (n = 175) replacements among cases and controls. The authors also controlled for confounding by providing each patient with a yes versus no propensity score regarding whether the patient had had a dental visit during the period of data abstraction. The score took into account several covariates—including sociodemographic and behavioral information, comorbidities, and the American Society of Anesthesiologists score—that influenced a patient's propensity to visit a dentist. The authors also controlled for covariates such as antibiotic prophylaxis, sex, and joint effect. The regression models included all of these covariates and confounding variables.

The regression modeling used odds ratios (ORs), and the results showed no statistical association between having undergone high-risk dental procedures without antibiotics and PJIs at either 6-months (OR = 0.8; 95% confidence interval [CI], 0.4-1.7) or 2-years (OR = 0.8; 95% CI, 0.4-1.6) after the procedure. High-risk dental procedures with antibiotics were statistically significant at 6 months (OR = 0.5; 95% CI, 0.3-0.9), but not at 2 years (OR = 0.7; 95% CI, 0.5-1.1). All 4 of these ORs are below the null value of 1, indicating that case patients

ABBREVIATION KEY. **AAOS:** American Academy of Orthopaedic Surgeons. **ADA:** American Dental Association. **CPG:** Clinical practice guideline. **PJI:** Prosthetic joint infection.

had lower odds of having undergone dental procedures than did control patients.

The 2014 Panel identified 3 additional case-control studies via its updated literature search process.[8-10] The first study was by Skaar and colleagues.[9] They extracted data (*International Classification of Diseases, Ninth Revision, Clinical Modification* for procedures associated with hospital use in the United States: codes 81.5, 81.51, 81.52, 81.54, 81.56, 81.57, 81.80, 81.81, 81.84, 81.9, and 996.99) for the years 1997 through 2006 from the Medicare Current Beneficiary Survey. The nested case-control study included 168 participants who had undergone total arthroplasty—42 case participants who had PJIs matched according to age group, sex, and number of comorbid conditions with 126 control participants who did not. Dental data were based on patients' self-reports, which are susceptible to recall bias. The authors reported that control participants were more likely to have undergone invasive dental procedures than were case participants, although this result was not significant (main results were expressed as time to event with hazard ratios [HRs] and association with ORs: HR = 0.78 [95% CI, 0.18-3.39]; OR = 0.56 [95% CI, 0.18-1.74]; $P = .45$; neither the HR nor the OR was significant). Invasive dental procedures, as defined by Skaar and colleagues,[9] included teeth cleaning (including periodontal procedures), extractions, and endodontic procedures. The authors noted that the statistical power for their study was low. Despite the risk of bias, the study results appeared to be valid, generalizable, and consistent with those of other related studies in which investigators failed to demonstrate an association between dental procedures and PJI.

The second study also was a nested case-control study in which Swan and colleagues[10] addressed events associated with PJI. They identified 17 patients (of 1,641 who underwent arthroplasty between 1998 and 2006 in a tertiary referral center) in whom PJI developed more than 3 months postoperatively. The authors identified 51 control patients from a central institutional audit database, but it was unclear whether case and control participants were demographically similar. In addition, there was high susceptibility for recall bias because the exposure data were collected via telephone. The 2 factors most associated with PJI were having cellulitis or having more than 4 comorbidities. The authors used data for dental procedures as published in the article to create a 2×2 table and calculate the OR as 1.53 (95% CI, 0.13-18.03). We did not calculate a *P* value, but the CI was wide enough and includes the null value of 1; therefore, it failed to demonstrate an association between dental procedures and PJI.

The third study was a nested case-control study in which Jacobson and colleagues[8] recruited case participants from approximately 2,700 patients with prosthetic knee or hip joints that had been placed in 1 of 2 hospitals from 1970 through 1983. The authors identified 30 case participants with late (> 6 months after implant placement) PJI and 100 control patients, although it was unclear whether or how the control patients were matched with the case patients. The authors reviewed dental charts, but they did not mention masking of data abstractors or the types of dental procedures that were performed. The authors did not account for any confounding factors such as age, sex, smoking status, or medical conditions. The authors performed a Fisher exact test, and from the published data we calculated an OR of 0.07 (95% CI, 0.01-0.56). This result provided evidence that there is an association between dental procedures and PJI; however, the OR and Fisher exact test results implied that those undergoing dental procedures were at lower risk of developing PJI. The methodological limitations of this study affect the validity and generalizability of its results; furthermore, the results are inconsistent with other studies in which investigators failed to show an association between dental procedures and PJI.

CLINICAL RECOMMENDATION AND RATIONALE

Using eTable 1 (available online at the end of this article) as a guide, the 2014 Panel judged with moderate certainty that there is no association between dental procedures and the occurrence of PJIs. The 2014 Panel made this judgment on the basis of the following 2 considerations. The first was consistency between results, in that the results of 3 of 4 studies failed to show an association between dental procedures and PJI, and the results of the fourth study showed a protective effect of dental procedures on PJI. The second was that although the number of studies was limited, it is unlikely that the results of the additional studies would have changed the conclusion. The 2014 Panel made the assumption that the evidence regarding hip and knee joint infections can be extrapolated to all joints on the basis of the morphologic and physiological characteristics of the tissues involved. This extrapolation is necessary for clinical relevance because, to our knowledge, no studies have been published addressing the relationship between dental treatment and infections of other types of prosthetic joints. Using the ADA's methods for generating clinical recommendation statements as described in eTable 2 (available online at the end of this article), when there is moderate certainty of no association, the strength of the recommendation is *against*. The term *against* means that evidence suggests not implementing this intervention or discontinuing ineffective procedures (eTable 3, available online at the end of this article).

On the basis of this rationale, the 2014 Panel makes the following clinical recommendation as depicted in the Sidebar at the end of the article: In general, for patients with prosthetic joint implants, prophylactic antibiotics are not recommended prior to dental procedures to prevent prosthetic joint infection. The practitioner and

patient should consider possible clinical circumstances that may suggest the presence of a significant medical risk in providing dental care without antibiotic prophylaxis, as well as the known risks of frequent or widespread antibiotic use.

This report is intended to assist practitioners with making decisions about the prophylactic use of antibiotics to prevent PJIs. The recommendations in this document are not intended to define a standard of care and rather should be integrated with the practitioner's professional judgment and the patient's needs and preferences.

RISK FACTORS FOR DEVELOPING PROSTHETIC JOINT INFECTION INDEPENDENT OF DENTAL PROCEDURES

One case-control study[7] identified a number of nondental risk factors for developing PJI. In this study, Berbari and colleagues[7] evaluated both preoperative and postoperative factors associated with PJI. The most clinically relevant of these factors were postoperative, especially wound drainage after arthroplasty (OR = 18.7; 95% CI, 7.4-47.2). Other postoperative factors associated with PJI were wound hematoma after arthroplasty (OR = 2.5; 95% CI, 1.3-9.5) and postoperative urinary tract infection (OR = 2.7; 95% CI, 1.04-7.1). The OR for surgical site infection could not be calculated because there were no PJIs among the control subjects. Thus, the patients at the highest risk of developing PJI had drainage, an infection, or both after undergoing arthroplasty. There were no data regarding whether use of prophylactic antibiotics decreased the risk of developing PJIs in patients with these specific postoperative conditions.

Other conditions, as defined by Berbari and colleagues,[7] with significant ORs (ranging from 1.8 to 2.2) for PJI independent of dental procedures, were preoperative factors including prior operation/arthroplasty on the index joint, diabetes mellitus, and/or being immunocompromised (defined[7] as rheumatoid arthritis or current use of systemic steroids/immunosuppressive drugs or diabetes mellitus or presence of a malignancy or a history of chronic kidney disease). However, the magnitude of these ORs may not be clinically relevant. Observational studies such as those with a case-control design do not involve the use of randomization and are more prone to the effects of bias and confounding. Therefore, some epidemiologists maintain that in case-control studies significant ORs of less than 4 may not be large enough to be clinically relevant.[11] The upper limit of the 95% CIs for the preoperative factors did not include values of 4 or greater in the results of the case-control study by Berbari and colleagues.[7] Thus, although these factors were significant, the effects of these medical conditions on the risk of developing PJI may not be clinically relevant. Independent of having undergone a dental procedure, it appears that postoperative factors such as drainage or infection after undergoing arthroplasty were associated more strongly with PJI than are having undergone previous surgery or arthroplasty of the index joint, being immunocompromised, or having a medical condition such as diabetes mellitus.

FURTHER CONSIDERATIONS

The following considerations contribute to the argument against antibiotic prophylaxis.

Antibiotic resistance. There is a long-standing and increasing concern that repeated exposure to antibiotics is a risk factor for the development of resistant bacterial species (for example, penicillin-resistant streptococci).[12-14]

Adverse drug reactions. Although there are no data regarding the risk of developing a drug reaction from 1 dose of amoxicillin prescribed to prevent a distant site infection such as PJI, older data involving prophylaxis regimens that included intramuscular injections and multiple oral doses suggest that more people who are given antibiotic prophylaxis would experience drug reactions from penicillin-type drugs—some of which may be fatal—than would be prevented from developing PJI.[15] Of all allergens, penicillin is the most frequent medication-related cause of anaphylaxis in humans, and its use is the cause of approximately 75% of fatal anaphylaxis cases in the United States each year.[16] Other potential antibiotic-associated adverse reactions include nausea, vomiting, and diarrhea. There also is an increased risk of experiencing adverse reactions with increasing patient age (that is, in patients 70 years or older),[17] which is compounded by the increased frequency of arthroplasty in older patient cohorts.[18]

Prolonged treatment with antibiotics is associated with infections secondary to changes in the gastrointestinal microbial flora, which includes that involved in the development of oral thrush. For example, *Clostridium difficile* infection potentially can cause pseudomembranous colitis after patients are prescribed antibiotics to treat other infections.[19] Recognizing that a single dose of antibiotics for prophylaxis of PJI is unlikely to cause a *C difficile* infection, comprehensive dental care often involves multiple appointments over a short period. In addition, patients may have taken antibiotics for other medical conditions in the past, increasing their risk of experiencing changes in the gastrointestinal flora. The Centers for Disease Control and Prevention has estimated that annually there are approximately 250,000 people with *C difficile* infections that require hospitalization or already affect hospitalized patients, resulting in 14,000 deaths per year.[20] Investigators have identified clindamycin, cephalosporins, and fluoroquinolones as the inducing agents.[19]

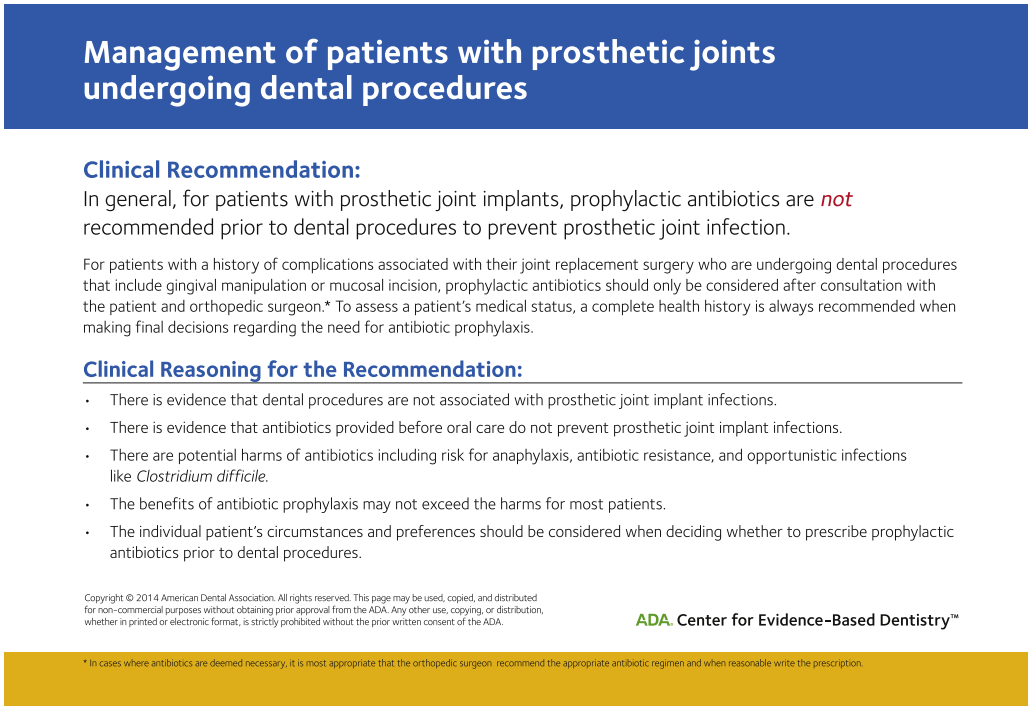
Cost. The results of a 2013 report indicate that the annual cost of amoxicillin administered to patients with hip and knee prostheses before dental procedures in the United States may exceed $50 million.[21]

CONCLUSIONS

Evidence fails to demonstrate an association between dental procedures and PJI or any effectiveness for antibiotic prophylaxis. Given this information in conjunction with the potential harm from antibiotic use, using antibiotics before dental procedures is not recommended to prevent PJI. Additional case-control studies are needed to increase the level of certainty in the evidence to a level higher than moderate. ■

SUPPLEMENTAL DATA

Supplemental data related to this article can be found at http://dx.doi.org/10.1016/j.adaj.2014.11.012.



Management of patients with prosthetic joints undergoing dental procedures

Clinical Recommendation:

In general, for patients with prosthetic joint implants, prophylactic antibiotics are *not* recommended prior to dental procedures to prevent prosthetic joint infection.

For patients with a history of complications associated with their joint replacement surgery who are undergoing dental procedures that include gingival manipulation or mucosal incision, prophylactic antibiotics should only be considered after consultation with the patient and orthopedic surgeon.* To assess a patient's medical status, a complete health history is always recommended when making final decisions regarding the need for antibiotic prophylaxis.

Clinical Reasoning for the Recommendation:

- There is evidence that dental procedures are not associated with prosthetic joint implant infections.
- There is evidence that antibiotics provided before oral care do not prevent prosthetic joint implant infections.
- There are potential harms of antibiotics including risk for anaphylaxis, antibiotic resistance, and opportunistic infections like *Clostridium difficile.*
- The benefits of antibiotic prophylaxis may not exceed the harms for most patients.
- The individual patient's circumstances and preferences should be considered when deciding whether to prescribe prophylactic antibiotics prior to dental procedures.

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* In cases where antibiotics are deemed necessary, it is most appropriate that the orthopedic surgeon recommend the appropriate antibiotic regimen and when reasonable write the prescription.

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Appendix 1
UPDATED LITERATURE SEARCH

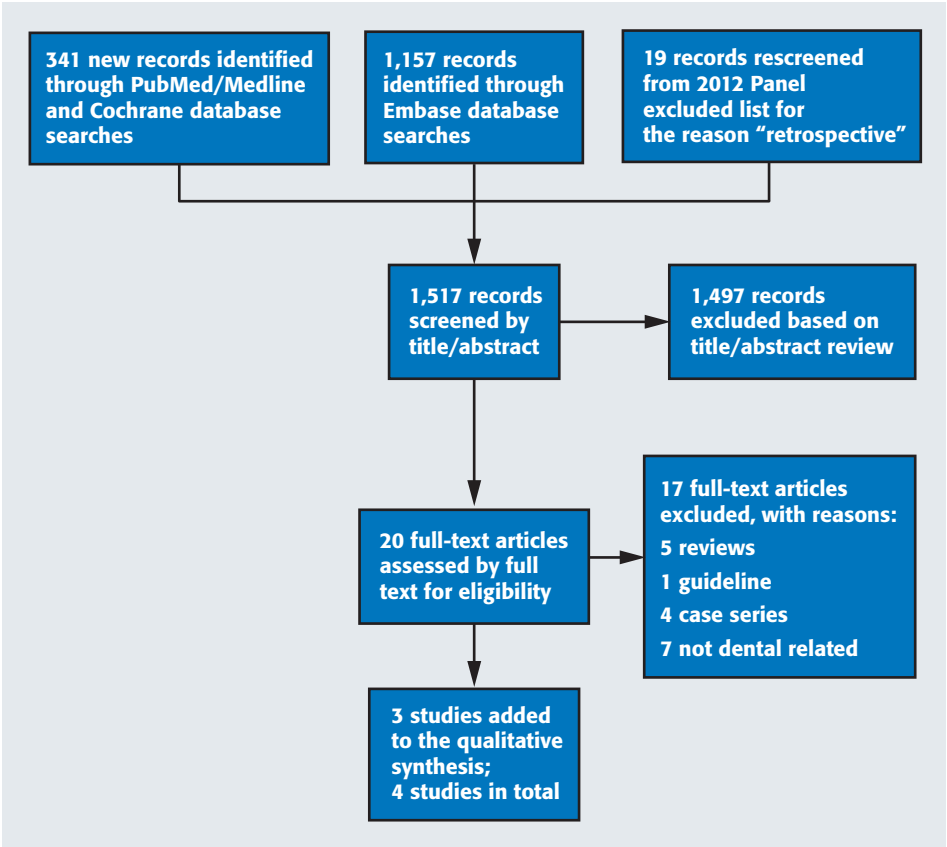
We conducted an updated literature search in February 2014 by using the identical search strategy as that described in Appendix IV of the 2012 Panel's article[1] to identify any articles published since the previous search was conducted in 2011. The updated literature search and full-text review process compelled the 2014 Panel to review the list of articles excluded at the full-text stage in the 2012 Panel's manuscript (Table 58 in Appendix III of the 2012 Panel's article[1]) for the reason that they were retrospective. According to the study selection criteria,[1] only retrospective case series were eligible for exclusion; therefore, the 2014 Panel judged that 2 additional case-control studies[2,3] that had been rejected should be included in the evidence. We screened all records independently and in duplicate. The eFigure shows the results of these searching and screening procedures. The articles that we excluded at the full-text stage are shown in eTable 4[4-20] with reasons for the exclusions. eTable 5[21-24] shows the critical appraisal results for each of the four included studies.

Appendix 2
PROCESS FOR DEVELOPING CLINICAL RECOMMENDATIONS

The level of certainty in the effect estimate is judged as high, moderate, or low, according to a grading system (eTable 1) amended from the *ADA Clinical Practice Guidelines Handbook: 2013 Update*.[25] The level of certainty refers to the probability that the 2014 Panel's assessment of the effect estimate is correct. The criteria for assessment include several components of the evidence, including the number of studies, number of participants, methodological quality, believability of results, applicability of the results to populations of interest, and consistency of findings across studies.

The level of certainty is combined with the net benefit rating as shown in eTable 2 to arrive at clinical recommendation strengths (that is, *strong*, *in favor*, *weak*, *expert opinion for*, *expert opinion against*, or *against*). eTable 3 shows the definitions of these strengths of recommendations.

The 2014 Panel approved clinical recommendations by means of a unanimous vote. The 2014 Panel sought comments on this report from other subject matter experts, methodologists, epidemiologists, and end users before finalizing the recommendations. The ADA Council on Scientific Affairs approved the final report for publication.



eFigure. Results of literature search and screening procedures.

eTABLE 1

Level of certainty categories.

LEVEL OF CERTAINTY IN EFFECT ESTIMATE	DESCRIPTION
High	The body of evidence usually includes consistent results from well-designed, well-conducted studies in representative populations. This conclusion is unlikely to be affected strongly by the results of future studies. This statement is established strongly by use of the best available evidence.
Moderate	As more information becomes available, the magnitude or direction of the observed effect could change, and this change could be large enough to alter the conclusion. This statement is based on preliminary determination from the current best available evidence, but confidence in the estimate is constrained by 1 or more factors, such as ▬ the number or size of studies; ▬ risk of bias of individual studies leading to uncertainty in the validity of the reported results; ▬ inconsistency of findings across individual studies; and ▬ limited generalizability to the populations of interest.
Low	More information could allow a reliable estimation of effects on health outcomes. The available evidence is insufficient to support the statement, or the statement is based on extrapolation from the best available evidence. Evidence is insufficient, or the reliability of estimated effects is limited by factors such as ▬ the limited number or size of studies; ▬ important flaws in study design or methods leading to lack of validity; ▬ substantial inconsistency of findings across individual studies; and ▬ findings not generalizable to the populations of interest.

eTABLE 2

Balancing level of certainty and net benefit rating to arrive at clinical recommendation strength.

LEVEL OF CERTAINTY	NET BENEFIT RATING		
	Benefits Outweigh Potential Harms	**Benefits Balanced With Potential Harms**	**No Benefit, Potential Harms Outweigh Benefits, or No Association**
High	Strong	In Favor	Against
Moderate	In Favor	Weak	Against
Low	Expert opinion for or expert opinion against		

eTABLE 3

Definitions for the strength of the recommendation.

RECOMMENDATION STRENGTH	DEFINITION
Strong	Evidence strongly supports providing this intervention.
In Favor	Evidence favors providing this intervention.
Weak	Evidence suggests implementing this intervention after alternatives have been considered.
Expert Opinion For	Evidence is lacking; the level of certainty is low. Expert opinion guides this recommendation.
Expert Opinion Against	Evidence is lacking; the level of certainty is low. Expert opinion suggests not implementing this intervention.
Against	Evidence suggests not implementing this intervention or discontinuing ineffective procedures.

eTABLE 4

Articles excluded at full-text stage.

ARTICLE	REASON FOR EXCLUSION
Bell and Colleagues,[4] 1990	Narrative review
Chen and Colleagues,[5] 2014	Not a study; work group question and answer
Dubee and Colleaues,[6] 2013	No dental exposure
Gomez and Colleagues,[7] 2011	Question and answer
Jacobsen and Murray,[8] 1980	Retrospective case series
Jacobson and Matthews,[9] 1987	Retrospective case series from same population as 1986 article that is included
LaPorte and Colleagues,[10] 1999	Case series
Legout and Colleagues,[11] 2012	Review
Marculescu and Colleagues,[12] 2006	No measure of dental outcomes
McGowan and Hendrey,[13] 1985	Narrative review
Mercuri,[14] 2012	Narrative review
Sendi and Colleagues,[15] 2011	Retrospective cohort with no dental exposure
Sendi and Colleagues,[16] 2011	Retrospective cohort with no dental exposure
Seymour and Colleagues,[17] 2003	Narrative review
Tornero and Colleagues,[18] 2012	Retrospective case series
Waldman and Colleagues,[19] 1997	Retrospective case series
Zywiel and Colleagues,[20] 2011	No measure of dental exposures

eTABLE 5

Critical appraisals of the included studies.

QUESTIONS	SKAAR AND COLLEAGUES,[21] 2011	SWAN AND COLLEAGUES,[3] 2011	BERBARI AND COLLEAGUES,[22] 2010	JACOBSON AND COLLEAGUES,[2] 1986
Did the Study Address a Clearly Focused Issue?	Yes: 1,000 participants from Medicare Current Beneficiary Survey. This was the cohort from which the 168 participants of the case-control study were selected.	Yes: It addressed sentinel events associated with prosthetic joint infection.	Yes: The population was selected on the basis of outcomes, which were patients with and without prosthetic joint infection. The risk factors (exposure) were high- and low-risk dental procedures with and without antibiotics.	Yes: The study examined the association between dental procedures and late prosthetic joint infection.
Did the Authors Use an Appropriate Method to Answer Their Question?	Yes: A nested case-control study is appropriate to answer the clinical question.	Yes: A nested case-control study is appropriate to answer the clinical question.	Yes: A case-control study starts with the outcome and typically looks retrospectively for differences in exposure. Case-control studies are excellent for rare diseases or outcomes, and this study addressed the study question.	Yes: A nested case-control study is appropriate for answering the clinical question.
Were the Case Participants Recruited in an Acceptable Way?	Yes: Case participants were recruited from the Medicare Current Beneficiary Survey database from 1997 through 2006. Case participants were defined clearly as having experienced a prosthetic joint infection.	Yes: Case participants were patients with prosthetic joint infection developing more than 3 months postoperatively, in 1,641 patients undergoing arthroplasty between 1998 and 2006 at a tertiary referral center. Seventeen case patients were identified.	Yes: Case participants were patients with a prosthetic hip or knee infection who were hospitalized at the Mayo Clinic (Rochester, MN) from December 2001 through May 2006. Case patients appeared to represent a geographically diverse population as well (Table 2 in the article). At 80% power, we would need a total sample of approximately 240 patients, or 120 per group. The study had 339 patients per group. The power calculation is as follows: $(0.30 - 0.15) \div \sqrt{0.225(1 - 0.225)} = 0.36$, which is the standardized difference. Using Altman's nomogram[23] gives the total sample at 240 patients.	Yes: The case participants were recruited from approximately 2,700 hospital and dental charts from 2 hospitals in Michigan from 1970 through 1983. The authors identified 30 patients with late prosthetic joint infection.
Were the Control Participants Selected in an Acceptable Way?	Yes: Selection of control patients in a case-control study is complex. The nested case-control study format was advantageous in that the control patients were selected from the same Medicare Current Beneficiary Survey database during the same period as the case patients.	Unable to determine: Control patients were identified from a central institutional audit database. It is unclear whether they were similar to case patients treated at the tertiary referral center. Appropriate selection of control patients is 1 of the major problems with case-control studies, and it is curious why control patients were not selected from the same referral center or geographic area. Control patients were matched in a 3:1 ratio, resulting in 51 control patients.	Yes: Selection of control patients in a case-control study is rather complex. This study's authors selected for control patients those with a prosthetic hip or knee, hospitalized on an orthopedic service, who did not have a prosthetic joint infection. Paired matching was not performed (that is, individual matching to attributes such as age, sex, or smoking status). However, frequency matching was performed on the joint arthroplasty location, resulting in exactly the same number of prosthetic hip ($n = 164$) and knee ($n = 175$) replacements in the case and control groups.	Unable to determine: The authors identified 100 patients without prosthetic joint infection as control patients. It is unclear whether they were from the same institutions or were matched to case patients in any way.

eTABLE 5 (CONTINUED)

QUESTIONS	SKAAR AND COLLEAGUES,[21] 2011	SWAN AND COLLEAGUES,[3] 2011	BERBARI AND COLLEAGUES,[22] 2010	JACOBSON AND COLLEAGUES,[2] 1986
Was the Exposure Accurately Measured to Minimize Bias?	Unable to determine: The authors obtained the dental records from the Medicare Current Beneficiary Survey, but those records were based on patient self-reporting. Thus, the exposure is susceptible to recall bias. In addition, there did not appear to be any masking of those assessing the dental records, raising the possibility of detection bias.	No: The exposure data were collected by means of phone calls to both case and control patients. This method is highly susceptible to recall or memory bias.	Yes: Although measurement bias cannot be ruled out owing to uncertainty about what exactly was being measured, the authors obtained and analyzed dental records. This method minimized recall bias, which commonly is assessed by using a patient's memory for details on exposure. Furthermore, investigators were masked during dental record analysis, minimizing detection bias.	Unable to determine: Although the authors used dental charts in this study, there is no mention of assessor masking or a detailed explanation of what type of dental procedures were performed.
A. What Confounding Factors Have the Authors Accounted For? **B. Have the Authors Taken Account of the Potential Confounding Factors in the Design, Their Analysis, or Both?**	A. They were matched for age, sex, and Charlson comorbidity index, which measures many different medical conditions. The authors selected control cases in a 3:1 ratio. B. Yes: For design owing to matching. Unable to determine for analysis because there was no mention of logistic regression analysis.	A. Age, sex, and date of surgery were the criteria the authors used for matching. This method has its limitations, and cases should have been matched based on medical, socioeconomic, and geographic factors. B. Partially: The authors used stepwise logistic regression analysis to examine which predictor variables (sentinel events, including dental procedures) were associated significantly with prosthetic joint infection.	A. The authors used geographic location, education level, history of kidney disease, history of malignancy, diabetes mellitus, use of systemic corticosteroids, rheumatoid arthritis, use of immunosuppressive medications, smoking history, body mass index, American Society of Anesthesiologists status, and sex. B. Yes: The authors controlled for many important confounding factors by using many covariates in a propensity score, which was calculated using logistic regression analysis. The authors used the propensity score to control for the propensity to visit a dentist (exposure).	A. The authors have not accounted for any confounding factors. They should have accounted for many, including age, sex, smoking status, multiple medical conditions, American Society of Anesthesiologists status, and geographic location. B. No: The authors performed no regression analysis to account for the effects of confounding variables.
What Are the Results of This Study?	The authors expressed main results as both time to event with hazard ratios (HRs) and association with odds ratios (ORs): HR = 0.78 (95% confidence interval [CI], 0.18-3.39); OR = 0.56 (95% CI, 0.18-1.74); $P = .45$. Neither the HR nor the OR was significant, although they indicated a trend for a reduction in the odds of having dental procedures for the PJI group. HRs were stable and did not move closer to the null value after adjustment for confounding factors. (This is a good thing and shows that results are not likely to be spurious owing to confounding).	The 2 factors most associated with PJI were having more than 4 comorbidities (risk ratio [RR] = 3.4; 95% CI, 1.5-7.7) and having cellulitis (RR = 2.7; 95% CI, 1.15-6.3). RR is not the appropriate summary statistic to use because risk cannot be calculated with case-control studies. OR should have been used because it also is the output of logistic regression analysis. In addition, the P values of 1.000 reported in Table 4 of the article are incorrect, further complicating the statistical analysis presented in the article. The crude OR we calculated for dental infection was 1.53, which by itself is not clinically relevant for association with prosthetic joint infection.	The authors reported the main results as an OR of 0.8 (95% CI, 0.4-1.6; $P = .56$) for high-risk dental procedures without antibiotics.	The authors performed a hypothesis test (Fisher exact test) and reported that $P = .0005$, although in the text it was stated as .005. A Fisher exact test is a form of χ^2 test and is appropriate for obtaining a P value for binary data when cells contain values less than 5. We performed a crude calculation for an OR of 0.07, confirming strong evidence against the null hypothesis of no association between dental procedures and prosthetic joint infection. There was no adjusting for confounding, and the results imply that dental procedures are associated with protection from PJI.

eTABLE 5 (CONTINUED)

QUESTIONS	SKAAR AND COLLEAGUES,[21] 2011	SWAN AND COLLEAGUES,[3] 2011	BERBARI AND COLLEAGUES,[22] 2010	JACOBSON AND COLLEAGUES,[2] 1986
How Precise Are the Results? How Precise Is the Estimate of Risk?	*P* values showed extremely weak evidence against the null hypothesis. CIs were rather wide, meaning there is a lack of precision around the summary estimates (HR and OR). However, the CIs were similar to those in the Berbari and colleagues[22] study, which had a much bigger sample, which shows the statistical efficiency of a nested case-control study—that is, by 3:1 matching, one maintains a great degree of statistical power.	The CIs were wide, indicating imprecision with the summary estimate.	The CIs were wide, owing to the low number of events in each group.	We have no measure of precision because the authors did not report CIs.
Do You Believe the Results?	Yes: Owing to good methodology and because we were not rejecting the null value, the results appeared valid—that is, observational studies with positive results are likely to have false–positive findings.[24]	No: ORs are always further away from the null value than are RRs, and it seems as if more than 4 comorbidities and cellulitis would have ORs around 4.5 or 5. The magnitude of these ORs would appear to be clinically relevant to developing PJI. However, the many methodological and statistical shortcomings with this article render the results unreliable.	Yes: This study's authors did a good job on several fronts from a power calculation, selection of control patients, propensity score, masking outcomes assessors, and seeking dental records rather than relying on patients' memories of dental visits.	No: Given the lack of information about control patients, and no matching or adjusting for confounding factors, it is unclear how accurate the results presented actually are.
Can the Results Be Applied to the Local Population?	Yes: The Medicare Current Beneficiary Survey would appear to be a representative sample of patients receiving prosthetic joints.	Yes: The patient population in this study appears to be similar in nature to the local population.	Yes: The participants appear to be similar to many populations undergoing this type of orthopedic surgery.	Unable to determine: Although the patient population was probably representative of patients with prosthetic joint infection, given the methodological and statistical shortcomings of the article, its external validity can be questioned.
Do the Results of This Study Fit With Other Available Evidence?	Yes: This study's results are in alignment with those of other case-control studies showing no association between dental procedures and prosthetic joint infection.	Yes: Certainly the association between prosthetic joint infection and cellulitis and, to a certain, extent comorbidities fits with what has been reported in other studies on this topic.	Yes: The results are consistent with those of other observational studies.	No: The authors of the 3 other case-control studies all failed to reject the null value. This study's authors presented strong evidence against the null value.

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