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Antibiotic Prophylaxis for Prosthetic Joint Patients Undergoing Invasive Dental Procedures: Time for a Re-Think?

Brief Title – Prosthetic Joint Infections and Invasive Dental Procedures

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Abbreviations:

AAOS = American Academy of Orthopaedic Surgeons
ADA = American Dental Association
AP = Antibiotic prophylaxis
IDP = Invasive dental procedure
LPJI = Late prosthetic joint infection
PJI = Prosthetic joint infection
UK = United Kingdom
US = United States of America

Abstract (257/250)

Background.

In the United States, it has been common practice to recommend that dentists provide antibiotic prophylaxis (AP) before invasive dental procedures (IDP) to prevent late peri-prosthetic joint infections (LPJIs) in patients who have prosthetic arthroplasties despite lack of evidence for a causal relationship between IDP and LPJI, and a lack of evidence for AP efficacy.

Methods.

A recent study quantified the IDP incidence over the 15-month period prior to LPJI hospital-admissions in the United Kingdom for which dental records were available. A case-crossover analysis compared IDP incidence in the 3 months before LPJI admission with the preceding 12 months. The English population was used because guidelines do not recommend AP and any relationship between IDP and LPJI should be fully exposed.

Results.

No significant positive association was identified between IDP and LPJI. Indeed, the incidence of IDP was lower in the 3 months before LPJI hospital admission than in the preceding 12 months.

Conclusions.

In the absence of a significant positive association between IDP and LPJI, there is no rationale to administer AP before IDP in patients with prosthetic joints, particularly given the cost and inconvenience of AP, the risk of adverse drug reactions, and the potential for unnecessary AP use that promotes antibiotic resistance. These results should re-assure orthopedic surgeons and their patients that dental care of patients who have prosthetic joints should focus on maintaining good oral hygiene rather than on recommending AP for IDP. Moreover, it should also re-assure those in other countries where AP is not recommended that such guidance is sufficient.

Replacing arthritic joints with prostheses is one of the great advances of modern medicine with 2.9 million joint arthroplasties performed annually worldwide.[1, 2] Successful joint arthroplasties improve quality of life, provides pain relief, mobility, as well as independence for patients. There are already greater than 7 million people with prosthetic arthroplasties in the United States,[3, 4] and this number is increasing rapidly with approximately 4 million new hip and knee arthroplasties projected annually in the by 2030.[5]

Although a vast majority of joint arthroplasties are successful, peri-prosthetic joint infections (PJIs) remain one of the leading causes of arthroplasty failure. Early infections, defined as occurring within 3 months of joint arthroplasty, are likely due to wound contamination at the time of surgery. Early-infection rates in the 1950s were approximately 12%; since then, peri-operative antibiotic prophylaxis (AP) administered before joint arthroplasty and laminar airflow operating rooms have reduced this to around 1 to 2%,[4, 6-8] and refocused attention on late peri-prosthetic joint infections (LPJIs), which occur greater than 3 months after joint arthroplasty surgery. Although relatively uncommon, LPJIs are most likely due to hematogenous spread of infection from a distant site.

The economic, societal, and personal costs of PJI are substantial. The cost of treating PJIs are 4 to 6 times that of the original arthroplasty[9-12] and was projected to reach $1.62 billion annually in the United States by 2020[13] without accounting for personal and societal costs of long-term disability and impact on the patient quality of life.[14] PJI is, therefore, of major concern for the 28,000 orthopedic surgeons in the United States and the greater than7 million individuals who have prosthetic arthroplasties.[3, 4] Following the successful reduction in early PJI rates, there was a resultant desire to identify ways of reducing LPJI, particularly those due to hematogenous spread of infection from other anatomic sites. Not surprisingly, orthopedic surgeons recognized the efforts of the American Heart Association (AHA) to reduce the risk of infective endocarditis (IE) following invasive dental procedures (IDP) as a paradigm that could have applicability to PJI prevention.

The use of AP to prevent IE in susceptible individuals undergoing IDP had become well-established following a series of guidelines first published by the AHA in 1955 and supported by the American Dental Association (ADA).[15] By the 1970 to 80s, this led orthopedic surgeons to call for dentists to give AP to patients with prosthetic joints undergoing IDP,[16-19] a practice supported by greater than 90% of United States orthopedic surgeons at the time.[20, 21] However, unlike IE, where 30 to 40% of cases are due to hematogenous spread of oral bacteria, mainly oral viridans group streptococci (OVGS),[22-26] these bacteria account for few cases of LPJI.

Although, joint prostheses remain at infection risk throughout a patient's life, LPJI resulting from hematogenous seeding of bacteria from a remote site is rare. In the largest study that examined this scenario, a cohort of 6,101 arthroplasty patients (4,002 hip and 2,099 knee) were followed for a mean 70 months.[27] During this time, 553 had distant infections, mainly cystitis episodes, pneumoniae, skin and soft tissue infections, gastrointestinal infections, etc., and there were also 3 dental abscesses. Although there were 71 PJIs in the cohort (incidence 71 of 6,101 = 1.16%), only 7 (0.01%) of these were secondary to a remote infection and none of these were dental in origin.[27] Therefore, the risk of hematogenous spread of infection from a distant site to a prosthetic joint was low and may have been responsible for only approximately 10% of all PJIs (7/71). Moreover, dental-related "seeding" appears uncommon.

Microbiological studies also suggest OVGS are an uncommon cause of LPJI. An analysis of 14 large studies of PJI microbiology, including >2,400 patients who had hip or knee arthroplasty infections, found that 54% of all PJIs were attributable to staphylococci, but only 8% to streptococci, with other causes including enterococci (3%), aerobic gram-negative bacteria (9%), anaerobes (4%), other (3%), polymicrobial infection (15%), and culture negative (14%).[27] Despite accounting for less than 10% of PJIs, *Streptococcus* is a diverse genus with only a few species included as OVGS, and few studies have examined streptococcal species in sufficient detail to quantify the prevalence of OVGS. Two investigations with the largest cohorts published to date identified only 3% of 339 and 4.9% of 281 PJI cases due to OVGS, respectively.[28, 29]

Overall, recognizing that there are so few cases of PJI due to OVGS, any benefit of AP in preventing

LPJI following IDP is likely to be extremely limited. For this reason, many countries no longer recommend AP coverage of invasive dental procedures for those patients who have prosthetic arthroplasties including Australia, Brazil, Canada, Denmark, France, the Netherlands, Norway, Portugal and the United Kingdom including England, Scotland, Wales, and Northern Ireland.[30]

For AP to be effective, a positive causal association must exist between IDP and LPJI, and currently, supporting data are lacking.[31] Moreover, only five studies have previously evaluated whether such an association exists. In 1977, Waldman *et al,*.[32] performed a retrospective case review of 62 late peri-prosthetic knee joint infection patients and identified 7 (11%) of them with a temporally associated IDP. In a related study, LaPorte *et al*.,[33] temporally associated 3/52 (6%) late peri-prosthetic hip joint infections with IDP. However, neither study included a control group, making it impossible to draw conclusions regarding a possible association between IDP and LPJI. In contrast, a case-control study by Kaandorp *et al.*,[34] reported that none of the 37 LPJI cases had undergone an IDP in the previous 3 months, but 10% of controls had. In a similar study of 42 LPJI Medicare patients by Skaar *et al.*,[35] only 4 (9.5%) had undergone an IDP in the previous 3 months as compared to 15.9% of controls. However, differences were not statistically significant in either study. In the largest study, Berbari *et al*.,[28] found that 48% of 303 PJI patients had undergone an IDP in the previous 2 years compared with 34% of 318 controls, but a high proportion had received AP. A sub-analysis of those who had not received AP, however, identified 33 (11%) of PJI patients who had an IDP in the previous 2 years compared with 49 (14%) controls. None of the differences were statistically significant and each study had a small sample size with a resultant lack of statistical power. The case-control studies also suffered from selection bias and risk-factors confounding between cases and controls. Furthermore, there was confounding due to the wide-spread use of AP in the populations studied. In addition, recall bias for IDP was a limitation in some studies.

However, a recent study by our group has produced more conclusive evidence regarding the possible relationship between IDP and subsequent LPJI.[36] This study included all 9,427 LPJI hospital admissions in the United Kingdom between December 25th, 2011 and March 31st, 2017, for whom dental

records were available. This cohort is more than 30 times larger than that in any previous study and calculations showed that it had more than sufficient statistical power to detect any clinically significant association between IDP and LPJI. Furthermore, confounders caused by AP use in previously investigated populations was avoided by using the English population, where use of AP to prevent LPJI has never been advocated.[30] Thus, any association between IDP and LPJI should have been fully exposed. Recall bias was eliminated by inclusion of health records of all events and their timing. Additionally, a major advantage of the case-crossover design used in this study was the avoidance of selection bias since each individual served as their own control, and it also implicitly accounted for potential confounders (e.g., differences in oral hygiene, comorbidities, age, sex, etc.).[37, 38] The study showed that there was no association between IDP and subsequent LPJI. Indeed, there was a lower incidence of IDP in the three months prior to LPJI (incidence rate ratio = 0.89, 95% confidence interval 0.82 to 0.96, p=0.002) than in the preceding 12 months.[36] Furthermore, a sensitivity analysis showed that when the exposure window for IDP was extended to 4 or 5 months before LPJI hospital admission, there was still no significant association between IDP and subsequent LPJI.[36]

If there is no significant association between IDP and subsequent LPJI, then how do we account for the very small proportion of PJI due to OVGS? The reality is that oral bacteria do not only enter the vascular circulation during IDP, but also do so during common daily activities such as tooth brushing, flossing, and other oral hygiene procedures.[39-41] This may also occur during mastication, particularly if there is tooth mobility.[40, 42] However, the frequency with which bacteremia occurs is influenced by an individual's oral hygiene status and periodontal health.[29, 40, 43] Those patients who have good oral hygiene and little or no gingival inflammation are less likely to experience bacteremia following daily activities than those who have poor oral hygiene. The frequency of such bacteremia, particularly in those who have poor oral hygiene, is likely to pose a far more important overall risk for OVGS PJI than an occasional dental office procedure. [28, 41, 44] However, it is neither practical nor sensible to attempt to cover frequent daily events with AP – even in those patients who have poor oral hygiene. It does, however, seem reasonable to improve oral hygiene and eradicate disease around the teeth in all patients

who have prosthetic joints to reduce episodes of OVGS bacteremia.[29, 40] Indeed, the Berbari study found that patients with more than one dental hygiene visit were 30% less likely to develop a prosthetic hip or knee infection, although the study was not sufficiently large for this difference to be statistically significant.[28]

It can be argued that just as obesity, diabetes mellitus, immunosuppression, and rheumatoid arthritis are considered risk factors associated with PJI,[4] and *poor oral hygiene should also be considered as a risk factor*.

In the absence of a positive association between IDP and subsequent LPJI, there is no rationale for providing AP in those with prosthetic arthroplasties undergoing IDP for LPJI prevention. This conclusion is also supported by the only study to evaluate AP efficacy in preventing LPJI, which demonstrated that AP had no effect in reducing the risk of subsequently developing total hip or knee infection (adjusted Odds Ratio, 0.9, 95% confidence interval 0.5-1.6, *p*=NS).[28]

The "downside" of administering AP before dental procedures for patients who have prosthetic arthroplasties must also be considered. AP is a major cost burden on patients and healthcare systems. The annual cost of providing AP in the United States is approximately $59,640,000.[3] There is also a risk of adverse drug reactions due to AP.[45, 46] Although amoxicillin AP is relatively safe in those who do not have a history of penicillin allergy, around 10% of the population report being allergic to penicillins.[47] Moreover, clindamycin, the antibiotic most frequently recommended as an AP alternative for those who have a history of penicillin allergy, has a much worse safety record, with 13 fatal and 149 non-fatal adverse reactions per million AP prescriptions – mainly due to *Clostridioides difficile* (previously known as *Clostridium difficile*) infections.[45, 46] There is also widespread concern that unnecessary use of antibiotics for AP purposes leads to the development of antibiotic resistance among bacteria with the resultant loss of effectiveness of these agents.[48, 49]

It could be argued that all the focus on recommending AP for dental procedures to prevent OVGS PJI is detracting from other measures that are far more likely to be effective in reducing the risk of PJI e.g.,

improving oral hygiene and taking other actions to prevent the vast majority of LPJI caused by a panoply of other organisms.[4] In particular, staphylococci account for more than half of all LPJIs and are common skin and nasal commensals.[4, 36] Indeed, coagulase-negative staphylococci are the predominant causes of PJI and are inherently able to adhere to prosthetic joint surfaces with subsequent biofilm formation. Other indwelling prosthetic devices, vascular catheters, percutaneous procedures, hemodialysis procedures, skin ulcers, injection drug usage, etc. are all associated with an increased risk of staphylococcal bacteremia.[4, 50, 51].[52, 53]

Non-OVGS streptococci are frequently associated with genitourinary tract, gastrointestinal tract, and skin colonization, and have been associated with PJIs following gastrointestinal endoscopy,[54, 55] colorectal neoplasia,[4] cystoscopy,[55] cellulitis,[56] urinary tract infection, etc.[57] One study evaluating PJI risk following esophago-gastro-duodenoscopy found it was increased, particularly after esophago-gastro-duodenoscopy with biopsy (adjusted OR 4, 95%CI 1.5-10), and the most common pathogens were staphylococci, followed by gut-related streptococci, enterococci, gram-negative bacteria, and anaerobes.[54]

Conclusions

These data suggest there is no rationale for patients who have prosthetic joints to receive AP before IDP. Indeed, the risk of adverse drug reactions and contributions to the development of antibiotic resistance, suggest that continuing this practice is likely to be harmful to individual patients and to society, in general. Thus, orthopedic surgeons in many countries have accepted that AP should not be recommended for prosthetic joint patients undergoing IDP. Moreover, there is no evidence that the incidence of LPJI is any higher in the countries where AP is not advocated.

Therefore, it is time to consider recommending against the use of AP before IDP to prevent LPJI in the United States, and instead to focus on the importance of eradicating dental-related disease and establishing good oral hygiene in patients who have prosthetic joints. This is something that dentists and orthopedic surgeons should strongly support to benefit their patients.

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