EDITORIAL COMMENTARY

Antibiotics for Prevention of Periprosthetic Joint Infection Following Dentistry: Time to Focus on Data

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(See the article by Berbari et al, on pages 8–16.)

The population of individuals with artificial joints is steadily increasing, because more devices are implanted, and the life span of people with implants is longer. During a 10-year period, the total number of knee replacements increased from 270,000 to 550,000 per year, and the total number of total hip replacements increased from 120,000 to 200,000 per year in the United States [1]. Prosthetic joint–associated infection (PJI) is a devastating complication that occurs in 0.3%–1% of those patients who undergo total hip arthroplasty and in 1%–2% of patients after total knee arthroplasty [2]. Of these episodes, 35%–40% occur by the hematogenous route [3]. Most of these episodes are sequelae of *Staphylococcus aureus* sepsis, skin infection, or urosepsis [4–6].

It is conceivable that a small portion of these PJI episodes are caused by transitional bacteremia during dental work. However, clinical experience does not favour this hypothesis, and to date, only few indirect data were available for discussion. The potential origin of <10% of the microorganisms isolated from individuals with PJI is oral or dental [7]. In a study of 189 episodes of late infection that occurred after total joint replacement, only 4 (2.1%) of the episodes were due to viridans streptococci [8]. Moreover, a potential oral or dental origin is less likely to be linked to a dental procedure than to poor dental hygiene. Bartzokas et al [9] reported 4 cases in which the infecting organism in the prosthesis was indistinguishable from isolates of the same species obtained from the oral flora on cell wall polypeptide electrophoresis. Examination of the patients' mouths revealed periodontal disease and caries in all patients. In contrast, and to the best of our knowledge, the molecular proof of hematogenously caused PJI as a direct sequel of previous dental treatment is still lacking. Nevertheless, it cannot be excluded that a small minority of hematogenous PJIs are caused by bacteremia directly triggered by dental manipulation. The rate of PJI attributable to bacteremia after dental procedures has been estimated from 0 of 112 cases [6] to 7 (0.2%) of 3490 cases [10].

This low number of cases can be also explained by the bacterial density and the duration of bacteremia during or after dental manipulation. These 2 factors are crucial for successful seeding on extravascular devices [11]. In an experimental model, the presence of a foreign body decreased the minimal abscess-forming dose >100,000 fold [12]. This is attributable to a locally acquired granulocyte defect [12]. Therefore, implants may be endangered during episodes of bacteremia that are induced by dental manipulation. However, the density and duration of bacteremia is much lower during dental work than it is during overt sepsis. After dental extraction in children, it ranges from 1 through 28 colony-forming units (CFU) per milliliter of blood and does not exceed 15 min [13, 14]. In a guinea pig model, the critical bacterial density in the bloodstream resulting in permanent infection associated with extravascular foreign bodies was at least 100 CFU *S. aureus* per mL blood [11]. Similarly, in a rabbit prosthetic knee joint model, 3 intravascular injections of high doses (>10^9 CFU) of *S. aureus* were required to cause PJI [15]. This indicates that hematogenous PJI does not generally occur during transient low-inoculum bacteremia but, rather, occurs during clinically overt sepsis.

In view of the devastating consequences of PJI, many experts have published their opinion regarding the possible benefit of antibiotic prophylaxis before dental work in patients with joint replacements. None of these publications was based on an appropriate clinical trial. Therefore, it does not astonish that some of the experts ar-

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gued in favor of and others against prophylaxis [16, 17]. In this confusing situation, the American Academy of Orthopedic Surgeons (AAOS) and the American Dental Association published a statement reflecting the panel opinion on this topic [18]. Interestingly, the original statement of an expert panel of dentists, orthopedic surgeons, and infectious disease specialists concluded that "antibiotic prophylaxis is not indicated for most dental patients with total joint replacements" [18]. In the meantime, a new statement by the AAOS informs: " … the AAOS recommends that clinicians consider antibiotic prophylaxis for all total joint replacement patients prior to any invasive procedure that may cause bacteremia" [19]. This discrepancy is hard to understand. Because physicians and dentists will follow the most recently published AAOS information statement, this has several unfavorable consequences: First, general prophylaxis increases the (unjustified) use of antibiotics; second, the risk of adverse effects (eg, toxicity and allergy) may not be counterbalanced by prevention of PJI; and third, the dentist may be sued for not giving antibiotics according to the published consensus statement. This unjustified liability problem can only be tackled with conclusive data from a clinical study.

In this issue of *Clinical Infectious Diseases*, Berbari et al [20] present a case-control study to examine the association between dental procedures—with or without antibiotic prophylaxis—and PJI. The rationale for this study was the discrepancy between the multitude of expert opinions and the lack of evidence regarding the benefit of antibiotic prophylaxis before dental procedures. The authors found no increased risk of PJI after dental procedures. In addition, antibiotic prophylaxis was not associated with risk reduction.

Infectious diseases specialists envy the sample sizes in clinical studies performed by investigators who have access to very large numbers of patients (eg, cardiology studies), in which small differences in outcomes can be thoroughly tested for their statistical significance. However, PJI is a rare event that occurs in ~1% of all primary arthroplasties. The estimated proportion of these cases attributed to dental procedures is small (~10%, or ~0.1% of all primary arthroplasties) [6, 10]. Therefore, even when antibiotic prophylaxis could prevent 80% of all potential hematogenous PJIs after dental procedure, the absolute risk reduction would be only ~0.08%. These figures indicate that at least 1250 individuals must be treated with prophylactic antibiotics during dental procedures to prevent a single PJI. In other words, proof of superiority of antibiotic prophylaxis with a power of 80% in a placebo-controlled trial would require several hundred thousands persons with joint replacements to undergo dental work, with a follow-up of at least 2 years. Therefore, a case-control study, as performed by Berbari et al [20], is the only feasible option.

As with every case-control study, there is an increased susceptibility to sampling and differential measurement bias. Berbari et al [20] elegantly minimized these potential biases by sampling the case patients and control subjects in the same way, by using data (ie, dental charts) recorded before the outcome (PJI) occurred, and by blinding the reviewer of the dental records to the case or control status of the patient. However, matching was not performed on any variable. Yet, given the prospective surveillance of this study and the high number of variables reported to be associated with an increased risk for PJI, it is impossible to find a sufficient number of control subjects with the same value of potential confounding variables. Taken together, the study performed by Berbari et al [20] is methodologically well conducted and provides data on the topic of antibiotics for prevention of PJI during dental procedures.

In 35 of the 339 episodes, PJI was potentially caused by a microorganism from the oral or dental flora. This number is difficult to interpret, because the body site of the bacteria's origin was not examined, and the PJI population includes both hematogenously and intraoperatively acquired infections. However, antibiotic prophylaxis could not lower the risk of PJI. Although it is conceivable that hematogenous seeding from the oral flora to the prosthetic joint does occur, these events seem not to be directly associated with dental procedures.

Good dental hygiene may, therefore, be much more relevant than antibiotic prophylaxis before dental manipulation. Berbari et al [20] showed that more control subjects than patients with PJI had multiple dental hygiene visits [63% vs 54%] and that there was a trend for a lower risk for developing a PJI if a patient had at least 1 dental hygiene visit (odds ratio, 0.7; 95% confidence interval, 0.5–1.03; $P = .07$). This observation is important, because the fear of bacteremia may prevent people with joint replacement from consulting the dentist or undergoing dental hygiene.

In conclusion, the study by Berbari et al [20] has the potential to reassure the responsible physicians and dentists that antibiotic prophylaxis is not needed for all patients with total joint replacement prior to any dental procedure and to convince individuals with joint replacement that meticulous dental hygiene is important.

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