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Is there scientific evidence to support antibiotic prophylaxis in patients with periodontal disease as a mean to decrease the risk of prosthetic joint infections?

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ABSTRACT

Objective: Re-assess the scientific literature to ascertain if there is scientific evidence to support antibiotic prophylaxis in patients with periodontal disease as a means to decrease the risk of prosthetic joint infections.

Introduction: Prosthetic joint infections occur in approximately 0.3 – 2% of patients and, of these, around 6 – 13% are thought to be caused by oral bacteria. Antibiotic prophylaxis prior to dental procedures as a means to prevent a prosthetic joint infection has been controversial throughout the years. It remains unclear to what extent it has a beneficial effect. We do know that bacteraemia of oral origin is directly proportional to any ongoing inflammation or infection, and that a diseased *periodontium* may act as an entry for bacteria to spread to distant locations, through the bloodstream, and potentially be the cause of distant site infections.

Materials and Methods: Updated literature search using the Pubmed (Medline), and the ISI web of knowledge (Thompson Reuters) databases, to identify eligible articles since the previous searches up to April 2019 (last 5 years).

Results: No studies that relate periodontal disease to the development of a prosthetic joint infection were found.

Conclusion: The literature concerning periodontal disease as a risk factor for prosthetic joint infection is, to date, scant. Further research is needed to determine if the patients' periodontal status should be added to the variables in consideration for determining the at-risk patients. Meanwhile clinicians should use their own judgement and experience while avoiding the overstated prescription of antibiotic prophylaxis.

Key-words: prosthetic joint infection, PJI, periodontal disease, periodontitis, oral microbiota, periodontal pathogens, antibiotic prophylaxis

RESUMO

Objetivo: Reavaliar a literatura científica disponível de forma a determinar se há evidência científica que suporte a utilização de profilaxia antimicrobiana em pacientes com doença periodontal como via para a diminuição do risco de infecção de uma prótese articular.

Introdução: As infecções de prótese articular ocorrem em aproximadamente 0.3-2% dos pacientes, dessas, pensa-se que cerca de 6-13% são causadas por bactérias orais. A utilização de profilaxia antimicrobiana em tratamentos dentários, como forma de prevenção de uma possível infecção de prótese articular, tem sido amplamente debatida ao longo dos anos. Até hoje não se chegou a uma conclusão sobre o seu verdadeiro benefício. No entanto, é sabido que a bacteremia de origem oral é diretamente proporcional a qualquer processo inflamatório ou infeccioso ativos e que um periodonto afetado pode constituir uma porta de entrada para bactérias periodontais, permitindo que estas causem infecções à distância por disseminação hematogénica.

Materiais e Métodos: Pesquisa bibliográfica nas bases de dados *Pubmed (Medline)* e *ISI web of knowledge (Thompson Reuters)*, de forma a encontrar artigos de interesse publicados desde a última revisão sistemática até abril de 2019 (últimos 5 anos).

Resultados: Não foi encontrado nenhum estudo que prove a relação entre doença periodontal e a infecção de uma prótese articular.

Conclusão: À data ainda não foi possível provar através de evidência científica direta a existência de uma relação entre doença periodontal e o desenvolvimento de uma infecção de prótese articular. Assim sendo, será necessário realizar mais investigações neste âmbito para determinar se o estado periodontal deve ser acrescentado ao conjunto de fatores que definem os pacientes de risco. Entretanto, os profissionais de saúde devem basear-se na sua experiência e sentido crítico, evitando a sobre prescrição de profilaxia antimicrobiana nestes pacientes.

Palavras-chave: infecção de prótese articular, doença periodontal, periodontite, microbiota oral, bactérias periodontais, profilaxia antimicrobiana

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Ao meu pai, à minha mãe e à minha irmã.

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Aos meus amigos.

ABBREVIATIONS

AAOS – American Academy of Orthopaedic Surgeons

ADA – American Dental Association

AUC - Appropriate Use Criteria

MCBS - Medicare Current Beneficiary Survey

PJI – Prosthetic Joint Infection

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INTRODUCTION

As life expectancy increases worldwide and elderly people remain active for a longer period of time, the number of elective arthroplasties will also continue to rise. Therefore, it becomes necessary for other areas of healthcare to acknowledge and treat patients with prosthetic joints accordingly. ^(1, 2)

Prosthetic joint infections (PJIs) may be categorized as “early”, “delayed” or “late”. Early PJIs occur up to 3 months after the initial placement of the prosthesis and delayed PJIs appear 3 to 24 months after said surgery. These types of PJIs are commonly associated with the surgery itself. Late PJIs may be due to a delayed growth of bacteria introduced into the surgical site at the time of the procedure or related to a distant focus infection, possibly in the oral cavity, which gains access to the joint by hematogenous spread. ⁽²⁻⁴⁾ Transient bacteraemia may enter the bloodstream, not only due to dental procedures, but also during normal oral activities, such as teeth clenching and brushing, or even during chewing, even though the amounts are smaller. ⁽¹⁻³⁾ Currently, prosthetic joint infections occur in approximately 0.3 – 2% ⁽⁵⁾ of patients and, of these, around 6 – 13% are thought to be caused by oral bacteria^(1, 6). Overall, PJIs result in functional impairment of the prosthesis and may even require graft extraction and replacement. ⁽²⁻⁴⁾

In 2012, the American Dental Association (ADA) in cooperation with the American Academy of Orthopaedic Surgeons (AAOS) released a paper outlining the guidelines concerning the management of patients with articular prosthesis when performing dental procedures. In summary, they introduced three main guidelines: that appropriate oral hygiene is of the utmost importance in patients with prosthetic joints; that the physician “might consider discontinuing the prescription of antibiotics in patients with prosthetic hip or knee implants”⁽⁷⁾ and, that they were unable to recommend with certainty the use or not of topical antimicrobials in these patients because of the limited evidence available.^(6, 7)

In 2014, with the purpose of clarifying some doubts among practitioners concerning the previous guidelines, the ADA alone elaborated another paper on the topic based on the previous ADA/AAOS's 2012 guidelines and on an updated literature search. In this paper, they stated that with "moderate certainty the prophylactic prescription of antibiotics in patients with joint prosthetics prior to dental procedures should be avoided"⁽⁸⁾. Thus, contradicting the more careful position of the AAOS. The 2014 ADA Panel based their conclusions on the fact that they found no new evidence demonstrating an association between dental procedures and PJI or any effectiveness for antibiotic prophylaxis, and based on the potential harmful consequences of antibiotics use. ⁽⁸⁻¹¹⁾

In 2017, the Appropriate Use Criteria (AUC) for Management of Patients with Orthopaedic Implants Undergoing Dental Procedures was adopted and approved by the AAOS and the ADA. The 2012 AAOS/ADA and 2014 ADA clinical practice guidelines were the evidence base for this work. The AUC aims to identify the cases in which the use of antibiotic prophylaxis is appropriate in at-risk patients that have orthopaedic implants and are undergoing dental procedures. A total of 64 clinical scenarios were elaborated and voted on by a panel of 14 physicians from various medical and dental specialties. The variables evaluated included: planned dental procedure, immunocompromised status, diabetic glycemic control, history of periprosthetic or deep prosthetic joint infection that required surgery and timing since joint replacement procedure (Sup. Table II). The panel came to the conclusion that in the majority (61%) of the scenarios analysed antibiotic prophylaxis was rarely appropriate. However, they determine that some risk factors, such as: a severely immunocompromised status, absence of glycemic control and history of PJI may constitute as plausible reasons for chemoprophylaxis prior to invasive dental procedures. ^(12, 13)

In order to facilitate the decision-making process, the AAOS made available an electronic tool that identifies the cases where antibiotic prophylaxis is or may be appropriate following the parameters stated above:
https://aaos.webauthor.com/go/auc/default.cfm?auc_id=224965&actionxm=Terms.

^(12, 13)

The sets of guidelines presented by these different entities dismiss the patients' periodontal status. Periodontal health has been shown to affect the incidence of oral bacteraemia, because poor oral hygiene and periodontal infections may produce bacteraemia even in the absence of dental procedures. Furthermore, a simple dental extraction in a patient with periodontitis will result in a greater bacterial load than in a healthy patient. And some of the procedures usually implemented in the treatment of periodontal disease are associated with a relatively high prevalence of bacteraemia. (3, 5, 14, 15)

The aim of this systematic review is to re-assess the scientific literature on the topic to ascertain if there is scientific evidence to support antibiotic prophylaxis in patients with periodontal disease as a means to decrease the risk of prosthetic joint infections. In other words, if periodontal status should be added to the variables in consideration for determining the at-risk patients for a PJI.

MATERIALS AND METHODS

This systematic review was conducted to answer the PICO question: “Is there scientific evidence to support antibiotic prophylaxis in patients with periodontal disease as a mean to decrease the risk of prosthetic joint infections?” It followed the guidelines of Cochrane Collaboration ⁽¹⁶⁾ and Transparent Reporting of Systematic Reviews and Meta-Analyses (PRISMA statement)⁽¹⁷⁾.

Eligibility criteria

All studies, in humans, that reported/evaluated the occurrence of prosthetic joint infections after dental treatment, written in English, Spanish or Portuguese, were considered eligible. Restrictions were also applied to article type, being automatically excluded reviews, letters and case-reports.

Updated literature search

The systematic reviews conducted by the AAOS/ADA (2012 Panel) and the ADA (2014 Panel) were used as the baseline for this literature search. During their extensive search, the 2012 Panel came across with 1 well-conducted case-control study. And, on the updated literature search conducted by the 2014 Panel, 3 additional case-control studies were found.

From this point, we conducted a new updated literature search using the Pubmed (Medline), and the ISI web of knowledge (Thompson Reuters) databases, to identify eligible articles since the previous search up to April 2019 (last 5 years). A structured search strategy was performed with the following keywords used individually and combined with Boolean operators: “prosthetic joint infection”, “PJI”, “periodontal disease” and “periodontitis”.

In order to fully understand the topic and complement this review’s discussion, an additional search was made using other keywords, but following the same strategy: “oral microbiota”, “periodontal pathogens” and “antibiotic prophylaxis”.

Screening, selection and exclusion

The information portrayed in the title and the abstract of the articles attained was used to find the eligible ones. The selected articles were then read in full, and were excluded if they had a study purpose not related to the aim of this systematic review; or, if they didn't evaluated/had reports of the patients' periodontal status before the performed dental treatment. Finally, the articles' individual references were also screened for any additional papers that might be relevant to this review.

Articles found during the updated literature search but not considered eligible or excluded after full-text reading were used latter in the discussion, if relevant.

RESULTS

Search and selection results

The comprehensive updated search retrieved 2 additional papers that respected the eligibility criteria. The full text reading of all eligible papers, 4 from the past systematic reviews and the 2 newly found, revealed that no mention of the patients' periodontal health status was made in any of them, as described below. Accordingly, all studies were excluded.

Berberi et al. (Panel 2012) conducted a large, prospective case-control study to determine if dental procedures with or without antibiotic prophylaxis could act as risk factors for the development of a PJI. The study included a total of 339 patients with a diagnosis of hip or knee PJI (from 2001 up to 2006) who were pared with 339 patients whose prothesis were not infected. The patients oral and systemic health status was evaluated using various parameters and diagnostic tests. Because probing depth measures were not available in all the patients' dental records, it was disregarded. So, no information concerning the presence of periodontal disease was provided. ⁽¹⁵⁾

Jacobson and colleagues (Panel 2014) conducted a case-control study with the objective of relating dental procedures to late PJIs and identifying systemic conditions that may predispose the patients to this type of infection. In addition, the researchers aimed to identified the most common bacteria that cause PJIs. The study included 30 patients

(from 2693 patients with prosthetic knee or hip joints placed between 1970 and 1983) diagnosed with late PJI (> 6 months after the arthroplasty) and matched them with 100 patients that did not develop PJI, serving as controls. Only 1 case (0,04%) of PJI could be associated with dental procedures. In a further analysis of that case it was discovered that the patient had received right hip arthroplasty 10 years previously and had developed the PJI 4 months after undergoing the extraction of 7 periodontally compromised mandibular teeth. If the late PJI was indeed triggered by the oral surgery, the hematogenous bacterial spread was most likely the underlying cause. Unfortunately, no data was provided to support that hypothesis. ⁽¹⁸⁾

The case-control conducted by Swan et al. (Panel 2014) aimed to determine if sentinel events or co-morbidities presented by the patients could be associated to a greater risk of developing a late PJI by hematogenous seeding. This retrospective study identified 17 patients (of 1641 who had a prosthetic joint placed between 1998 and 2006) that had undergone a knee arthroplasty and developed a PJI more than 3 months postoperatively, and matched them with 51 control cases based on age, gender and date of surgery. The co-morbidities accounted for included: diabetes mellitus, ischaemic heart disease, chronic renal failure, chronic obstructive lung disease and chronic liver disease. As for the sentinel infective events, the researchers included: cellulitis, open wound, distant infection, knee procedure, fall, urinary tract infection and dental procedure. In the end, they concluded that only the presence of 4 or more co-morbidities ($P < 0.001$) and an infection of the skin or soft tissues (cellulitis) ($P < 0.011$) were significant predictors of haematogenous prosthetic knee infection. In this case-control study, no reference to the patient's oral health status, and more specifically to the presence of periodontal disease, was made. ⁽¹⁹⁾

Skaar et al. (Panel 2014) performed a nested case-control study with the intent of assessing the association between dental procedures and PJIs. They used the Medicare Current Beneficiary Survey (MCBS), which is a public database, and collected data from 1997 up to 2006. Their study included 42 patients that had undergone a total arthroplasty and developed a PJI, who were matched according to age, sex and number of co-morbidities with 126 patients who did not. Dental treatments were divided into

invasive (teeth cleaning, extractions and endodontic procedures) and non-invasive. This study concluded that all dental procedures, including the invasive ones, did not constitute risk factors for PJIs. Unfortunately, once again, the presence of periodontal disease is neither discussed nor assessed. ⁽²⁰⁾

Kao and colleagues (updated literature review) performed a retrospective cohort study using a national database (Taiwan National Health Insurance Research Database). They gathered a total of 57066 patients who undertook total hip or knee arthroplasty (from 1997 to 2009) and were diagnosed with PJI; and, matched them 1:1 with patients who did not. The researchers aimed to determine if invasive dental treatments (periodontal treatment, surgical and nonsurgical extractions within 2 years after the arthroplasty) may increase the risk of a PJI. No mention of the patients' periodontal health status was made. The researchers found no relation between the dental procedures analysed and PJI. Furthermore, they performed a subcohort of 6513 matched pairs of patients to evaluate the need for antibiotic prophylaxis prior to said dental procedures and concluded that its use does not decrease the risk of developing a PJI. ⁽²¹⁾

Ehrlich et al. (updated literature review) performed a study to evaluate prosthetic joint infected and native knees undergoing total arthroplasty for the presence of periodontal pathogens. In order to identify the colonizing microorganisms, they used the Ibis technology and compared the results with deep 16S sequence analysis and/or 16S FISH. The study lasted 7 years and involved 40 patients. Despite the interesting methodology, the study purpose is not directly related to the aims of this systematic review and once more the patients' periodontal status was not evaluated. ⁽²²⁾

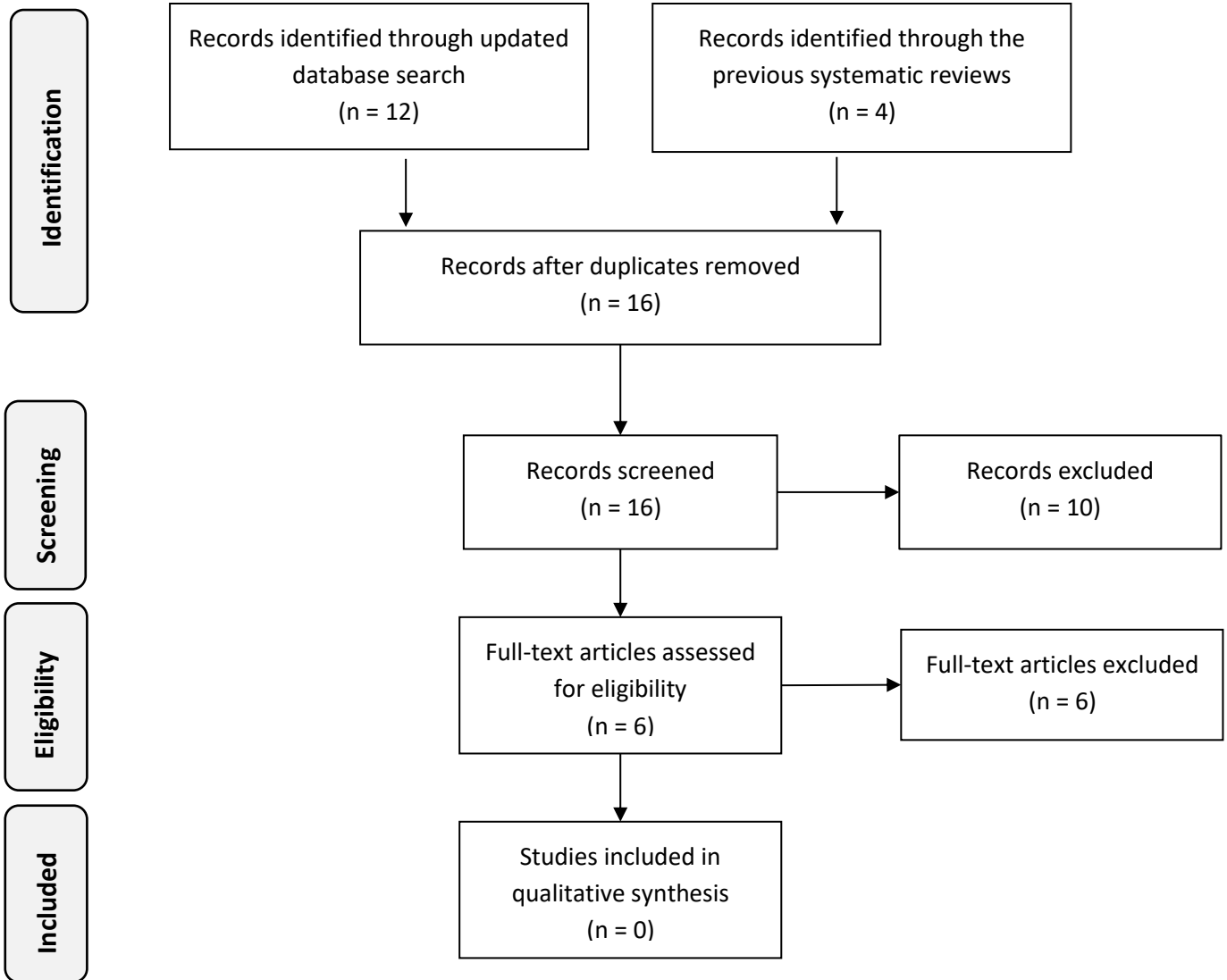


Figure 1 - Flowchart of literature search and selection

DISCUSSION

The 2017 AUC for Management of Patients with Orthopaedic Implants Undergoing Dental Procedures was released by the AAOS/ADA consortium.^(12, 13) However, the presented clinical scenarios neglected the patients' periodontal status. The aim of this systematic review was to re-assess the scientific literature to ascertain if periodontal status should be considered for determining the at-risk patients for a PJI.

Main results

A comprehensive and updated literature search was made in the most relevant scientific databases but no studies able to clarify our study question were found.

In fact, only well-conducted clinical trials or case-control studies would effectively allow us to answer said question. However, the indirect scientific evidence attained suggests a plausible relationship between periodontal disease and the development of late PJIs.

Oral microbiota and PJIs

The oral microbiota is diverse and the human mouth offers multiple environments for microbial multiplication and colonization. More than 300 species of microbes have been identified in the human mouth and an estimated 10^{14} organisms occupy it. This being said, it is of the outmost importance to understand if there is a relation between these oral bacteria and distant site infections, such as PJIs.^(23, 24)

The most prevalent oral infectious diseases include dental caries and periodontal disease. Periodontal disease affects up to 90% of the world's population and may be divided into two main forms: gingivitis and periodontitis. Gingivitis is a reversible inflammation of the gums caused by the accumulation of bacterial plaque. Clinically, the tissues affected become red, edematous and bleed while brushing. This condition may remain stable for months or years, and will not progress to periodontitis unless there are changes in the environment or in the host's susceptibility. The progression of gingivitis leads to the irreversible loss of gingiva, periodontal ligament fibres and alveolar bone – i.e. periodontitis.^(23, 24)

When the *periodontium* is healthy bacteria cannot enter the gingival tissue, but as periodontal disease develops, bacteria gain access through the pocket epithelium and reach the underlying gingival connective tissue. Thus, allowing bacteria to spread, through the bloodstream, and potentially be the cause of distant site infections. ^(23, 24)

Early PJIs are usually caused by virulent organisms such as *Staphylococcus aureus*, gram-negative *bacilli*, anaerobic organisms or mixed infections. Delayed PJIs are due to less virulent pathogens such as *Enterococci*, coagulase-negative *Staphylococci* or *Propionibacterium* species. And, late PJIs are typically caused by *S. aureus* and *Streptococcus epidermidis* (57%) or by *viridans-group streptococci* (2%). ^(23, 25, 26) The question here is whether or not some of these bacteria might originate from the oral cavity or even be implicated in periodontal disease.

Berberi et al. concluded that *Staphylococci* (*S. aureus* and *coagulase-negative staphylococci*) were the most frequently encountered bacteria in PJIs. Furthermore, 10.3% of the PJIs analysed were caused by microorganisms of potential oral or dental origin, such as: *beta-hemolytic streptococci*, Anaerobes (*Peptostreptococcus* species and *Actinomyces* species), *viridans-group streptococci*, *Abiotrophia/Granulicatella* species, *Streptococcus*-like organisms not further identified and *Gemella* species. ⁽¹⁵⁾

Besides that, in the parallel literature review conducted (Sup. Table I), several case reports were found that relate normal oral or dental procedures to the development of PJIs. Even though it is difficult to establish a direct relation, it is reasonable to assume that haematogenous seeding was the underlying cause of these PJIs, given the timing of the infection, the organism identified and the known association between dental procedures and transient bacteraemia. Nevertheless, it is important to acknowledge that other sources of infection may not be excluded.

Furthermore, it was noted that various periodontal pathogens have been implicated in PJIs, such as: *Rothia spp.*, *Granulicatella spp.* and *Fusobacteria nucleatum*. Albeit rare causes of infection, it should be kept in mind that they may lead to PJI in patients with

chronic pulmonary disorders, rheumatoid arthritis or with an immunosuppressed system, as these constitute predisposing factors for opportunistic infections. (26, 27)

Dental procedures as risk factors for PJIs

The role of dental procedures in the development of PJIs has been debated for more than 3 decades. Unfortunately, a direct relation between specific dental treatments and a higher risk for a PJI is yet to be established. What is indeed known is that, transient bacteraemia following normal oral and dental activities, such as chewing or tooth brushing, occurs in up to 51% of individuals and is usually cleared by the host's defences within 10 minutes. Dental procedures generate a greater bacteraemia than any physiological function, but it is also of low grade and duration. Thus, it seems that the bacteraemia needed to cause hematogenous seeding capable of producing a PJI is far higher than that caused by any dental procedure or physiologic activity. (3, 15, 28) Overall, dental procedures can be classified as high- and low-risk, based on the levels of bacteraemia they induce (Table I). (3, 23) The AUC for Management of Patients with Orthopaedic Implants Undergoing Dental Procedures classifies dental procedures only based on the manipulation or not of gingival or periapical tissues, or perforation of the oral mucosa (Sup. Table II). The procedures that involve manipulation of the gingiva or periapical tissues, or perforation of the oral mucosa, are those associated with a higher risk of bacteraemia. (12, 13)

Incidence of bacteraemia	Dental procedure
Low	Restorative dentistry (operative and prosthodontic) Local anesthetic injections Intracanal endodontic treatment, post placement and build-up Placement of rubber dam Post-operative suture removal Placement of removable prosthodontic/orthodontic appliances Taking of oral impressions Fluoride treatments Taking of oral radiographs Orthodontic appliance adjustment
High	Dental extractions Periodontal procedures, including surgery, subgingival placement of antibiotic, scaling and rootplaning, probing, recall maintenance Dental implant placement and replantation of avulsed teeth Endodontic instrumentation beyond the apex Endodontic surgery Placement of retraction cord Initial placement of orthodontic bands but not brackets

Intraligamentary and intraosseous local anesthetic injections
 Prophylactic cleaning of teeth or implants where bleeding is anticipated

Table I - Incidence of bacteraemia in dental procedures (adapted from Kotzé Marthinus, 2009) ⁽³⁾

Nowadays, it is known that bleeding caused by dental procedures cannot be seen as a predicting factor for odontogenic bacteraemia above the physiological level. However, a simple dental extraction in a patient with periodontitis will result in a greater bacterial load than in a healthy patient. And some of the procedures usually implemented in the treatment of periodontal disease are associated with a relatively high prevalence of bacteraemia (Table II). ^(3, 5, 14, 15)

Dental procedure	Prevalence of bacteraemia
Single extraction	51%
Multiple extractions	68-100%
Endodontics (intra-canal instrumentation)	0-31%
Endodontics (extra-canal instrumentation)	0-54%
Periodontal surgery (flap procedure)	36-88%
Periodontal surgery (gingivectomy)	83%
Scaling and root planning	8-80%
Periodontal prophylaxis	0-40%
Tooth brushing	0-26%
Dental flossing	20-58%
Interproximal cleaning with toothpicks	20-40%
Irrigation devices	7-50%
Chewing	17-51%

Table II - Prevalence of bacteraemia after dental procedures (taken from Kotzé Marthinus, 2009) ⁽³⁾

As a preventing measure, it is advisable that all patients who are undergoing total joint arthroplasty have good oral health and are encouraged to seek dental care, as suggested by the international consensus on periprosthetic joint infection⁽³⁾. This is important because bacteraemia of oral origin is directly proportional to any ongoing inflammation or infection. Dental treatment prior to the arthroplasty should be aggressive in order to eliminate all infections. So, if restorative, endodontic or periodontal treatments are not successful the involved teeth should be extracted to minimize the risk of a late PJI. ^(3, 15, 29)

Antibiotic prophylaxis in dental procedures

Antibiotic prophylaxis in patients with prosthetic joints prior to dental procedures has been of particular controversy throughout the years. It remains unclear to what extent antibiotic prophylaxis has a beneficial effect on the incidence, duration, and amount of bacteraemia. The literature suggests that there is an unknown risk reduction of an already very low risk of dental PJIs. ^(28, 30) When prescribing an antibiotic, physicians should take into consideration its possible side effects, resistance by the bacteria, costs and drug interactions. The side effects are mainly of the gastrointestinal system (10-60%): nausea, vomiting, and diarrhea, or allergic reactions (4%). So, narrow spectrum antibiotics should be considered the first choice because they produce the least alterations in the gastrointestinal tract. Severe side effects such as anaphylactic shock or death are also described, but none of these complications have been reported after 1 dose of amoxicillin prescribed to prevent a distant site infection such as a PJI. ^(1, 4, 11, 28, 30)

Apart from the AAOS and ADA, several other international entities and researchers have focused on this subject over the years.

The AFSSAPS/ANSM (French health authorities), in 2011, stated that antibiotic prophylaxis is not required prior to dental procedures in patients with prosthetic joints, no matter the age of the implant, the patient's health status or the type of procedure. On the other hand, they enhanced the quality of daily oral hygiene and the need to treat any possible dental infection site before the joint replacement, as the most important means to prevent PJIs.⁽³⁰⁾ Similarly, a joint committee of the Dutch Orthopaedic and Dental Societies, conducted a systematic literature review on the use of antibiotic prophylaxis in patients with joint prosthesis. They came to the conclusion that "antibiotic prophylaxis should not be used to prevent PJIs of dental origin in these patients, whether they had a normal or an impaired immune system". They also stated that guidelines from other countries tend likewise not to recommend generalized antibiotic prophylaxis, but often include high-risk groups of patients in which prophylaxis may be justified.⁽⁵⁾ For example, the Australian Orthopaedic Association, British Orthopaedic Association, Swiss Society for Infectious Diseases and New Zealand

Orthopaedic Association have all made similar suggestions for prescribing prophylactic antibiotics only to patients at an increased risk of infection.⁽⁴⁾

As said earlier, in 2017, the AUC for Management of Patients with Orthopaedic Implants Undergoing Dental Procedures concluded that in the majority of the cases antibiotic prophylaxis is rarely appropriate. However, they determine that some risk factors, such as: a severely immunocompromised status, absence of glycemic control and history of PJI may constitute as plausible reasons for chemoprophylaxis prior to invasive dental procedures.^(12, 13)

Antibiotic prophylaxis in periodontally compromised patients

Indirect scientific evidence suggests that periodontal disease and the procedures used to treat it are associated with higher levels of bacteraemia than those produced during physiological activities or normal oral hygiene. Furthermore, some bacteria often linked to the development of periodontal disease may be causative microorganisms of PJIs through hematogenous seeding.

Albeit there is a general consensus on the rational use of antibiotics, it is reasonable to assume that patients with periodontitis that undergo invasive dental procedures may constitute a plausible at-risk group. Ultimately the decision on whether antibiotic prophylaxis may or not be prescribed, in this clinical scenario, relies on the physician's own experience and clinical judgment and on the patient's values and opinion.^(12, 13) Because this is a controversial topic an overstated prescription of antibiotic prophylaxis is still observable, in the absence of better evidence.^[3]

Patient type	Antibiotic	Protocol (single dose 30-60 minutes before dental procedure)	
		Adults	Children
Patients not allergic to penicillin	Amoxicillin	2g	50 mg/kg
Patients not allergic to penicillin and unable to take oral medication	Ampicillin or	2g IM* or IV	50 mg/kg IM or IV
	Ceftriaxone	1g IM or IV	50 mg/kg IM or IV
Patients allergic to penicillin	Cephalexin*** or	2g	50 mg/kg
	Azithromycin or clarithromycin	500mg	15 mg/kg
Patients allergic to penicillin and unable to take oral medication	Ceftriaxone ⁺ or	1g IM or IV	50 mg/kg IM or IV
	Azithromycin or clarithromycin	Equivalent dose 500 mg IV	Equivalent dose

Table III - Most commonly suggested antibiotic prophylaxis regimens (taken from the Appropriate Use Criteria for Management of Patients with Orthopaedic Implants Undergoing Dental Procedures, 2017).⁽¹³⁾ For a user-friendly version of criteria, access www.orthoguidelines.org/auc.

*Intramuscular injections should be avoided in people receiving anticoagulants;

**Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage.

⁺Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillin or ampicillin

CONCLUSION and FUTURE PRESPECTIVES

In summary, the literature concerning periodontal disease as a risk factor for PJI is, to date, scant. And, this systematic review showed a major knowledge gap on the topic. Currently, there is no evidence to support or exclude the need of antibiotic prophylaxis as a means to decrease the risk of prosthetic joint infections in patients with periodontal disease.

Meanwhile, clinicians should use their own judgement and experience while avoiding the overstated prescription of antibiotic prophylaxis.

Part of this knowledge gap could be explained by the difficulties in conduct such studies. Longitudinal prospective studies raise obvious ethical questions and retrospective studies may be difficult to conduct due to lack of data concerning the patients' periodontal status or heterogeneities in the definition of periodontal disease. As so, well-designed transversal case-control studies could be a good starting point, despite the less evidence for causal inference.

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SUPPLEMENTAL DATA

Bacteria	Bacteria characteristics	Study report
<i>Streptococcus sanguis</i> spp.	Commensal to the oral microbiota.	Christos A Bartzokas et al. demonstrated that the <i>S. sanguis</i> isolated from patient's mouths are similar to those found in the infected prosthesis. An hematogenous dissemination of these bacteria originating in the mouth is the most likely source of infection. ⁽³¹⁾
<i>Streptococcus gordonii</i>	Commensal to the oral microbiota. Normally not pathogenic, but it initiates colonisation by creating surfaces for other bacteria to adhere to.	Rick Klein et al. described a rare case of PJI related to a vigorous dental flossing regimen that allowed these bacteria to spread through the bloodstream. These bacteria had previously been identified as a cause for other systemic infections, but their role in PJIs is extremely rare, with only one other case reported in the literature. ⁽²⁵⁾
<i>Rothia</i> spp.	Form the normal oral and respiratory tract microbiota. Commonly associated with the development of caries, periodontal disease and various systemic and oral infections.	Manish N. Trivedi et al. presented a case report where a PJI was caused by <i>Rothia</i> species. In this case, the source of infection was thought to be haematogenous spread originating from the chipping of a tooth and facial swelling. ⁽²⁷⁾ Firat Ozan et al. reported the first case of PJI caused by <i>R. denticariosa</i> . In this case, the patient had undergone a tooth extraction. ⁽²⁶⁾ Furthermore, a total of 7 PJIs have been reported in the literature as being caused by <i>R. mucilaginoso</i> . ⁽²⁶⁾
<i>Granulicatella</i>	Commensal to the oral microbiota. Rarely act as human pathogens.	5 cases of PJIs have been reported in the literature as being caused by the genera <i>Granulicatella</i> . Nora Renz et al. reported a case of PJI in a patient diagnosed with severe periodontitis. The causative microorganism was identified as <i>Granulicatella para-adiacens</i> and it most likely originated from a periapical dental abscess. ⁽³²⁾
<i>Fusobacteria nucleatum</i>	Ubiquitous to the oral cavity and periodontal pathogen.	Previous studies had already proven the ability of <i>F. nucleatum</i> to translocate hematogenously to distant sites, but a study by Stéphanie Témoins et al. suggests that these bacteria can specifically translocate from the oral cavity to the synovial cavity, where they may play a role in PJIs. ⁽²⁴⁾ Corona et al. published a case report where the patient had moderate to severe periodontitis and developed an acute PJI. ⁽³³⁾ JC. Rodríguez Duque et al. described a transient bacteraemia related to teeth extractions as being the rare cause of PJI by <i>F. nucleatum</i> . ⁽³⁴⁾

<i>Actinomyces spp.</i>	Normally found in the gastrointestinal, respiratory and female genitourinary tracts.	Brown et al. and Strazzeri et al. both mentioned <i>Actinomyces spp.</i> originating from a dental cleaning and a dental procedure, respectively, as the causes for a PJI. ⁽³⁴⁾
<i>Veillonella spp.</i>	Ubiquitous to the oral cavity.	Zannetti-Schaerer et al. presented a case where a PJI was associated with the bloodstream spread of these specimens from the oral cavity as a result of a dental intervention. ⁽³⁴⁾
<i>Parvimonas micros</i> (formerly <i>Micromonas</i>)	Normally found in the oral microbiota and gastrointestinal tract. May act as periodontal pathogens.	Bartz et al. described a case of PJI caused by <i>Parvimonas micros</i> associated with a tooth extraction. ⁽³⁴⁾

Supplemental Table IV - Resume of the data acquired in the literature review performed

Indication	Classification(s)
Planned Dental Procedure	<ul style="list-style-type: none"> a. Dental procedures that do not result in the manipulation of gingival or periapical tissues, or perforation of the oral mucosa b. Dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa
Immunocompromised Status	<ul style="list-style-type: none"> a. Not severely immunocompromised b. Severely Immunocompromised
Glycemic Control	<ul style="list-style-type: none"> a. No current or active diabetes diagnosis b. Active known diabetic, Hemoglobin A1C < 8 or Blood Glucose < 200 c. Active known diabetic, Hemoglobin A1C ≥ 8 or Blood Glucose ≥ 200 d. Active known diabetic, Hemoglobin A1C Unknown, Glucose Unknown
History of periprosthetic or deep prosthetic joint infection of the hip or knee that required an operation:	<ul style="list-style-type: none"> a. No b. Yes
Timing since hip or knee joint replacement procedure:	<ul style="list-style-type: none"> a. < 1 year b. ≥ 1 year

Supplemental Table II - Patient indications and classifications (taken from the Appropriate Use Criteria for Management of Patients with Orthopaedic Implants Undergoing Dental Procedures, 2017). ⁽¹³⁾

Declaração

Monografia de Investigação/ Relatório de Atividade Clínica

Declaro que o presente trabalho, no âmbito da Monografia de Investigação/Relatório de Atividade Clínica, integrado no Mestrado Integrado em Medicina Dentária, da Faculdade de Medicina Dentária da Universidade do Porto, é da minha autoria e todas as fontes foram devidamente referenciadas.

Porto, 24 de maio de 2019

A autora,

Ana Isabel de Sousa Moreira

(Ana Isabel de Sousa Moreira)

Parecer do Orientador

Informo que o Trabalho de Monografia desenvolvido pela estudante Ana Isabel de Sousa Moreira, com o título: "*Is there scientific evidence to support antibiotic prophylaxis in patients with periodontal disease as a mean to decrease the risk of prosthetic joint infections?*", está de acordo com as regras estipuladas na FMDUP, pois foi por mim conferido e encontra-se em condições de ser apresentado em provas públicas.

Porto, 24 de MAIO de 2019

A orientadora

LUZIA MARTINS MENDES GONÇALVES

(Professora Doutora Luzia da Conceição Martins Mendes Gonçalves)