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Development of a dental clinical decision support system

Rademacher, W.M.H.

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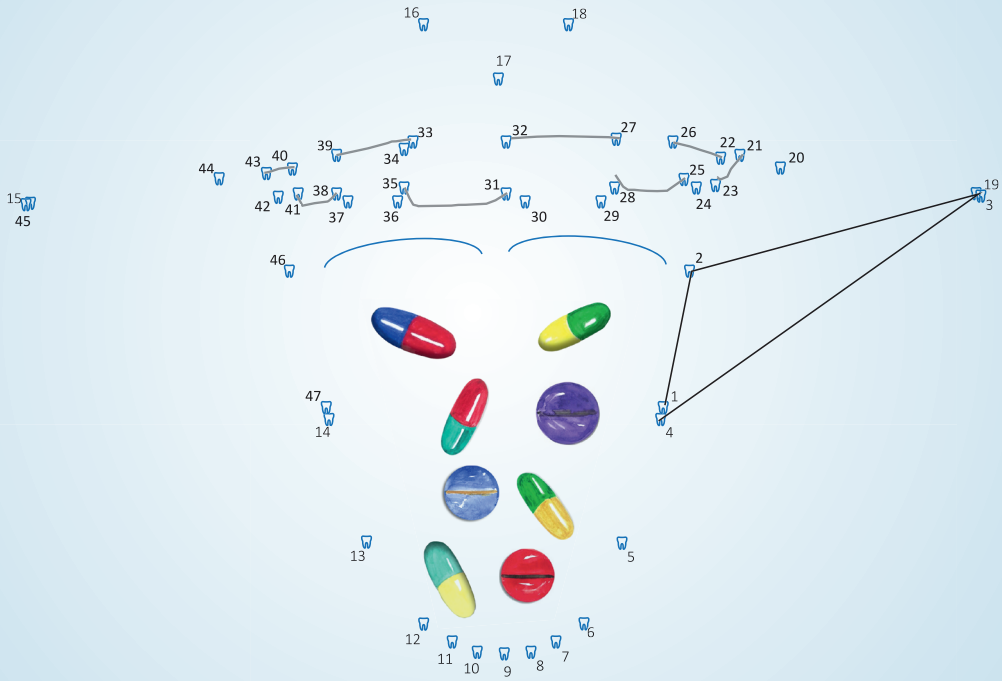
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2 Antibiotic prophylaxis is not indicated prior to dental procedures for prevention of periprosthetic joint infections: A systematic review and new guidelines of the Dutch Orthopaedic and Dental Societies

This chapter is based on the following publication:
Antibiotic prophylaxis is not indicated prior to dental procedures for prevention of periprosthetic joint infections: A systematic review and new guidelines of the Dutch Orthopaedic and Dental Societies

Willem M.H. Rademacher; Geert H.I.M. Walenkamp; Dirk Jan F. Moojen; Johannes G.E. Hendriks; Theo A Goedendorp and Frederik R. Rozema

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ABSTRACT

To minimize the risk of hematogenous periprosthetic joint infection (HPJI) international and Dutch guidelines recommended antibiotic prophylaxis prior to dental procedures. Unclear definitions and contradicting recommendations in these guidelines have led to unnecessary antibiotic prescriptions. To formulate new guidelines a joint committee of the Dutch Orthopaedic and Dental Societies conducted a systematic literature review to answer the following question: is antibiotic prophylaxis recommended in patients (with joint prostheses) undergoing dental procedures in order to prevent dental HPJI?

The Medline, Embase and Cochrane databases were searched for RCTs, reviews and observational studies until July 2015. Studies were included if they reported on patients with joint implants undergoing dental procedures, and either considered HPJI as an outcome measure or described a correlation between HPJI and prophylactic antibiotics. A guideline was formulated using the GRADE-method and AGREE II guidelines.

Nine studies were included in this systematic review. All were rated “very low quality of evidence”. Therefore, additional literature was consulted to address clinical questions that provide further insight into pathophysiology and risk factors. The 9 studies did not provide evidence that using antibiotic prophylaxis reduces the incidence of dental HPJI, and the additional literature supported the conclusion to discourage antibiotic prophylaxis in dental procedures.

Prophylactic antibiotics should not be prescribed in order to prevent dental HPJI to patients with a normal or an impaired immune system function. Patients are recommended to maintain good oral hygiene and visit the dentist regularly.

INTRODUCTION

Worldwide, the number of patients with artificial joint prostheses has been increasing for decades. Prosthetic joint infections (PJIs) occur in approximately 0.3-2% of the patients and infection rates continue to rise.[1, 2] PJI is caused by bacterial contamination perioperatively or via hematogenous routes. Hematogenous PJIs (HPJIs) are responsible for about one third of the PJI cases and are thought to occur mainly as late PJI (>2 years post-implantation), but the proportion of HPJI in early PJI (<3 months post-implantation) is in fact unknown.[1, 3] Bacteria causing HPJI originate from distant anatomic sites such as the skin, urinary tract, and to a lesser extent the oral cavity (10% of all HPJI).[1,4] The hypothesis that transient bacteremia from the oral cavity can cause HPJIs in humans seems plausible but is mainly based on animal experiments and human studies in which bacteremia are used as a surrogate marker for the risk of HPJI.[5-7]

To reduce the risk of HPJI due to oral bacteremia, several national guidelines recommend antibiotic prophylaxis prior to dental procedures. Interestingly however, the literature is inconsistent with regard to the efficacy of antibiotic prophylaxis in reducing the incidence of HPJI of dental origin.[8, 9] Due to the lack of convincing supporting evidence, and possibly the fear of legal consequences, the AAOS/ADA guideline recommendations have been contradictory and confusing and resulted in defensive healthcare practices. European guidelines have often adopted AAOS/ADA guidelines, but tend to recommend antibiotic prophylaxis less frequently.

In the Netherlands, the 2010 guidelines advised antibiotic prophylaxis in cases involving dental procedures in “infected” oral pathology and in patients with “reduced immune capacity”.[10] These poorly defined indications were confusing. As a result, physicians formulated their own regional guidelines with varying indications for antibiotics which possibly lead to unnecessary antibiotic prescriptions.[11]

Therefore, the Dutch Orthopaedic and Dental Societies appointed a joint committee to formulate new and better defined guidelines for the prudent use of antibiotics for prophylaxis. This committee conducted a systematic literature review to answer the following question: is antibiotic prophylaxis recommended in patients (with joint prostheses) undergoing dental procedures in order to prevent dental HPJI?

MATERIAL AND METHODS

The committee consisted of orthopaedic surgeons (GW,JH,DM), a dental practitioner (TG), an oral maxillofacial surgeon (OMFS) (FR) and an OMFS resident (WR). The committee was supported by a medical literature specialist of the Knowledge Institute of Medical Specialists who: formulated the systematic literature searches, supported the literature quality assessment by the committee and ensured that the recommendations were formulated according to the AGREE II guidelines.

A systematic literature review was performed using the electronic Medline, Embase and Cochrane database. The search parameters were concentrated on literature published between 1980-2015 in English, German, French and Dutch. Only systematic reviews and original randomized controlled trials were eligible for full-text analysis, provided that they reported on patients with joint implants (e.g. knee, hip, shoulder) undergoing dental treatment, and either considered HPJI as 1 of the outcome measures or described a direct correlation between HPJI and antibiotic prophylaxis. The search strategy was conducted and results were analyzed according to criteria that were specified a priori.[12] All committee members individually screened the articles for title and abstract, and if eligible, read them full-text. Since this search provided just 1 eligible publication, a second similar search and analysis was performed, this time including observational studies. Finally, additional literature was found through the reference list of the selected publications. Two investigators (GW,WR) extracted information from the included trials on: 1) study characteristics (i.e. design, follow-up course) and inclusion and exclusion criteria; 2) overall participant demographics (e.g. prosthesis type, joint age); 3) methods of diagnosing dental HPJI (e.g. questionnaires, microbiological tests) and outcome measures (e.g. incidence of PJI and HPJI, type of dental treatment, use of prophylactic antibiotics). Relative risk reduction in dental HPJI due to antibiotics was the primary outcome measure. The final systematic literature searches were performed until July 2015.

The GRADE-method was used to determine the risk of bias of the included studies. In light of the limited quantitative and qualitative results presented by the systematic review, we formulated several additional questions that might provide further insight into the pathophysiology of dental HPJI, risk factors and risk procedures (Table 1). These questions were answered using literature from additional searches.

Table 1. Additional clinical considerations

1.	Which bacteria are able to cause a HPJI, in what numbers are they required and can antibiotic prophylaxis influence bacteremia?
2.	Is there an increased risk for HPJI in the first 2 postoperative years?
3.	Is bleeding during dental treatment an indicator of a higher risk of HPJI?
4.	Are prophylactic antibiotics indicated in patients with an impaired immune status?
5.	What are the risks and benefits of antibiotic prophylaxis for HPJI?
6.	Is antibiotic prophylaxis a cost-effective means of preventing HPJI?
7.	Is dental screening indicated before and/or after prosthesis placement?
8.	Is antibacterial mouthwash indicated before dental treatment?
9.	What are the international recommendations on antibiotic prophylaxis and dental HPJI?

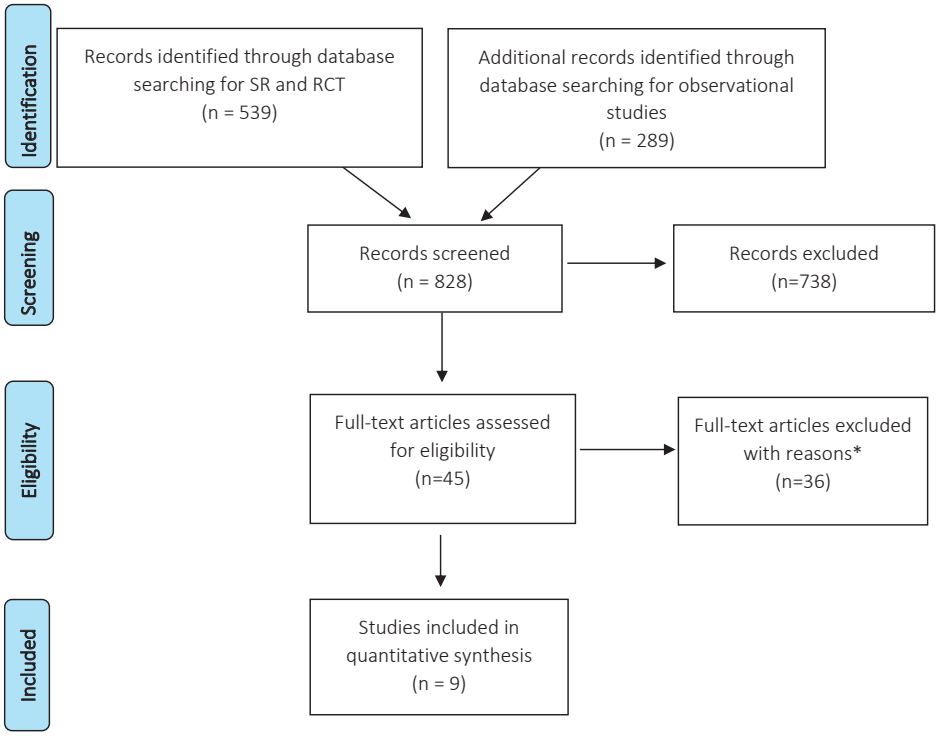
To increase the support of the guidelines and reduce potential bias, the draft guidelines were sent to 7 relevant Dutch medical societies. With help of their comments a definitive guideline was written and accepted by the Dutch Orthopaedic and Dental Societies in February 2016. Thereafter, more recent studies and reviews were included for the completeness of this manuscript.

RESULTS

In the systematic literature review, 828 studies were screened for title and abstract, of which 45 were selected for full-text critical appraisal. Following the exclusion of 36 full-text articles for systematic reasons (Table A2, see appendix), 9 eligible studies remained: 6 as a result of the systematic searches and 3 by checking the references of the included studies (Figure 1). Study characteristics are presented in Table 3. The incidence of PJI varied in these studies between 1.2-2.0% and the incidence of HPJI 0.1-1.7%. Based on indirect evidence, the incidences of dental HPJI ranged from 0.03-0.2%. None of the studies reported a significant reduction of dental HPJI associated with antibiotic prophylaxis.

Due to methodological limitations of the individual study designs, all studies were assigned an a priori ranking of “low quality of evidence” and finally downgraded to “very low quality of evidence” on the basis of inconsistency and indirectness of evidence (Table A4, see appendix). Because of this very low quality the risk of bias across studies was not assessed and no meta-analysis was performed.

Figure 1: Flow diagram presenting literature analysis



*The reasons for exclusion were various and are to be found in Table A2 in the appendix.

DISCUSSION

The purpose of this renewed guideline was to provide recommendations on the use of antibiotic prophylaxis in the prevention of dental HPJI. Based on this systematic review we conclude that there is *no* evidence that antibiotic prophylaxis has a positive or negative impact on the incidence of dental HPJI.

However, decisive studies are deemed unfeasible due to the low incidence of dental HPJI and difficulties of matching HPJI bacteria to the oral flora. Therefore, extra literature searches were performed on additional clinical questions that were necessary for the formulation of this guideline (Table 1):

1. Which bacteria are able to cause HPJI, in what numbers are they required and can prophylactic antibiotic prevent bacteremia?

PJIs were predominantly caused by *Staphylococcus Aureus* and *coagulase-negative species*. Oral bacteria like *Peptostreptococcus species*, *Actinomyces species* and

Table 3. Characteristics of included studies

Authors / year of publication	Study design	Joint type (number of patients)	Incidence DHPJI	Conclusion on effect of prophylactic antibiotics on HPJI
Jacobsen and Murray 1980	Retrospective observational	Hips (n=1885)	0.05%	The recommended prophylactic antibiotics should be based on drug sensitivity
Ainscow and Denham 1984	Prospective observational	Hips (n=885) Knees (n=115)	No significant influence of dental treatment on incidence of HPJI	Prophylactic antibiotics would not have prevented the HPJI cases
Waldman et al. 1997	Retrospective observational	Knees (n=3490)	0.2%	Indicated before extensive dental treatment in patients with systemic disease that compromises host defense mechanisms against infection
LaPorte et al. 1999	Retrospective observational	Hips (n=2973)	0.1%	Indicated before extensive dental treatment in patients with systemic disease that compromises host defense mechanisms against infections
Cook et al. 2007	Retrospective observational	Knees (n=3013)	0.03%	n.m.
Uçkay et al. 2009	Prospective observational	Hips (n=4002) Knees (n=2099)	No significant influence of dental treatment on incidence of HPJI	n.m.
Berbari et al. 2010	Prospective case-control	Hips (n= 328) Knees (n=350)	No significant influence of dental treatment on incidence of HPJI	Prophylactic antibiotics do not decrease the risk for DHPJI
Swan et al. 2011	Retrospective case-control	Knees (n=1641)	No significant influence of dental treatment on incidence of HPJI	n.m.
Skaar et al. 2011	Retrospective case-control	Hips (n=468) Knees (n=501) Other (n=31)	No significant influence of dental treatment on incidence of HPJI	Prophylactic antibiotics do not decrease the risk for DHPJI

DHPJI = dental treatment related hematogenous prosthetic joint infection; n.m. = not mentioned

beta-haemolytic streptococcus accounted for 10%.[16, 17] Animal studies showed that bacteremia could lead to HPJI, but the required number of bacteria (colony forming units (CFU)) was high (i.e. >1000 CFU/mL) and often resulted in sepsis.[5, 18, 19]

Based on the risk for subsequent bacteremia, dental procedures are often categorized into "low-risk" (e.g. dental filling, endodontic treatment) and "high-risk" (e.g. dental extraction, periodontal treatment).[17] However, everyday oral-activity leads to bacteremia as well; for example, the incidence of bacteremia after mastication and interdental flossing ranged between 8-51% and 20-58%, respectively.[20] Guntheroth (1984) calculated the 1-month cumulative exposure to bacteremia on the basis of incidence and duration of bacteremia after mastication, tooth brushing, and eventually dental extraction. Out of a total of 5376 minutes of bacteremia, only 6 minutes were attributable to the extraction. In 296 patients, the duration of bacteremia after tooth brushing or dental extraction was less than 20 minutes, and the serum concentration did not exceed 10^4 CFU/ml.[8] The beneficial effect of antibiotic prophylaxis prior to dental procedures on the incidence, duration and height of a bacteremia remains unclear. [8, 9, 21] The eventual clinical relevance will depend on the amount of reduction of these bacteremia parameters, but the literature indicates that there is an unknown risk reduction of an already very low risk for dental HPJI. Moreover, it must be realized that bacteremia is used as a surrogate marker for HPJI, but that there is little evidence that bacteremia truly directly relates to the incidence of dental HPJI.

2. Is there an increased risk for HPJI in the first 2 postoperative years?

In animal experiments, the susceptibility of prostheses for infections is the highest in the first postoperative weeks and decreases rapidly thereafter.[5, 6] Since the follow-up of these experiments is short they do not provide information on long term susceptibility. In 1993, Osmon et al. presented to the Musculo Skeletal Infection Society (MSIS), an incidence of HPJI in humans of 0.14 per 100 prosthesis years in the first 2 postoperative years, and 0.03 thereafter. This unpublished data was cited by Hanssen et al. (1996), and since then used in the consecutive AAOS guidelines, and copied by other authors. Deacon et al. (1996) confirmed that 50% of the HPJI occurred in the first 2 years. More recent studies in humans could not confirm the supposed higher risk in the first 2 years, but even found an increased susceptibility in higher joint ages of >2 or >5 years.[3, 17, 22, 23]

3. Is bleeding during dental treatment an indicator for a higher risk of HPJI?

For a long time, bleeding during dental treatment was considered a marker for the risk of bacteremia and therefore HPJI. This was first identified, though unsupported by literature, by a panel of experts from the American Heart Association.[24, 25] Indeed, in the event of generalized oral bleeding there was an 8-fold increased risk of bacteremia after tooth brushing in patients with higher dental plaque and calculus scores.[8] Roberts (1999) found that dental manipulations of the gingiva (including mastication) and subsequent alternating positive and negative pressure in the capillaries might lead to bacteremia, but that bleeding itself was not an independent predictor. The positive capillary pressure could possibly even prevent bacteria from entering the circulation.

4. Are prophylactic antibiotics indicated in patients with an impaired immune function?

Patients with an impaired immune system (e.g. rheumatoid arthritis, leukopenia) are thought to have an increased risk for HPJI.[23, 26, 27] However, in cases involving dental treatments and HPJI, these risk factors have never been confirmed so far.[17, 28] In our perception, patients with an impaired immune system will have comparable daily bacteremia analogous to healthy individuals as there is no evidence suggesting a higher incidence of HPJI in those patients.

5. What are the risks and benefits of antibiotic prophylaxis?

Only rough calculations were possible for the Dutch setting due to the lack of exact data. For example, we calculated a prevalence of patients with hip and knee prosthesis in the Netherlands ranging from 400,000-800,000, of which 300,000-600,000 would require antibiotics prophylaxis every year. Internationally reported variables had the same magnitude of uncertainties, these included: HPJI after dental procedures, the repercussions of HPJI (e.g. morbidity, mortality)[29], the efficacy of antibiotic prophylaxis[30], and risks associated with antibiotics (e.g. drug-interactions, bacterial resistance).[31, 32] Sendi et al. (2016) confirmed these uncertainties, but were able to calculate a number needed to treat of 625-1,250 patients. We could not calculate a reliable risk-benefit ratio.

6. Is antibiotic prophylaxis a cost-effective means of preventing HPJI?

Lockhart et al. (2013) concluded that the individual costs of antibiotic prophylaxis in relation to dental procedures were low, but the potential total costs for the American healthcare were high. In 1991, the costs for preventing one case of dental HPJI were

calculated at $480,000/year.[33] Several authors compared the cost-effectiveness for prophylaxis with penicillin versus no prophylaxis. They concluded that for the prevention of dental HPJI the regime of no prophylaxis was more cost-effective.[29, 30, 34, 35] Antibiotic prophylaxis was only cost-effective when the risk for HPJI after dental treatment was at least 1.2%[36], or when assuming an antibiotic prophylactic effectiveness of 100% in cases with evident oral infections.[37] However, these assumptions are unrealistic since the risk is probably lower and the 2 studies included did not show a prophylactic effectiveness of 100%.[15, 17]

7. Is dental screening indicated before and/or after prosthesis placement?

Over the last decades there has been an increasing awareness of the association between oral cavity diseases (e.g. gingivitis, periodontitis) and systemic diseases (e.g. rheumatoid arthritis, cardiovascular diseases). Some studies showed a higher incidence of bacteremia in patients with gingivitis or periodontitis after daily dental activities or dental treatment compared to healthy individuals.[38-40] Lockhart et al. (2009) could not confirm these results. It is plausible that the beneficial relation between a healthy oral condition and general health also applies to HPJI[28, 40-42], and in the absence of adverse effects it seems reasonable to recommend good oral hygiene and regular dental controls.

Similar to endocarditis prophylaxis, radiotherapy and intensive chemotherapy treatment, some authors suggested preoperative dental screening prior to orthopaedic implant placement. Interestingly, in 1 study chronic oral foci were left untreated in leukemic and autologous stem cell transplantation patients receiving intensive chemotherapy. The authors concluded that these foci did not increase infectious complications during intensive chemotherapy.[43] It is likely that these cancer patients would be more susceptible to infectious complications than patients planned for arthroplasty. Only 1 study reported on the efficacy of dental screenings before arthroplasty. Out of 100 patients 23 had untreated oral pathologies before arthroplasty. None of them developed PJI within 90 days after implant placement[44]; however, the study may have been underpowered to be conclusive.

8. Is antibacterial mouthwash indicated before dental treatments?

The antibacterial effect of chlorhexidine could reduce the oral bacterial load. Several randomized trials reported a significant reduction of incidence of bacteremia after using antibacterial mouthwash. The authors advised chlorhexidine 0.2% mouthwash before dental procedures.[45, 46] On the other hand, other reports found that chlorhexidine did not reduce the incidence of bacteremia.[21, 42] Given the cost implications and

limited but existing adverse effects (e.g. burning sensation, dental/lingual discoloration) associated with chlorhexidine mouthwash, more decisive studies are necessary before it can be recommended for routine use.

9. What are the international recommendations on antibiotic prophylaxis and dental HPJI?

Finally, we conducted an analysis of considerations and recommendations from international guidelines and expert-opinions on possible indications for antibiotic prophylaxis, dental treatment before arthroplasty and the need for good oral health in order to prevent HPJI. To be well-informed we focused especially on the arguments used in favor of antibiotic prophylaxis. In summary, other guidelines also tend towards recommending no antibiotic prophylaxis, but often include specific risk patients in whom prophylaxis may be justified (Table A5, see appendix).

CONCLUSION

In conclusion, we are convinced that HPJI can occur, and also after dental procedures. Nonetheless, the "very low level of evidence" found in our systematic literature review suggests that there is no convincing proof in the literature that antibiotic prophylaxis is helpful in preventing dental HPJI. At present, we cannot justify recommending antibiotic prophylaxis in so many prosthesis patients undergoing dental procedures, since their efficacy in preventing or reducing HPJI is insufficiently evident. This is supported by the answers (A) to the 9 additional questions:

A1: Bacteremia are common after dental treatment, but also very frequent in daily life. The effect of antibiotic prophylaxis on bacteremia and eventually dental HPJI remains unclear;

A2: The literature is indecisive on the duration of increased susceptibility. It is likely that there is a higher susceptibility for HPJI in a postoperative phase; however, it is unclear whether this phase last up to 2 years. Recent literature even shows an inversed relationship with more HPJI with increasing prosthesis age;

A3: Bleeding during a dental procedure is not correlated with an increased HPJI risk;

A4: Even in patients with an impaired immune system function, antibiotic prophylaxis before dental treatment for prevention of HPJI is not indicated;

A5: It was not possible to perform a reliable risk-benefit analysis with the available Dutch data and the international literature;

A6: Antibiotic prophylaxis for dental treatment in patients with a joint arthroplasty is not cost-effective;

A7: Preoperative dental screening before arthroplasty cannot be recommended on the basis of the literature. However, it is advised to inform patients on the effect of the oral health on systemic diseases and to prevent oral diseases by good daily oral hygiene and regular dental care;

A8: There is insufficient evidence to advise antibacterial mouthwash before dental treatment to prevent HPJI;

A9: Although prevailing opinions and guidelines increasingly tend to advise against the use of prophylactic antibiotics, they often offer exceptions on the basis of inconsistent literature.

The results of this extended literature search fail to deliver sufficient arguments in favor of antibiotic prophylaxis. They showed that risk factors such as joint age and bleeding during dental procedures, which are often presented in guidelines as reason for administering prophylactic antibiotics, appear to be unsupported by literature and are even illogical from a pathophysiological standpoint. Since there are increasing indications that the oral health affects aspects of the general health, we view regular dental control as beneficial; this might help to reduce even a minimal risk of dental HPJI and would have no serious adverse effects or increase in costs.

In other countries, guidelines also tend towards recommending no antibiotic prophylaxis, but often include specific risk patients in whom prophylaxis may be justified. However, daily bacteremia is frequent in both healthy and risk patients and dental treatment contributes only a small fraction to the overall bacteremia. It is also probable that bacteremia could cause dental HPJI only in septic patients. In septic patients, whether or not they have joint arthroplasty, the medical specialist may prescribe antibiotics for therapeutic rather than prophylactic reasons; this also includes patients with an impaired immune system. In a reverse case scenario involving oral infections (e.g. abscess or apical periodontitis), a dentist could indicate antibiotics for therapeutic rather than prophylactic purposes. Exceptions made in most guidelines on antibiotic prophylaxis are unnecessary and only lead to over defensive and

inconsistent healthcare, in which imprudent use of antibiotics has already yielded bacterial resistance throughout the world.

The strength of the current guideline is the combination of expertise and consensus from both orthopedic surgeons, dental practitioners and oral maxillofacial surgeons. Especially when evidence is lacking or the research is impossible to perform, expert consensus from the concerning professions is essential for guidelines to receive broad support and, in this case, for limiting clinicians in prescribing prophylactic antibiotics unnecessarily.

IN SUMMARY, THE GUIDELINE CONCLUDES:

1) There is *no* indication that antibiotic prophylaxis should be prescribed prior to dental procedures in order to prevent HPJI in patients with a joint implant;
2) Neither is there any indication for antibiotic prophylaxis in patients in whom an impaired immune system is supposed or confirmed;
3) Patients are advised to maintain good oral hygiene and to visit the dentist regularly.

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APPENDIX

Table A2: Reasons for exclusion after full-text analysis

Authors	Reason for exclusion
Primary search: systematic reviews and randomized controlled trials	
Aminoshariae & Kulild 2010	Review, no primary research
Brennan et al. 2007	Subject: bacteremia after tooth extraction in children
de Andrade et al. 2012	Subject: effect Chlorhexidine mouth wash on biofilm in dental prosthesis
Deacon et al. 1996	Review, no primary research
Dinsbach 2012	Review, no primary research
Drangsholt 1998	Commentary letter to the editor, no primary research
Esposito et al. 2003	Subject: antibiotic prophylaxis during dental implant placement
George 1995	Subject: questionnaire amongst dermatologists
Jones et al. 1997	Subject: hematogenous infections in vascular prosthesis
Krijnen et al. 2001	Subject: cost and effectiveness in patients with rheumatoid arthritis and orthopedic prosthesis
Kuong et al. 2009	Review, no primary research
Lauber et al. 2007	Subject: questionnaire on antibiotic prophylaxis prescriptions in Canada
Legout et al. 2012	Review, no primary research
Little et al. 2010	Authors opinion on AAOS 2009 guideline, no primary research
Little 1994	Review, no primary research
Marculescu & Osmon 2005	Review, no primary research
Pineiro et al. 2010	Subject: effect of chlorhexidine mouthwash on bacteremia after dental implant placement
Rosengren & Dixon 2010	Subject: review on dermatological infection and antibiotic prophylaxis
Salvi et al. 2008	Subject: review on effect of Diabetes Mellitus II on periodontitis and dental peri-implantitis
Schwartz & Larson 2007	Review, no primary research
Seymour et al. 2003	Review, no primary research
Shurman & Benedetto 2010	Subject: review on antibiotic prophylaxis in dermatology
Strom et al. 2000	Subject: risk factors for endocarditis
Sziegoleit et al. 1999	Subject: analysis of oral microbiome
Tong & Theis 2008	Subject: questionnaire in New Zeeland, no primary research
Tornos et al. 2005	Subject: review on endocarditis
Treister & Glick. 1999	Subject: review on oral health care and rheumatoid arthritis
Uçkay et al. 2008	Review, no primary research
Uyemura 1995	Review, no primary research
Van der Bruggen & Mudrikova 2007	Review, no primary research
Watters et al. 2013	Review of AAOS/ADA guideline ‘12, no primary research

Table A2: Reasons for exclusion after full-text analysis (*continued*)

Authors	Reason for exclusion
Wijngaarden & Kruize 2007	Review, no primary research
Secondary search: observational studies	
Hamilton & Jamieson 2008	Subject: prospective study on PJI, but no description of dental treatment related HPJI
Lacassin et al. 1995	Subject: study on endocarditis risk factors
Meer (van der) et al. 1992	Subject: endocarditis
Meijndert et al. 2010	Subject: oral microbiome
Powell et al. 2005	Subject: periodontal treatment
Wicht et al. 2004	Subject: effect of Chlorhexidine mouthwash on caries prevention
Young et al. 2014	Review, no primary research

Table A4. Bias assessment of included studies according to the GRADE-method

Study reference	Bias due to a non-representative or ill-defined sample of patients?[1]	Bias due to insufficiently long, or incomplete follow-up, or differences in follow-up between treatment groups?[2]	Bias due to ill-defined or inadequately measured outcome?[3]	Bias due to inadequate adjustment for all important prognostic factors?[4]
Ainscow and Denham 1984	unlikely	likely	unclear	likely
Berbari et al. 2010	likely	unclear	unlikely	unlikely
Cook et al. 2007	unlikely	unclear	unlikely	likely
Jacobsen and Murray 1980	unlikely	unclear	unclear	likely
LaPorte et al. 1999	unlikely	unclear	likely	likely
Skaar et al. 2011	unlikely	unclear	likely	unlikely
Swan et al. 2011	likely	unlikely	likely	unlikely
Uçkay et al. 2009	unlikely	unclear	unlikely	unlikely
Waldman et al. 1997	unlikely	unclear	unlikely	unlikely

[1]Failure to develop and apply appropriate eligibility criteria: a) case-control study: under- or over-matching in case-control studies; b) cohort study: selection of exposed and unexposed from different populations.
[2]Bias is likely if: the percentage of patients lost to follow-up is large; or differs between treatment groups; or the reasons for loss to follow-up differ between treatment groups; or length of follow-up differs between treatment groups or is too short. The risk of bias is un-clear if: the number of patients lost to follow-up; or the reasons why, are not reported.
[3]Flawed measurement or differences in measurement of outcome in treatment and control group; bias may also result from a lack of blinding of those assessing outcomes (detection or information bias).
[4]Failure to adequately measure all known prognostic factors and/or failure to adequately adjust for these factors in multivariate statistical analysis.

Table A5. An overview of international recommendations

Country	Year	Reference	Society / profession	AB-prophylaxis should be considered				Recommendations for good oral health	Recommendations for chlorhexidine mouthwash	Dental screening before implant placement	Type of recommendation
				Always	In patients with risk factors	In specific dental procedures with an increased risk	Postoperative risk period				
USA	1997	American Dental Association and American Academy of Orthopaedic Surgeons 1997	ADA + AAOS	no	yes	yes	2 years	yes	n.m.	yes	Advisory statement
	2003	American Dental Association and American Academy of Orthopaedic Surgeons 2003	ADA + AAOS	no	yes	yes	2 years	yes	n.m.	yes	Advisory statement
	2009	American Academy of Orthopaedic Surgeons 2009	AAOS	yes	yes	yes	n.m.	yes	n.m.	n.m.	Information statement
	2012	American Academy of Orthopaedic Surgeons and American Dental Association 2012	ADA + AAOS	no	yes	n.m.	n.m.	yes	indecisive	n.m.	Evidence based guideline
	2014	Chen et al. 2014	AAOS	no	yes	n.m.	Life-time for high-risk patients	n.m.	n.m.	n.m.	International expert consensus
	2015	Sollecito et al. 2015	ADA	no	yes	n.m.	n.m.	n.m.	n.m.	n.m.	Evidence based guideline

Table A5. An overview of international recommendations (*continued*)

Country	Year	Reference	Society / profession	AB-prophylaxis should be considered				Recommendations for good oral health	Recommendations for chlorhexidine mouthwash	Dental screening before implant placement	Type of recommendation
				Always	In patients with risk factors	In specific dental procedures with an increased risk	Postoperative risk period				
UK	1992	Simmons et al. 1992	BSAC	no	no	n.m.	n.m.	n.m.	n.m.	n.m.	Expert opinion
	2003	Seymour et al. 2003	BOA + BDA	no	yes	n.m.	n.m.	yes	yes	yes	Expert opinion
Australia	2005	Scott et al. 2005	OS + OMFS	no	yes	yes	n.m.	yes	n.m.	yes	Expert opinion
New Zealand	2003	New Zealand Dental Association 2003	NZDA	no	yes	yes	n.m.	yes	n.m.	yes	Code of practice
	2013	New Zealand Dental Association 2013	NZDA	no	yes	n.m.	n.m.	yes	n.m.	yes	Code of practice
Canada	2016	Canadian Agency for Drugs and Technologies in Health 2016	CADTH	no	no	n.m.	n.m.	n.m.	n.m.	n.m.	Conclusion of review
South-Afrika	2009	Kotzé 2009	OMFS	no	yes	yes	n.m.	yes	n.m.	yes	Conclusion of review
France	2012	Legout et al. 2012	AFSSAPS + ANSM	no	no	no	no	yes	n.m.	yes	Evidence based guideline
Switzerland	2005	Rossi et al. 2005	SGINF	no	yes	yes	n.m.	n.m.	n.m.	n.m.	Conclusion of review and expert opinion

Table A5. An overview of international recommendations (*continued*)

Country	Year	Reference	Society / profession	AB-prophylaxis should be considered				Recommendations for good oral health	Recommendations for chlorhexidine mouthwash	Dental screening before implant placement	Type of recommendation
				Always	In patients with risk factors	In specific dental procedures with an increased risk	Postoperative risk period				
	2010	Uçkay et al. 2010	OS	no	yes	no	n.m.	yes	n.m.	n.m.	Conclusion of review
	2016	Sendi et al. 2016	OS + I	no	no	yes	n.m.	yes	yes	yes	Conclusion of review
Italy	2009	Termine et al. 2009	D	no	yes	n.m.	n.m.	n.m.	n.m.	n.m.	Conclusion of review
Norway	2010	Olsen et al. 2010	OS + MI	no	n.m.	n.m.	n.m.	yes	n.m.	n.m.	Conclusion of review
Sweden	2012	Swedish Guideline 2012	OS	no	yes	n.m.	<3 months	yes	n.m.	yes	Evidence based guideline
the Netherlands	2011	Swierstra et al. 2011	OS	no	yes	yes	n.m.	n.m.	n.m.	n.m.	Evidence based guideline

AAOS = American Academy of Orthopaedic Surgeons; ADA = American Dental Association; AFSSAPS/ANSM = French health authorities; BASC = British Society for Antimicrobial Chemotherapy; BOA =British Orthopaedic Association; DE = dentists; IN = infectiologists; n.m. = not mentioned; NZDA = New Zealand Dental Association; MI = microbiologists; OMFS = oral and maxillofacial surgeons; OS = orthopaedic surgeons; SGINF = Swiss Society for Infectious Diseases