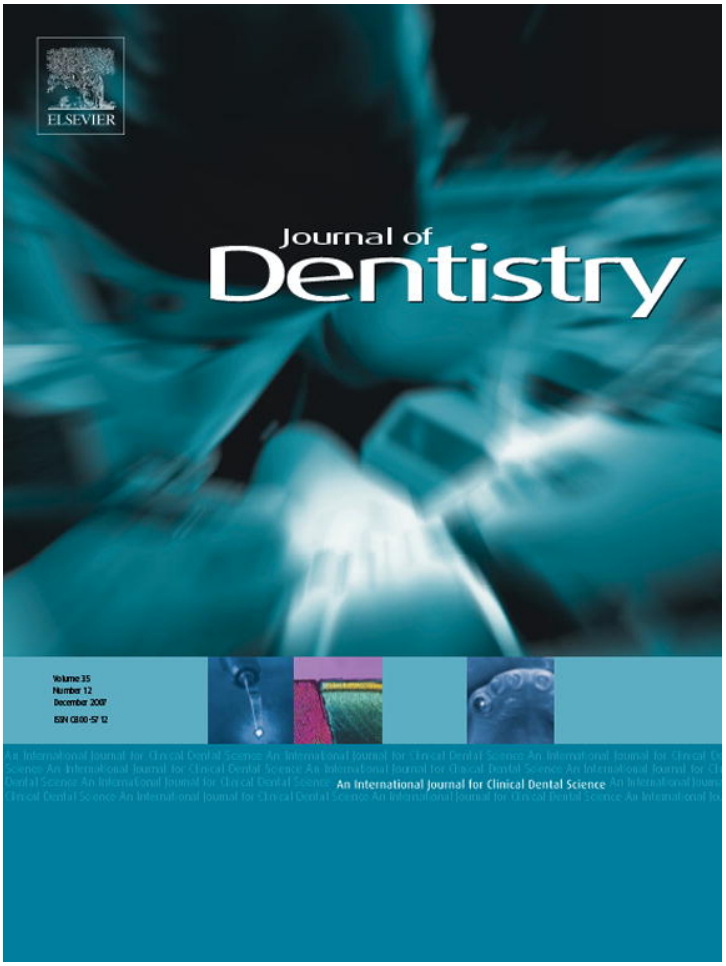

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Review

Antibiotic prophylaxis and postoperative complications after tooth extraction and implant placement: A review of the literature

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ABSTRACT

Objectives: To assess published evidence regarding the use of preoperative antibiotic prophylaxis among children and adults undergoing dental extraction or implant placement.
Data: Research published between 12/31/97 and 6/30/07 in English.
Sources: MEDLINE, PUBMED, EMBASE, EBM Reviews, and Cochrane Central Register for Controlled Trials using the following search terms linked with Boolean AND logic: prophylactic antibiotics, dentistry, tooth, third molar, extraction, implant, endosseous, prophylaxis, prophylactic, infective endocarditis, bacterial, infection, and bacteremia.
Study selection: Eight randomized clinical trials and one retrospective study was found involving preoperative use of antibiotics before tooth extraction. Four additional non-randomized intervention studies among patients undergoing implant placement were found. These 13 studies comprised all of the published research found that met our inclusion criteria. Overall, this body of literature was limited and of poor quality. In general, sample sizes were small and provided insufficient statistical power to avoid type II, or false-negative errors. In some studies no comparison group was included and/or it was difficult to determine the extent to which the intervention had actually been implemented.
Conclusion: With the recent improvements in the current standards of antibiotic prophylaxis in dentistry, further monitoring of antibiotic use among dental practitioners as well as continuing education for practitioners concerning the public health risks related to the over-prescription of antibiotics are needed.

Antimicrobial drug resistance poses a growing threat to public health, at least in part attributable to overuse or misuse of antibiotics.[1,2] Although there is some evidence that clinicians are changing their antibiotic prescribing patterns, there is continued concern about the global problem of resistance and the judicious use of antibiotics.[3,4] Hence, evidence regarding the effectiveness of use of antibiotic prophylaxis in dentistry warrants assessment.

In the spring of 2007, Wilson et al. published the most current AHA guidelines for the use of prophylactic antibiotics in the prevention of infective endocarditis.[5] Similarly, the American Heart Association (AHA), the American Dental Association

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(ADA) and the American Academy of Orthopaedic Surgeons (AAOS) recently changed their recommended protocols for antibiotic prophylaxis against infective endocarditis and against hematogenous total joint infections in patients with prosthetic joint replacement.[6] These guidelines recommend prophylactic regimens for patients at most risk for infective endocarditis and joint infections, and include modifications specifying dental procedures considered to be high risk for bacteremia.[7] Antibiotics in dentistry may also be administered to help prevent adverse outcomes (infection around surgical site) postoperatively, by which dentists make the clinical decision to prescribe antibiotics pre- and/or postoperatively. Unfortunately, literature suggests that dentists may be contributing to the selection of resistance by the misuse antibiotics.[8] The aim of this study was to assess the latest published evidence regarding the use of preoperative antibiotic prophylaxis among children and adults undergoing dental extraction or implant placement, for both the prevention of IE and/or the prevention of postoperative adverse outcomes, and compare these results to the latest guideline revisions.

1. Methods

1.1. *Search strategy*

A literature search was conducted to identify interventional studies involving patients undergoing two common dental procedures, either tooth extraction or implant placement, in which the independent variable was prophylactic antibiotics and the outcomes of interest were infective endocarditis, systemic bacteremia, localized infection, other related symptoms (e.g. swelling, trismus, purulent discharge around the surgical site, fever), and failure of implant retention. Five databases were used to conduct a detailed search for relevant studies published in English between 12/31/97 and 6/30/07 using MEDLINE, PUBMED, EMBASE, EBM Reviews, and Cochrane Central Register for Controlled Trials. Search terms which were linked with Boolean AND logic included 'prophylactic antibiotics' and 'dentistry' and, tooth, third molar, extraction, implant, endosseous, prophylaxis, prophylactic, infective endocarditis, bacterial, infection, and bacteremia. The selected study period corresponds to the latest revisions of antibiotic prescription guidelines in dentistry.

Two reviewers independently searched the literature and studies that met the inclusion criteria (studies of prophylactic use of antibiotics for tooth extraction or implant placement published between 12/31/97 and 6/30/07) then underwent a quality assessment review using a standardized grading sheet that was adapted from Jampel et al.,[9] Cooper et al.,[10] and Friedman et al.[11] The reviewers independently assessed each study and then met to assure inter-rater reliability. When there were differences in scoring, the reviewers discussed the study and reached consensus. Points were totaled and each study was given a percent quality score. The components included in the quality score are listed in Table 1.

2. Results

Eight randomized clinical trials were found involving preoperative use of antibiotics before tooth extraction. Six of nine extraction studies[11–16] were double blind randomized controlled trials (RCTs), two[14,15] were single blind RCTs, and one[19] was of retrospective design. We found no extraction studies in which the postoperative incidence rate of infective endocarditis was assessed. One[21] systematic review of the literature (Cochrane) on the use of antibiotics to prevent complications following dental implant treatment was found in our search, however the authors did not find any RCTs, and concluded that there is insufficient scientific evidence to recommend or discourage the use of prophylactic antibiotics to prevent

Table 1 – Factors used to score the quality of intervention studies[9–11]

Factor	Specific components	Maximum points
Representation of study population	1. Does the study describe patients' key characteristics at enrollment?	2
	2. Were detailed inclusion/exclusion criteria provided, so as to allow replication?	2
Description of intervention	1. Was there a complete description of intervention?	2
	2. Was there masking of treatment for supervisors, patients and outcome assessors?	2
	3. If more than one intervention was employed, how well did the study account for confounding factors?	2
	4. How adequately did the study describe the monitoring of interventions performed?	2
	5. If the intervention was monitored, how high was the compliance rate? (≥80% = 2 points, 50–79% = 1 point, ≤49% = 0 points)	2
Outcome assessment	1. How clearly defined were the outcome assessment procedures?	2
Control of Bias	1. How well did the study population represent the larger population (control for Selection bias)?	2
	2. How well did the study avoid Investigator Bias?	2
	3. How well did the study avoid Detection Bias?	2
	4. How well did the study avoid Attrition Bias?	2
Statistical quality and interpretation	1. Were the methods of statistical analysis properly described?	2
	2. Were the appropriate analyses and statistical tests performed (including power analysis) and did the study address differences between groups and degree of variability?	2

Percent quality score = [summed score (0–28)/maximum possible score (28)] × 100

Table 2 – Details of studies examining the relationship between prophylactic antibiotic use and adverse outcomes following dental extraction

Author	Country	Sample size	Study design	Intervention	Outcomes a ssessed	Results	Quality score (%)	Comments
Extractions								
Vergis et al.[18]	USA	36 patients	Randomized, single blind	Topical amoxicillin or oral amoxicillin vs. no antibiotic	Incidence, nature and duration of bacteremia	Bacteremia: topical antibiotic prophy vs. control, NS $P = 0.30$; oral prophy vs. control, statistically significant $P = 0.05$	85	Key characteristics at enrollment described; experimental and control groups had blood samples taken at same time postop; single blinded; unclear if the administration of antibiotics was monitored; no power analysis
Lockhart et al.[12]	USA	100 patients	Randomized, double blind	Single dose amoxicillin elixir vs. placebo	Incidence, nature and duration of bacteremia	Bacteremia: statistically significant decrease in bacteremia for exp. group $P < 0.001$ after dental extraction	93	Key characteristics at enrollment described; double blinded; power analysis included; no report of monitoring of antibiotic administration
Sekhar et al.[13]	India	151 patients	Randomized double blind	Metronidazole preop or postop TID vs. placebo	Pain score, swelling, trismus, purulent discharge around surgical site	NS differences in any outcomes assessed	79	Double blinded; attrition rates reported; patient key characteristics at enrollment not fully assessed; unclear description of monitoring interventions; outcome assessment procedures not clearly specified; no power analysis
Bulut et al.[14]	Turkey	30 patients, 60 molars	Randomized, double blind	Amoxicillin preop and 500 mg BID 5 days postop vs. placebo	Postop blood serum levels of C-reactive protein and antitrypsin-1	NS differences ($P > 0.05$)	79	Double blinded; clear description of intervention and outcome assessment; patient key characteristics at enrollment not fully described; inadequate explanation of inclusion/exclusion criteria and explanation for monitoring of intervention; no power analysis
Dios et al.[15]	Spain	221 patients, with a median of four extracted per patient	Randomized, double blind	Amoxicillin (AMX) 2 g preop vs. clindamycin (CLI) 600 mg preop vs. moxifloxacin (MXF) 400 mg preop vs. placebo	Postop level of bacteremia using anaerobic culture media and microbiological analysis of blood cultures	Statistically significant: postop times 30 s, 15 min, 1 h; in postop measurements of bacteremia: decrease in bacteremia for exp. groups AMX and MXF vs. placebo 30 s $P < 0.001$, 15 min $P < 0.001$, 1 h AMX and MXF, $P < 0.01$, 0.05, respectively	77	Double-blinded good control for confounding variables by taking baseline measurements of population; power analysis conducted; inadequate explanation of inclusion criteria. Unclear what type of extractions were analyzed; no control for selection bias; inadequate explanation for monitoring of intervention
Halpern et al.[16]	U.S.A	118 subjects	Randomized, double blind	Preop dose 15,000 units per kilogram penicillin (if allergic, 600 mg clindamycin) vs. placebo	Postoperative inflammation at surgical site, including alveolar osteitis (AO) or surgical site infection (SSI)	Significant difference between cases and controls for SSI ($P = 0.03$). No subjects diagnosed with AO	88	Double-blinded; patient key characteristics at enrollment not fully described; power analysis conducted; inadequate control for confounding variables (not mentioned); inadequate explanation for monitoring of intervention

Table 2 (*Continued*)

Author	Country	Sample size	Study design	Intervention	Outcomes a ssessed	Results	Quality score (%)	Comments
Lacasa et al.[17]	Spain	225 patients	Randomized, double blind	Single presurgical preop dose of two tablets amoxicillin/ clavulanate 1000/ 62.5 mg vs. postsurgical pre-emptive does of two tablets amoxicillin/clavulanate 1000/62.5 mg BID for 5 days vs. placebo	Infection, purulent discharge, excessive swelling with fluctuance, abscess, facial or cervical cellulites, increased pain, heat, erythema and or fever, and trismus	Significant difference: incidence of infection pre-emptive vs. placebo ($P = 0.014$), amelioration of pain for patients in pre-emptive therapy group vs. placebo ($P = 0.001$), comparing antibiotic strategies vs. placebo for ostectomy only, when considering difficulty of procedure ($P = 0.014$). NS difference: comparing postop infection rates between prophylaxis group and control group ($P = 0.064$)	88	Double-blinded; patient key characteristics at enrollment not fully described; control for confounding variables; power analysis conducted; inadequate explanation for monitoring of intervention; attrition bias not described
Yoshi et al.[19]	Japan	185 patients	Randomized, single blind	Preop dose LAPC or LAPC TID postop/3 days prophylaxis	Cellulitis, dry, socket, purulent discharge, pain/swelling	NS differences between experimental groups	82	Complete description of intervention and monitoring of intervention; attrition rates monitored; power analysis conducted; single blind; outcome assessment procedures not clearly specified; patients made intra-oral swelling assessments themselves; no control group
Roberts and Holzel[20]	England	92	Retrospective design	Preop mean dose 627 mg ampicillin vs. preop dose 6 mg/kg teicoplanin and 15 mg/kg amikacin	Percentage prevalence of positive blood cultures (BE)	NS differences + blood cultures between groups	23	Outcome assessment procedures clearly defined; no control group; inadequate monitoring of intervention; inadequate account for confounding variables; inadequate avoidance of all biases; no power analysis

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Table 3 – Details of studies examining the relationship between prophylactic antibiotic use and adverse outcomes following implant placement

Author	Country	Sample size	Study design	Interventions	Outcomes assessed	Results (survival)	Quality score (%)	Comments
Implant surgery								
Binahmed et al.[25]	Canada, USA	215 subjects, 747 implants	Correlational	Single preop i.v. Pen G vs. preop + postop Pen V QID or clindamycin TID (7 days)	Pain, swelling, redness, purulence of surgical site	NS between experiment and control groups ($P = 0.56$)	43	Complete description of intervention; inadequate description for methods of statistical analysis; no masking of treatment supervisors, patients and outcome assessors; insufficient description of the monitoring of the interventions; no mention of inter-rater reliability; no power analysis
Laskin et al.[22]	USA, New Zealand	702 patients, 3130 implants	Non-randomized trial	Preoperative antibiotics of clinicians' choice	3-year implant survival rate	Preoperative antibiotics (all regimens) improves implant survival ($P < 0.05$). Postoperative antibiotic NS (no P-value)	39	Incomplete definition of outcome assessment procedures with no mention of inter-rater reliability and no mention of who actually did the assessment; inadequate description of patients' key characteristics upon enrollment; no mention of monitoring of interventions
Morris et al.[23]	USA, Taiwan, Korea	1500 implants	Correlational	(a) Preop only, (b) postop only, (c) preop and postop	3–5-year implant survival rate	NS differences for all regimens	18	Partial explanation of intervention and patients' characteristics; unclear if supervisors were masked; insufficient description of monitoring of interventions and outcome assessment procedures; no mention of statistical analysis; no power analysis
Gynther et al.[24]	Sweden	279 patients, 1454 implants	Retrospective case-control	1 g penicillin preop and 1 g TID/days postop or no antibiotic	Postop infection, purulence or fistula, pain, tenderness, localized swelling, redness, fever	NS between groups early and late postoperative infection ($P = 0.9$) or implant survival rates maxilla $P = 0.123$, mandible $P = 0.395$	71	Complete description of intervention; patient's key characteristics and outcome assessment procedures inadequate; no power analysis

adverse outcomes after implant placement. Four additional non-randomized intervention studies among patients undergoing implant placement were found, in which cohort, descriptive, and retrospective designs were used.[22–25] Three studies were conducted in the United States, seven in other countries, and three studies were conducted in multiple sites in the United States and abroad. These 13 studies comprised all of the published research found that met our inclusion criteria (Tables 2 and 3).

Extraction studies overall had higher quality scores than dental implant studies but only a single study[12] scored above 90%. The most common flaws detected were failure to monitor the intervention (10/13, 77%) and failure to calculate statistical power or report a rationale for the selected sample size (7/13, 54%). Three tooth-extraction studies,[12,15,18] reported that preoperative antibiotics were associated with a significant reduction in transient bacteremia levels as compared to controls. In one implant study[22] investigators reported a significant improvement in the 3-year survival rate of implants following preoperative antibiotic administration. In 7 of the 13 studies (54%), no significant differences in postoperative complications were reported between experimental and control groups.

3. Extraction

In the four papers rated as having highest score (≥85%),[12,16–18] two studies[12,14] reported that a preoperative dose of antibiotics was associated with a significant reduction in postoperative transient bacteremia levels compared to controls, and two studies[16,17] reported that preoperative antibiotics were associated with a significant reduction in adverse outcomes around the surgical site, including purulence and other signs of infection. These four highest scoring papers all reported a power analysis, however there was no rationale provided for the small sample size ($n = 36$ patients) in the Vergis et al. study.[18] Only four studies[12,15,18,20] included oral disease status in their description of patients' key characteristics, a description not mentioned in the seven other papers. Because poor oral health could be a risk factor for postoperative bacteremia or other infection, it would be important to account for oral health in these studies to avoid potential confounding.

BACTEC (Becton Dickinson and Company, Sparks, MD, USA) instrumented blood culture system was used monitor bacterial blood levels for the four studies[12,15,18,20] measuring levels of postoperative bacteremia. Only Roberts et al. failed to show significant differences in postoperative transient bacteremia between groups, possibly due to the retrospective design of this study.

In a RCT, Bulut et al.[14] analyzed pre- and postoperative serum levels of C-reactive protein (CRP) and alpha-1 antitrypsin (AT) measurements, two acute phase proteins that rise in the setting of inflammation and tissue injury. After preoperative and postoperative administration of 500 mg amoxicillin trihydrate, there were no significant differences between experimental and control patients in the levels of acute phase proteins. No sample size calculation was reported and only 30 patients were studied.

Three studies[13,17,19] assessed postoperative pain as one outcome variable. These studies used instruments with unreported validity and reliability, and one study[19] did not have a control group. Yoshi et al. included a statistical power calculation, but P-values were not provided. In two[13,19] of the three studies no significant differences were found between the intervention and control groups in the postoperative incidence of dry socket/pain, swelling, trismus, and purulent discharge around the extraction site. Lacasa et al.[17] measured postoperative pain using a subject visual analogue pain scale ranging from 0 to 10, found that amelioration of pain was faster for patients in the pre-emptive therapy group over the placebo group ($P = 0.001$) with a trend towards this outcome 1 week postoperatively.

4. Dental implants

Three of the four implant studies received a quality score below 50%[22,23,25] and are summarized in Table 3 but not discussed further here. In the fourth study,[24] survival rates of dental implants with and without preoperative and postoperative antibiotic prophylaxis were retrospectively compared. The authors provided a complete description of the intervention, but patient inclusion criteria were not described. While the authors summarized patient characteristics, they did not compare potential risk factors associated with failure of implant retention between the intervention and control groups. It was unclear who assessed the study outcomes, whether they were masked as to treatment group, and what documentation was used to make such assessments. Statistical power calculations were not reported. Their criteria for defining infection were clear, and they noted the limitations of a retrospective design. The investigators found no statistically significant difference between groups who received pre- and postoperative antibiotics compared to controls ($P = 0.9$).

5. Discussion

Overall, the body of empirical literature regarding the impact of prophylactic antibiotics on infectious and other complications following dental extraction or implant placement was limited and of poor quality. In general, sample sizes were small and provided insufficient statistical power to avoid type II errors. In some studies no comparison group was included and/or it was difficult to determine the extent to which the intervention had actually been implemented. Such methodological deficiencies are neither unique to this topic nor to dental research, but they do pose a major problem regarding the quality of evidence.

Currently, with the newly adopted AHA guidelines on antibiotic prophylaxis in dentistry,[5] there are relatively few situations in which antibiotic prophylaxis is indicated in dentistry; however, a significant percentage of antibacterial agents that dentists prescribe are inappropriate.[6,26–28] A number of studies[8,28–31] have described the misuse of antibiotics in dentistry. A survey of antibiotic use in British Columbia revealed discrepancies in prophylactic use for patients with endocarditis or with large joint prostheses, and in prescribing antibiotics for clinical infection.[32] Based on this literature review and the current guidelines, there is little

evidence for the use of antibiotic prophylaxis in general dentistry. Nevertheless, it has been reported that dentists prescribe approximately 10% of all common antibiotics.[33] It is therefore unlikely that antibiotic prescribing by dentists is limited to those rare, high-risk situations identified in current guidelines. Clearly, as a public health preventative measure, dentists must consider the risks of overuse of antibiotics, including increased risk for allergic/toxic reactions, as well as the selection of antibiotic-resistant microorganisms. With the recent improvements in the current standards of antibiotic prophylaxis in dentistry, further monitoring of antibiotic use among dental practitioners as well as continuing education for practitioners concerning the public health risks related to the over-prescription of antibiotics are needed.

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