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Does antibiotic prophylaxis at implant placement decrease early implant failures? A Cochrane systematic review

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Key words *antibiotics, dental implants, prophylaxis, randomised controlled clinical trial, systematic review*

Conflict-of-interest statement: Marco Esposito is the first author of two of the included studies; however, he was not involved in the quality assessment of these trials.

This review is based on a Cochrane systematic review entitled 'Interventions for replacing missing teeth: antibiotics at dental implant placement to prevent complications' published in The Cochrane Library (see http://www.cochrane.org for more information). Cochrane systematic reviews are regularly updated to include new research, and in response to comments and criticisms from readers. If you wish to comment on this review, please send your comments to the Cochrane website or to Marco Esposito. The Cochrane Library should be consulted for the most recent version of the review. The results of a Cochrane Review can be interpreted differently, depending on people's perspectives and circumstances. Please consider the conclusions presented carefully. They are the opinions of the review authors, and are not necessarily shared by the Cochrane Collaboration.

Purpose: To assess the beneficial or harmful effects of systemic prophylactic antibiotics at dental implant placement versus no antibiotic/placebo administration and, if antibiotics are of benefit, to find which type, dosage and duration is the most effective.
Materials and methods: The Cochrane Oral Health Group's Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE were searched up to 2 June 2010 for randomised controlled clinical trials (RCTs) with a follow-up of at least 3 months comparing the administration of various prophylactic antibiotic regimens versus no antibiotics to patients undergoing dental implant placement. Outcome measures were prosthesis failures, implant failures, postoperative infections and adverse events (gastrointestinal, hypersensitivity, etc.). Screening of eligible studies, assessment of the methodological quality of the trials and data extraction were conducted in duplicate and independently by two review authors. Meta-analyses were conducted.
Results: Four RCTs were identified: three comparing 2 g of preoperative amoxicillin versus placebo (927 patients) and the other comparing 1 g of preoperative amoxicillin plus 500 mg four times a day for 2 days versus no antibiotics (80 patients). The meta-analyses of the four trials showed a statistically significantly higher number of patients experiencing implant failures in the group not receiving antibiotics: risk ratio = 0.40 (95% confidence interval (CI) 0.19 to 0.84). The number needed to treat (NNT) to prevent one

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patient having an implant failure is 33 (95% CI 17–100), based on a patient implant failure rate of 5% in patients not receiving antibiotics. The other outcomes were not statistically significant, and only two minor adverse events were recorded, one in the placebo group.

Conclusions: There is some evidence suggesting that 2 g of amoxicillin given orally 1 h preoperatively significantly reduce failures of dental implants placed in ordinary conditions. No significant adverse events were reported. It might be sensible to suggest the use of a single dose of 2 g prophylactic amoxicillin prior to dental implant placement. It is still unknown whether post-operative antibiotics are beneficial, and which is the most effective antibiotic.

Introduction

Some dental implant failures may be due to bacterial contamination at implant insertion[1]. Infections around biomaterials are difficult to treat and almost all infected implants have to be removed[1]. In general, antibiotic prophylaxis in surgery is only indicated for patients at risk of infectious endocarditis, for patients with reduced host-response, when surgery is performed in infected sites, in cases of extensive and prolonged surgical interventions and when large foreign materials are implanted. To minimise infection after dental implant placement, various prophylactic systemic antibiotic regimens have been suggested. More recent protocols recommend short-term prophylaxis, if antibiotics have to be used[2]. With the administration of antibiotics, adverse events may occur, ranging from diarrhoea to life-threatening allergic reactions. Another major concern associated with the widespread use of antibiotics is the selection of antibiotic-resistant bacteria. The use of prophylactic antibiotics in implant dentistry is controversial and controlled clinical trials (CCTs) have yielded contradictory results[3-6]. A previous version of the present Cochrane review[7] concluded that there was some evidence suggesting that 2 g of amoxicillin given 1 h preoperatively significantly reduces failures of dental implants placed in ordinary conditions; however, these findings were based only on two randomised controlled trials (RCTs)[8,9]. It would be useful to know whether prophylactic antibiotics are effective in reducing post-operative infections and failures of dental implants and which is the most effective antibiotic, at what dose and duration.

The primary objective of the present systematic review was to test the null hypothesis of no difference in the proportion of prosthesis failures, implant failures, post-operative infections and adverse events between patients receiving antibiotic prophylaxis and those receiving a placebo or no antibiotic at placement of dental implants, against the alternative hypothesis of a difference. The secondary objective was to test the null hypothesis of no difference in the proportion of prosthesis failures, implant failures, post-operative infections and adverse events between groups of patients receiving different prophylactic antibiotics or different doses/duration of the same antibiotic, against the alternative hypothesis of a difference.

Materials and methods

Criteria for considering studies for this review

All RCTs with a follow-up of at least 3 months evaluating the administration of prophylactic antibiotics versus no antibiotics/placebo, the administration of different antibiotics, and the administration of different doses or different duration of the same antibiotic at placement of dental implants were considered. Outcomes measures were:

- prosthesis that could not be placed or prosthesis failure if secondary to implant failures
- implant mobility and removal of stable implants dictated by progressive marginal bone loss or infection
- post-operative infections
- adverse events (e.g. gastrointestinal, hypersensitivity).

Search strategy for identification of studies

For the identification of studies included or considered for this review, detailed search strategies were developed for each database searched. For more details see the original Cochrane review[10]. The following databases were searched:

The Cochrane Oral Health Group's Trials Register (to 2 June 2010)

The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2010, Issue 5)

MEDLINE (1950 to 2 June 2010)

EMBASE (1980 to 2 June 2010).

The most recent electronic search was undertaken on 2 June 2010. Several dental journals, including *British Journal of Oral and Maxillofacial Surgery*, *Clinical Implant Dentistry and Related Research*, *Clinical Oral Implants Research*, *European Journal of Oral Implantology*, *Implant Dentistry*, *International Journal of Oral and Maxillofacial Implants*, *International Journal of Oral and Maxillofacial Surgery*, *International Journal of Periodontics and Restorative Dentistry*, *International Journal of Prosthodontics*, *Journal of Clinical Periodontology*, *Journal of Dental Research*, *Journal of Oral Implantology*, *Journal of Oral and Maxillofacial Surgery*, *Journal of Periodontology*, and *Journal of Prosthetic Dentistry*, were hand searched up to December 2009. There were no language restrictions. All of the authors of the identified RCTs were contacted, the bibliographies of all identified RCTs and relevant review articles were checked, and personal contacts were used in an attempt to identify unpublished or ongoing RCTs. In the first version of this review, more than 55 oral implant manufacturers and an Internet discussion group (implantology@yahoogroups.com) were contacted; however, this was discontinued due to poor yield.

Study selection and data extraction

The titles and abstracts (when available) of all reports identified through the electronic searches were scanned independently by two review authors. For studies appearing to meet the inclusion criteria, or for which there were insufficient data in the title and abstract to make a clear decision, the full report was obtained. The full reports obtained from all of the electronic and other methods of searching were assessed independently by two review authors to establish whether the studies met the inclusion criteria or not. Disagreements were resolved by discussion. Where resolution was not possible, a third review author was consulted. All studies meeting the inclusion criteria then underwent validity assessment and data extraction. Studies rejected at this or subsequent stages were recorded in the table of excluded studies, and reasons for exclusion recorded.

Data were extracted by two review authors independently using specially designed data extraction forms. The data extraction forms were piloted on several papers and modified as required before use. Any disagreement was discussed and a third review author consulted where necessary. All authors were contacted for clarification or missing information. Data were excluded until further clarification was available if agreement could not be reached. For each trial the following data were recorded: year of publication, country of origin and source of study funding; details of the participants including demographic characteristics; details of the type of intervention and details of the outcomes reported, including method of assessment and time intervals.

Quality assessment

Quality assessment was conducted using the recommended approach for assessing risk of bias in studies included in Cochrane reviews[11]. It is a two-part tool, addressing the six specific domains (namely sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and 'other issues'). Each domain includes one specific entry in a 'risk of bias' table. Within each entry, the first part of the tool involves describing what was reported to have happened in the study. The second part of the tool involves assigning a judgment relating to the risk of bias for that entry. This is achieved by answering a pre-specified question about the adequacy of the study in relation to the entry, such that a judgment of 'yes' indicates low risk of bias, 'no' indicates high risk of bias, and 'unclear' indicates unclear or unknown risk of bias.

The risk of bias assessment of the included trials was undertaken independently and in duplicate by

two review authors as part of the data extraction process. In the case that the paper to be assessed had one or more review authors in the authors list, it was independently evaluated only by those review authors not involved in the trials. After taking into account the additional information provided by the authors of the trials, studies were grouped into the following categories. The present authors assumed that the risk of bias was the same for all outcomes and each study was assessed as follows:

- low risk of bias (plausible bias unlikely to seriously alter the results) if all criteria were met
- unclear risk of bias (plausible bias that raises some doubt about the results) if one or more key domains were at unclear risk of bias
- high risk of bias (plausible bias that seriously weakens confidence in the results) if one or more criteria were not met[11].

Data synthesis

For each outcome, all of which were binary, the estimate of effect of an intervention was expressed as relative risk together with 95% confidence interval. Numbers needed to treat (NNT) were calculated for patients affected by implant failures. The statistical unit was the patient and not the implant(s). Meta-analyses were performed only if there were studies with similar comparisons reporting the same outcome measures. Risk ratios were combined for dichotomous data, using random-effect models provided there were more than three studies in the meta-analysis. The Cochrane Handbook[11] recommendations were followed for studies with zero-cell counts. The fixed value of 0.5 was added to all cells with zero-cell counts and risk ratios were calculated with RevMan software. If there were no events in both arms, no calculations were undertaken because in this situation the study does not provide any indication of the direction or magnitude of the relative treatment effect.

The significance of any discrepancies in the estimates of the treatment effects from the different trials was assessed by means of Cochran's test for heterogeneity and the I^2 statistic, which describes the percentage total variation across studies that is due to heterogeneity rather than chance.

Description of studies

Characteristics of the trial setting and investigators

Four RCTs were identified and included[8,9,12,13]. Two multicentre trials were conducted in Italy[9,13], one multicentre trial in Spain[12] and one single-centre trial in Belgium[8]. Two trials received free placebo and antibiotics from a patient working in a pharmaceutical company producing generic drugs[9,13]. One trial was supported by the implant manufacturer[12]. No external funding was received in the other trial[8]. The multicentre trials were conducted in private practices[9,12,13], and the single-centre trial in a university hospital[8].

Characteristics of the interventions

One trial[8] compared 1 g of amoxicillin given 1 h preoperatively plus 500 mg of amoxicillin four times a day for 2 days vs no antibiotics. All patients rinsed with chlorhexidine digluconate for 1 min just prior to surgery and post-operatively twice a day for 7–10 days. The perioral skin was disinfected for 30 s with cetrimonium bromide 0.5% and chlorhexidine 0.05% in water. Measures of asepsis included use of sterile drapes around the patient's mouth, head, and over the supine body of the patient, a meshed nose guard, and two suction tips (one only for the mouth and one only for the wound). Post-operative complications were assessed at 7–10 days and implant success at 5 months. An unknown type of dental implant was used.

Two placebo-controlled trials[9,13] compared 2 g of amoxicillin given 1 h preoperatively with identical placebo tablets. One week prior to implant placement, all patients underwent at least one session of oral hygiene instruction and professionally delivered debridement when required. All patients rinsed with chlorhexidine digluconate for 1 min just prior to surgery and post-operatively twice a day for at least 1 week. Operators were allowed to place and restore the implants according their routine procedures. Post-operative complications were assessed at 1 and 2 weeks, and implant success at 4 months. Various implant systems were used (Zimmer Dental, Dentsply Friadent, Nobel Biocare, Intra-Lock, Camlog,

Exclusion criteria	Studies
At risk for bacterial endocarditis	8, 9, 13
Having implanted biomaterials in the body (hip or knee prostheses, etc.)	9, 13
Immunosuppressed or immunocompromised	8, 9, 13
Affected by diabetes (controlled or uncontrolled)	9, 13
Uncontrolled diabetes mellitus	8
Received radiotherapy in the head and neck area; only if > 5000 rads	8, 9, 13; 12
Need of augmentation procedure concomitant with implant placement	9, 13
Allergic to penicillin	8, 9, 12, 13
Presence of chronic/acute infections in the vicinity of the planned implant site	9, 13
Already under antibiotic treatment for any other reasons	9, 12, 13
Treated or under treatment with intravenous amino-bisphosphonates	9, 13
Pregnant or lactating	9, 13
Hard and soft bone quality defined on radiographs	12

Table 1 Main exclusion criteria used in the included studies.

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?
Abu-Ta'a[8]	+	?	–	+	+	+
Anitua[12]	+	+	+	+	+	+
Esposito[9]	+	+	+	+	+	+
Esposito[13]	+	+	+	+	+	+

Table 2 Summary of the risk of bias assessment: review authors' judgments about each methodological quality item for each included study.

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One placebo-controlled trial[12] compared 2 g of amoxicillin given 1 h preoperatively with identical placebo tablets. Patients received, during the days prior to the intervention, appropriate prophylaxis and adequate oral hygiene instructions. Antibiotics and other medications were not allowed 15 days before the surgery. All patients rinsed with 2% chlorhexidine digluconate for 1 min just prior to surgery. Only single implants in medium bone quality were included and all implants were inserted after flap elevation. Before installation, implants were carefully humidified with liquid plasma rich in growth factors (PRGF). Peripheral blood (20 to 30 ml) from each patient was taken by venipuncture before surgery and placed directly into 9 ml tubes containing 3.8% (wt/vol) sodium citrate as anticoagulant. Liquid PRGF was prepared by centrifugation (PRGF System®, BTI, San Antonio, Spain) at 460 × g for 8 min at room temperature. The plasma fraction (1 ml) was collected and deposited in a glass dish. In order to initiate clotting, PRGF activator (calcium chloride) was added to the liquid PRGF preparation (50 µl PRGF activator per 1 ml of preparation). Postoperative infections were assessed at days 3, 10, 30 and 60. At 3 months, implant stability was evaluated using Osstell. BTI dental implants were used.

Characteristics of outcome measures

All trials reported all the outcome measures considered in the present review. Duration of follow-ups were: 3[12], 4[9,13] and 5[8] months after implant placement. One trial included only patients receiving single implants in medium soft bone as quantified radiographically (400 to 1100 Hounsfield units [HU])[8]. The main patient exclusion criteria used in the included trials are presented in Table 1. Groups appeared to be comparable at entry for all trials. In three trials the sample size was calculated[9,12,13]. The risk of bias assessment is reported in Table 2. Three trials were judged to be at low risk of bias[9,12,13] and one at high risk of bias[8].

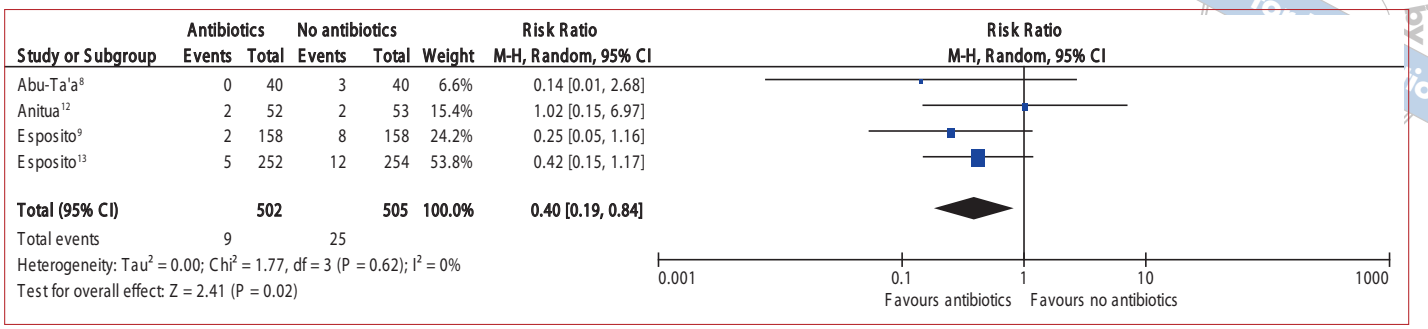

Fig 1 Forest plot comparing implant failures in the antibiotic treated group with the placebo/no antibiotic treated group.

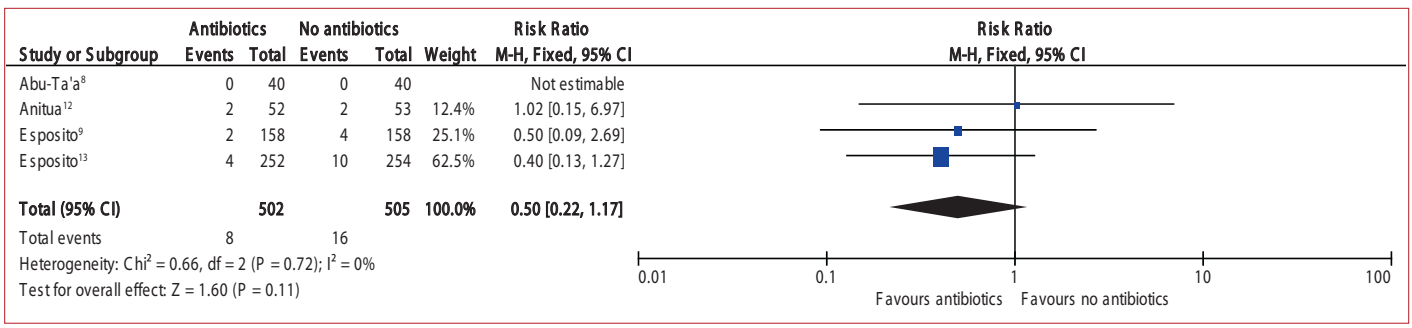

Fig 2 Forest plot comparing prosthetic failures in the antibiotic treated group with the placebo/no antibiotic treated group.

Effects of interventions

Four trials including a total of 1007 patients evaluated whether prophylactic antibiotics are effective in reducing failures and complications.

One trial[8] compared 1 g of amoxicillin given 1 h preoperatively plus 500 mg of amoxicillin four times a day for 2 days versus no antibiotics. Forty patients were included in each group and none dropped out after 5 months. No prostheses failed. Five implants failed in three patients who did not receive antibiotics. One patient in the antibiotic group and four patients in the control group experienced a post-operative infection. No adverse events were reported. No statistically significant differences were observed for any of the outcome measures.

One placebo-controlled trial[9] compared 2 g of amoxicillin given 1 h preoperatively with identical placebo tablets. One hundred and sixty-five patients were included in each group, but seven patients from each group had to be excluded from the analyses for various reasons. Two patients in the antibiotic group experienced a prosthesis failure versus four patients in the placebo group. Two patients (2 implants) in the antibiotic group experienced implant losses versus eight patients (9 implants) in the placebo group. Three patients in the antibiotic group presented signs of infection versus two patients in the placebo group. One minor adverse event was recorded in each group. No statistically significant differences were observed for any of the outcome measures.

One placebo-controlled trial[12] compared 2 g of amoxicillin given 1 h preoperatively with identical placebo tablets. Fifty-two patients were included in the antibiotic group and 53 in the placebo group. Two patients in each group experienced an implant/crown failure and six patients in each group experienced a post-operative infection. No adverse events were reported. No statistically significant differences were observed for any of the outcome measures.

One placebo-controlled trial[13] compared 2 g of amoxicillin given 1 h preoperatively with identical placebo tablets. Two hundred and fifty-four patients were included in the antibiotic group and 255 in the placebo group, but two patients from the antibiotic group and one from the placebo group had to be excluded from the analyses for various reasons. Four patients in the antibiotic group experienced a prosthesis failure versus 10 patients in the placebo group. Five patients in the antibiotic group experi-

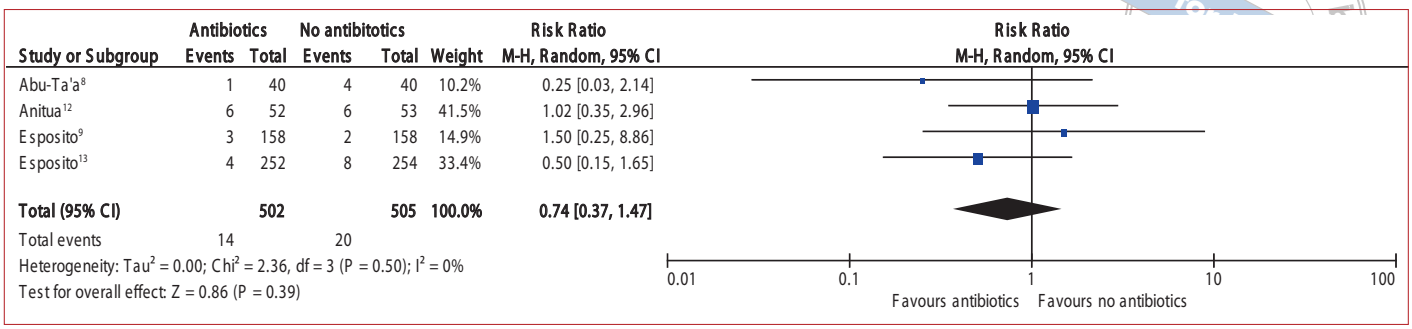

Fig 3 Forest plot comparing post-operative infections in the antibiotic treated group with the placebo/no antibiotic treated group.

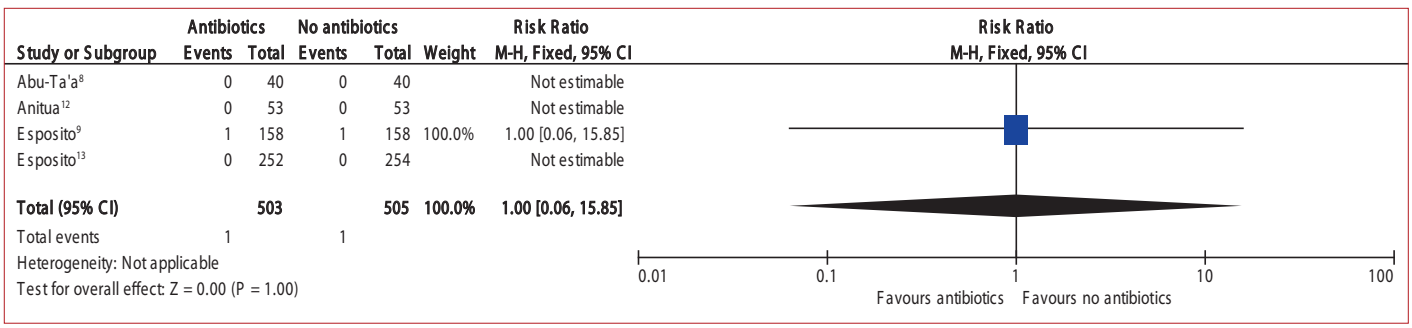

Fig 4 Forest plot comparing side effects in the antibiotic treated group with the placebo/no antibiotic treated group.

enced 7 implant losses versus 12 patients that lost 13 implants in the placebo group. Four patients in the antibiotic group presented clear signs of infection versus eight patients in the placebo group. No adverse events were reported. No statistically significant differences were observed for any of the outcome measures.

In total, 1007 patients were included in the four trials. More patients experienced implant losses in the group that did not receive antibiotics and this was statistically significant (Fig 1) (risk ratio [RR] 0.40, 95% confidence interval [CI] 0.19–0.84). In order to illustrate the magnitude of the effect of implant failures, the NNT, i.e. given antibiotics, to prevent one patient having an implant failure is 33 (95% CI 17–100). This is based on a patient implant failure of 5% in patients not receiving antibiotics, as seen in the meta-analysis. No heterogeneity was observed in the meta-analysis ($P = 0.62$; $I^2 = 0\%$). The meta-analyses of the four trials for the other outcomes showed no statistically significant differences for prosthesis failures (Fig 2), post-operative infections (Fig 3) and adverse events (Fig 4).

No trials evaluated which is the most effective antibiotic, dose or duration.

Discussion

The meta-analysis of four RCTs suggests that short-term antibiotics (2 g of amoxicillin administered 1 h prior to implant placement[9,12,13] or 1 g of amoxicillin administered 1 h prior to implant placement and 500 mg four times a day for 2 days post-operatively[8]) significantly decrease early implant failures. This observation has important clinical implications, meaning that antibiotics would prevent one patient experiencing an early implant loss for every 33 patients receiving antibiotics. Only two minor adverse events were reported, one in the antibiotic (diarrhoea and somnolence) and one in the placebo group (itching for 1 day), which suggest that the antibiotic regimens used may not have a tremendous negative impact on the patients' well-being. In other words, the benefit of using short-term antibiotics may outweigh the risks in the short term for individual patients.

All included trials appeared to be underpowered to detect a clinically significant difference, even though three trials showed clear trends favouring antibiotics. A statistically and clinically significant difference in implant failures was found after the

meta-analyses. This underscores the importance of meta-analyses to increase the sample size of individual trials to reach more precise estimates of the effects of interventions.

The studies were conducted in different environments: one trial was conducted in a hospital where very stringent asepsis procedures were implemented[8], whereas three trials[9,12,13] were conducted in various Italian and Spanish private practices where more 'relaxed' aseptic procedures might have been used. However, three trials[8,9,13] provided similar results, i.e. clear trends favouring the use of antibiotics, which strengthens the results of the meta-analyses. Conversely, one trial[12] did not show any trends, with both procedures achieving exactly the same results. It is difficult to explain this; however, the sample size was small and the results could have simply been affected by chance or by the different types of patients included (in fact, only patients receiving single implants in medium bone quality were included). It is possible that there is no benefit from using antibiotic prophylaxis when performing simple implant placement procedures in patients having ideal bone conditions. Therefore, dentists have to decide whether or not to provide prophylactic antibiotic cover according to the complexity of the placement procedure. On the other hand, it may not always be possible to predict with certainty the simplicity of a surgical procedure.

While the efficacy of antibiotics in reducing early implant losses was evident, no apparent significant effects of antibiotics on the occurrence of post-operative infection were observed. A possible explanation is that asymptomatic infections could have determined the loss of some implants. The histolopathology of the peri-implant tissues without apparent clinical signs of infection observed in a consecutive series of early failed implants was compatible with an asymptomatic infection failure modality[14].

In two trials[9,13], it was decided not to include patients undergoing bone augmentation procedures concurrent to implant placement because it was known that patients could be exposed to an unnecessary risk of infection. This was based on the findings of a pilot placebo-controlled RCT[15] comparing a preoperative single dose of 2 g penicillin phenethicillin with a placebo in 20 patients undergoing intraoral buccal onlay grafting with resorbable barriers to allow implant placement (the implants were not placed in the study). Two patients developed an infection at both the receptor and donor sites; two patients developed a wound infection at the receptor site; and one patient developed an infection at the donor site only. All of these patients (50%) were in the placebo group. No infections were observed in the antibiotic group. It could be concluded that there was a statistically significantly increased risk of having an infectious complication after bone augmentation with resorbable barriers without antibiotic prophylaxis.

Additional information can be obtained from two double-blinded RCTs evaluating the efficacy of prophylactic antibiotics used for bone augmentation procedures prior to implant placement[16,17]. One RCT[17] compared 2 g penicillin phenethicillin versus 600 mg of clindamycin as a single dose in patients treated with block-shaped bone graft harvested from the mandibular ramus and covered by resorbable barriers (the implants were not placed in the study). Seventy-five patients were included in each group and the presence of infection was assessed weekly for 8 weeks. No statistically significant differences were observed for post-operative infections (four infections at the augmented sites of the penicillin phenethicillin versus two in the clindamycin group, and three infections at the donor site of each group). The findings of this trial suggest that both penicillins and clindamycin are effective in reducing infection at augmented sites. No side effects related to the single administration of antibiotics were reported. In a similar RCT[16] the same group evaluated whether it was more effective to use a single dose of 600 mg clindamycin 1 h prior to onlay bone grafting procedures followed by either placebo or 300 mg clindamycin every 6 h for 1 day. Sixty-two patients were included in each group. No statistically significant differences were observed for post-operative infections (two infections at the augmented sites of the single dose group versus three infections in the 1-day group, and four infections at the donor sites of the single dose group versus two infections in the 1-day group). Again, no side effects related to the administration of antibiotics were reported.

There are public health concerns regarding prolonged antibiotics usage. However, the present authors were unable to find any evidence suggesting that a single dose of 2 g of amoxicillin was associated with a significant selection of antibiotic-resistant bacteria, and the included trials did not suggest a significant occurrence of adverse events. In addition, no statistically significant alterations in microflora composition were observed in one trial[12] where a preoperative and a 3-day post-operative microbiological evaluation were performed.

■ Conclusions

There is evidence from a meta-analysis including four trials with 1007 patients suggesting that 2 g of amoxicillin given orally 1 h preoperatively significantly reduces early failures of dental implants placed in ordinary conditions. More specifically, giving antibiotics to 33 patients will avoid one patient experiencing early implant losses. No statistically significant differences in post-operative infections and adverse events were observed. No major adverse events were reported. It might be sensible to suggest a routine use of a single dose of 2 g of prophylactic amoxicillin just before placing dental implants. It remains unclear whether an adjunctive use of post-operative antibiotics is beneficial, and which is the most effective antibiotic.

Priority in future research should be given to large pragmatic double-blinded RCTs evaluating the efficacy of prolonged antibiotic prophylaxis when compared to a single preoperative dose into those subgroups of patients where implant failures are more likely to occur, particularly in those patients receiving immediate post-extractive implants and augmentation procedures in conjunction with implant placement. It would also be useful to investigate the most effective antibiotic type.

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