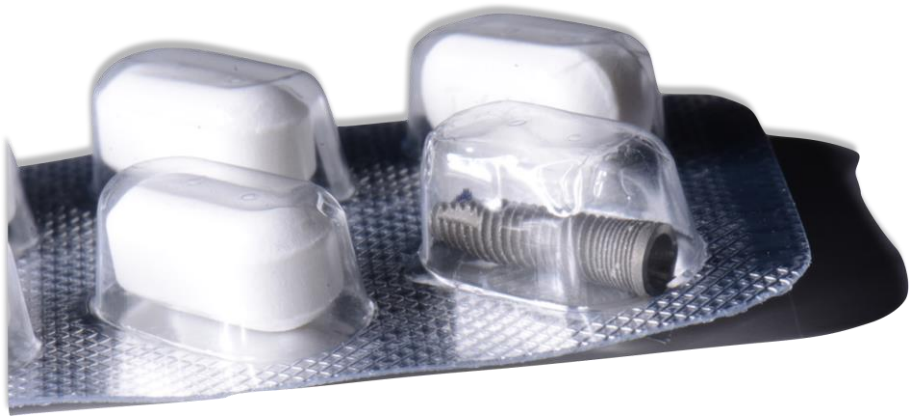
CLINICAL PRACTICE GUIDELINE FOR THE PRESCRIPTION OF PREVENTIVE ANTIBIOTICS IN ORAL IMPLANTOLOGY

Spanish Society of Implants

Sociedad Española de Implantes



Sociedad Española de Implantes

C/ Orense 51, Esc. Dcha. Bajo C

28020, Madrid

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1. PRESENTATION OF THE SEI

In its more than 50 years of history, the SPANISH SOCIETY of IMPLANTS (SEI – *Sociedad Española de Implantes* in Spanish*)* has become a forum for meeting and scientific debate in a professional and social world in which Oral Implantology treatments have become a daily reality in the dental care of our patients.

The SEI is a non-profit scientific society, with its legal status and full capacity to act, created to bring together all those professionals who demand a specific meeting point for Oral Implantology. Specifically, the SEI brings together dentists, stomatologists and maxillofacial surgeons, as well as other clinical and university specialists in the area of Health Sciences, with activities or links to Oral Implantology, as a platform to achieve the following objectives:

- To contribute to the continuing education of its members and promote scientific development in the field of Oral Implantology.
- To advise public and private institutions and official bodies on any social, clinical and scientific aspect related to Oral Implantology.
- To promote relations between Oral Implantology professionals, the University, Professional Associations and the sector's Industry.
- To promote and collaborate with other Scientific Societies in the implementation of political and social initiatives aimed at achieving recognition of Oral Surgery and/or Oral Implantology as a speciality by Official Bodies, as established by European Union (EU) guidelines and regulations.

ROLE IN THE GROWTH OF KNOWLEDGE

Since its foundation in 1956, the SEI has established itself as one of the most important and long-standing scientific societies in Dentistry at a national level. One of its priorities has always been to try to improve Oral Implantology by disseminating knowledge through annual scientific meetings, continuous training courses, conferences, and symposiums, both nationally and internationally.

It is for this reason that, when the time came, it was considered essential to draw up a Clinical Practice Guide (CPG) that establishes guidelines based on the available scientific evidence regarding the prescription of preventive antibiotics (PA) in procedures related to Oral Implantology. To this end, knowledge is organised and presented and evidence-based recommendations are made to be disseminated through the relevant social and scientific channels. These guidelines can be applied by implantologists, oral and/or maxillofacial surgeons in Spain in their clinical practice, thus benefiting the patient, as the end-user, as well as society by trying to encourage more responsible use of these drugs.

WHY CREATE THIS CLINICAL PRACTICE GUIDE?

The decision to carry out a CPG on the prescription of PA in Oral Implantology is supported by several aspects:

- The existence of groups with proven experience within the SEI to tackle this project with guarantees.
- The lack of guidelines or recommendations on the subject at an international level, together with the massive dissemination of implant treatments carried out, all of which is contextualised within the framework of the public health problem of antimicrobial resistance.
- This CPG aims to generate quality scientific evidence and lay the foundations for the generation of knowledge in this field. It also aims to promote the development of documents that update and clarify the state of the art and current science related to this topic.

2. AUTHORS

- **SALGADO PERALVO, ANGEL-ORIÓN.**

  Associate Professor of the master's degree in Family and Community Dentistry, University of Seville(US), Seville (Spain). Master's Degree in Implant Dentistry (US). Master's Degree in Family and Community Dentistry (US). Doctor in Dentistry (US). Representative of the Spanish Society of Implants in the working group in Dentistry of the National Plan against Antibiotic Resistance (PRAN) of the *Spanish Agency of Medicines and Health Products* (AEMPS).

- **VELASCO ORTEGA, EUGENIO.**

  Professor of Comprehensive Dentistry for Adults and Gerodontology. Faculty of Dentistry. Director of the Master in Implant Dentistry of the University of Seville (US). Principal investigator of the Research Group in Basic and Clinical Implantology in Oral Implantology. Regional Government of Andalusia. President of the Spanish Society of Implants.

- **PEÑA CARDELLES, JUAN FRANCISCO.**

  Associate Professor of the master's degree in Oral Surgery and Implantology, Rey Juan Carlos University (URJC), Madrid (Spain). Master in Oral Surgery and Implantology (URJC). Specialist in Oral Medicine, Complutense University of Madrid (UCM), Madrid (Spain). Master's Degree in Clinical and Basic Aspects of Pain (URJC). PhD researcher at the University Hospital La Paz, Madrid. Private practice of Dentistry, Oral Surgery and Implantology at clinical and hospital level.

- **KEWALRAMANI, NARESH.**

  Associate Professor of the master's degree in Advanced Implantology, Tissue Regeneration and Implant-Supported Prosthesis (URJC). Master's Degree of Science in Dentistry (UCM). Master's Degree in Advanced Implantology, Tissue Regeneration and Implant-Supported Prosthesis (URJC). Private practice of Dentistry, Oral Surgery and Implantology at clinical and hospital level.

- **MONSALVE GUIL, LORETO.**

  Assistant Professor of Comprehensive Dentistry for Adults and Gerodontology (US). Master in Implant Dentistry of the University of Seville (US). Investigator of the Research Group in Basic and Clinical Implantology in Oral Implantology. Regional Government of Andalusia.

- **JIMÉNEZ GUERRA, ÁLVARO.**

  Associate Professor of Comprehensive Dentistry for Adults and Computer Guided Oral Implantology (US). Master in Implant Dentistry of the University of Seville (US).

Investigator of the Research Group in Basic and Clinical Implantology in Oral Implantology. Regional Government of Andalusia. Secretary of the Spanish Society of Implants.

- **ORTIZ GARCÍA, IVÁN.**

  Associate Professor of Comprehensive Dentistry for Adults and Gerodontology (US). Master in Implant Dentistry of the University of Seville (US). Investigator of the Research Group in Basic and Clinical Implantology in Oral Implantology. Regional Government of Andalusia.

- **MORENO MUÑOZ, JESÚS.**

  Honorary Assistant Professor of Comprehensive Dentistry for Adults and Gerodontology (US). Master in Implant Dentistry of the University of Seville (US). Investigator of the Research Group in Basic and Clinical Implantology in Oral Implantology. Regional Government of Andalusia.

- **NÚÑEZ MÁRQUEZ, ENRIQUE.**

  Honorary Assistant Professor of Comprehensive Dentistry for Adults and Gerodontology. Master in Implant Dentistry of the University of Seville (US). Investigator of the Research Group in Basic and Clinical Implantology in Oral Implantology. Regional Government of Andalusia.

- **CABANILLAS BALSERA, DANIEL.**

  Professor of Dental Pathology and Therapeutics. Professor of the Official Master in Restorative, Functional and Aesthetic Dentistry of the University of Seville. Professor of Master in Implant Dentistry of the University of Seville.

EXTERNAL REVIEWERS

- **MARTÍNEZ GONZÁLEZ, JOSE MARÍA.**

  Professor of Oral Surgery. Professor of the Official Master in Dental Sciences (UCM). President of the Spanish Society of Gerodontology (SEGER).

- **APARICIO MAGALLÓN, CARLOS**

  Diploma in Implants. Master's Degree in Biomedical Research. Diploma in Periodontology. University of Gothenburg (Gothenburg, Sweden). Doctor in Medicine and Surgery. University of Barcelona (UB), Barcelona, Spain. Scientific consultant for the European Journal of Oral Implantology and Clinical Implant Dentistry and Related Research.

- **LORRIO CASTRO, JUAN MIGUEL.**

  Professor of Comprehensive dentistry for Special patients. Professor of Master in Oral Implantology and Supported-Implant prosthesis. University Alfonso X el Sabio of Madrid. Vice-president of the Spanish Society of Implants

- **KAISER CIFUENTES, RODRIGO.**

  Dental Surgeon. Specialist in Bucomaxillofacial Implantology. Coordinating Associate Professor of the Speciality in Oral Implantology. Finis Terrae University. Santiago de Chile (Chile). Former President of the Chilean Society of Oral Implantology. President of the International Federation of Oral Implantology.

METHODOLOGICAL SUPPORT

- **LÓPEZ LÓPEZ, JOSE.**

  Professor of Oral Medicine. Co-director of the master's degree in Oral Medicine, Surgery and Implantology (UB). Faculty Director and Head of the Medical-Surgical Area of the University of Barcelona Dental Hospital [HOUB]. Researcher of the IDIBELL Group [Oral Health and Masticatory System].

- **SEGURA EGEA, JUAN JOSE.**

  Full Professor of Dental Pathology and Therapeutics. Faculty of Dentistry, Director of the master's degree in Endodontics (US). Principal Investigator of the Research Group on Dental Pathology, Dental Surgery and Endodontics. Andalusian Regional Government.

- **BARONE, ANTONIO**

  Professor of Oral Surgery. Department of Surgical, Medical and Molecular Pathology and Critical Areas. Faculty of Dentistry, University of Pisa (Pisa, Italy).

- **RONDÓN ROMERO, JOSE LUIS.**

  Honorary Assistant Professor of Comprehensive Dentistry for Adults and Gerodontology (US). Professor of Master in Implant Dentistry of the University of Seville. Investigator of the Research Group in Basic and Clinical Implantology in Oral Implantology. Regional Government of Andalusia.

This Clinical Practice Guideline, developed by the Working Group of the Spanish Society of Implants (SEI), has received scientific recognition from the following DENTISTRY SOCIETIES:

Spanish Society of of Gerodontology [SEGER: *Sociedad Española de Gerodontología*]

Latin American Oral Implantology Society [SIOLA: *Sociedad de Implantología Oral Latinoamericana*]

International Federation of Oral Implantology [FIIO: *Federación Internacional de Implantología Oral*]

Which encompasses the following scientific societies:

Colombian Dental Implant Association [SOCI: *Asociación Odontológica Colombiana de Implantes*]

Mexican College of Oral and Maxillofacial Implantology AC [CMIBM: *Colegio Mexicano de Imlantología Bucal y Maxilofacial AC*]

Chilean Society of Oral and Maxillofacial Implantology

Brazilian Academy of Osseointegration [ABROSS: *Academia Brasileira de Osseointegração*]

Peruvian Association of Integral Oral Implantology [ASPIOI: *Asociación Peruana de Implantología Oral*]

3. INTRODUCTION OF THE WORK GROUP

Dental implants are the most predictable therapeutic option in the total or partial replacement of missing teeth, however, around 0.7–3.8% of them fail [1]. These failures can be "early" or "late" depending on whether they occur before or after functional loading, respectively [2]. Early failure occurs as a result of a failure in osseointegration derived from local and/or systemic factors and represents 5% of all failures [3,4]. Since the beginning of Oral Implantology, the prescription of PAs [5] has been incorporated into implant placement protocols due to the presence in the oral cavity of more than 500–700 bacterial species, in addition to other non-culturable microorganisms discovered by molecular biological techniques that can contribute to the development of postoperative infections [6, 7].

Antibiotics are used for longer periods than other drugs in dentistry, such as anaesthetics, analgesics, anti-inflammatories or anxiolytics, among others, which increases the risk of adverse reactions, such as allergies that can cause life-threatening complications [8,9] or toxicity on various target organs, alterations in the usual microflora [10] and/or bacterial resistance. The latter occur naturally, but the inappropriate and indiscriminate use of antimicrobials in humans, in food-producing animals and the environment is accelerating the process. It is essential that prescribing and use of antibiotics are urgently changed because, even if new ones are developed, resistance will continue to pose a serious threat unless current prescribing patterns are changed [11].

The current evidence is very limited. Despite this, it has been shown that for every 24–50 healthy patients treated with PAs, early failure will be avoided in one patient [12-15] and only one in 143 will avoid postoperative infection [16]. The value of this risk reduction must be placed in the context of the emerging problems with antibiotic resistance before robust guidelines can be formulated, and the biological cost of implant failure must be weighed against the economic cost incurred as fear of infection and fear of legal and economic repercussions motivate the vast majority of prescriptions of these drugs [17].

Antimicrobial resistance causes more than 33,000 deaths per year in the EU [18] and the associated healthcare costs and lost productivity are estimated at 1.5 billion euros per year, which, extrapolated to national figures, represents a cost of around 150 million euros per year [19]. According to data from the Minimum Basic Data Set Registry [20] (MBDS), in 2016, 2,956 people died in Spain as a result of this type of infection. If urgent action is not taken, in 35 years the number of deaths attributable to multidrug-resistant infections will reach 390,000 deaths per year across the EU (around 40,000 deaths per year in Spain) and resistance will overtake cancer as the leading cause of death [19].

The SEI conducted a retrospective study to determine the prescribing patterns of PAs among a representative sample of professionals involved in Oral Implantology. To this end, an anonymous electronic survey was sent to all members of the society (n=1,460), which was

available from April to July 2020. Previously published surveys were used as a reference [21,22], which were modified to obtain a greater knowledge of various aspects related to the prescription of these drugs by this group.

The questionnaire consisted of 19 closed questions grouped into 4 blocks (Annex 1). The first, composed of 7 questions, investigated general data on the professionals surveyed (demographic, academic and professional data). The second block, with three multiple-choice questions, sought to determine the frequency of prescribing according to various scenarios (implant procedures and patients with risk conditions). The third block, with three multiple-choice questions, studied the type of antibiotic, dose and dosage of administration in healthy patients without allergies depending on the regimen (pre- or postoperative), including a question on the antibiotic of choice in patients allergic to penicillins. The last block, consisting of a multiple-choice question, sought to determine the motivations for prescribing these drugs in implant treatments. All the questions were compulsory, as without answering one question it was not possible to move on to the next.

The information obtained was statistically analysed using IBM® SPSS Statistics v.26 (IBM® Corp., Armonk, N.Y., USA). All descriptive variables of the subjects were determined as crossover variables. All study variables were treated quantitatively. A normality test was previously applied, observing that none of the variables followed a normal distribution, so the Mann-Whitney U test was applied for the crossover for dichotomous variables and Kruskal-Wallis for variables with more than two categories. The factors determining the decision to prescribe PAs were treated qualitatively, for which the Chi^2 test was applied.

Of the 1460 SEI members, 303 participated in the survey, giving a response rate of 20.8%. The survey was answered by 219 men (72.3%) and 84 women (27.7%). The bulk of the respondents were aged between 31–40 years (24.4%) and 41–50 years (23.4%). The majority of the respondents were dentists (75.6%) and, to a lesser extent, stomatologists (22.1%) and maxillofacial surgeons (2.3%). Most of them had studied a master's degree related to oral implantology (61.1%) and had the experience of up to 5 years in this type of treatment (28.7%) or more than 20 years (30.7%), placed between 50 and 100 implants per year (57.4%) and did not practice exclusively in dental implant treatment (82.2%) (Table 1).

Table 1: Demographic and professional characteristics of all respondents (N., responses).

Variable		N	%
Gender	Male	219	72.3
	Female	84	27.7
Age (years)	< 30	51	16.8
	31–40	74	24.4
	41–50	71	23.4
	51–60	57	18.8
	> 60	50	16.5
Basic university education	Degree in Dentistry	170	56.1
	Degree in Dentistry (Bologna Plan)	59	19.5
	Stomatology	67	22.1
	Maxillofacial Surgery	7	2.3
Postgraduate training in Oral Implantology	Master's Degree	185	61.1
	Specialisation courses	69	22.8
	Non-accredited training (clinical placements, commercial firm courses, etc.)	34	11.2
	Master Degree students	15	5.0
Experience placing implants (in years)	< 5	87	28.7
	6–15	68	22.4
	16–20	55	18.2
	> 20	93	30.7
Average number of implants placed per year	< 50	59	19.9
	50–100	170	57.4
	> 100	67	22.6
Exclusive clinical practice in Oral Implantology	Yes	54	17.8
	No	249	82.2

Professionals dedicated to Oral Implantology prescribe PAs to a large extent, with only 1% never prescribing them, while 55.4% always prescribe them and 43.6% only "sometimes".

In healthy patients, the most frequent regimen is perioperative (36.3–52.2%). More complex treatments represent patients that most frequently require an antibiotic prescription, such as immediate implant placement with chronic infection of the tooth to be extracted (52.2%), bone regeneration and sinus lifts with a lateral window approach (49.8%). The second most frequently used guideline is postoperative (11.6–33%), except for immediate implant placement with chronic infection of the tooth to be extracted, which is preoperative (17.5%). The majority of respondents do not prescribe PAs in the prosthetic phase of implants, i.e., in second stage surgeries (92.1%) and in taking impressions and placement of the implant-supported prosthesis (95.1%) (Table 2).

Table 2: PA prescription guidelines according to the implant procedure in healthy patients (ATB, antibiotic; ID, dental implant; N, responses; PreOp, preoperative; PostOp, postoperative; PeriOp, perioperative; SL, sinus lift).

Procedure	ATB regimen				
	No ATB prescription	Only PreOp ATB prescription	Only PostOp ATB prescription	PeriOp ATB prescription	I perform this treatment
	N (%)	N (%)	N (%)	N (%)	N (%)
Single DI	71 (23.4)	31 (10.2)	91 (30.0)	110 (36.3)	303 (100.0)
Multiple DIs	33 (10.9)	34 (11.2)	93 (30.7)	143 (47.2)	303 (100.0)
Immediate DI placement in absence of active infection	43 (14.2)	32 (10.6)	97 (32.0)	125 (41.3)	297 (98.0)
Immediate DI placement in presence of active infection	6 (1.9)	53 (17.5)	35 (11.6)	158 (52.2)	252 (83.2)
Transcrestal SL	26 (8.6)	35 (11.6)	100 (33.0)	126 (41.5)	287 (94.7)
SL with lateral window	13 (4.3)	40 (13.2)	76 (25.1)	151 (49.8)	280 (92.4)
Bone augmentation	14 (4.6)	40 (13.2)	83 (27.4)	151 (49.8)	288 (95.0)
2nd stage implant surgery	279 (92.1)	3 (1.0)	7 (2.3)	10 (3.3)	299 (98.7)
Impression making	288 (95.1)	2 (0.6)	2 (0.6)	6 (1.9)	298 (98.3)
Placement of the implant-supported prosthesis	288 (95.1)	1 (0.3)	3 (1.0)	6 (1.9)	298 (98.3)

Patients with a smoking habit, diabetes mellitus, immunodeficiency (such as lymphopenia or treatment with immunosuppressive drugs, among others), hip prosthesis, heart valve prosthesis or at risk of infective endocarditis (IE) and/or psychiatric disorders were identified as risk factors. In these patients, the most commonly used guideline was also perioperative (25.4–67.0%), except in those with psychiatric disorders where the majority (43.2%) did not prescribe antibiotics. Patients with a history of IE and/or heart valve prosthesis (67.0%) and with immunodeficiency states (50.5%) are those in whom PAs are most commonly prescribed (Table 3).

Preoperative antibiotics are prescribed by 96.0% of the professionals surveyed. Of these, the majority (39.5%) start treatment two days before, followed by one day before (35.1%) and only 25.4% prescribe them one hour before or immediately prior to surgery. The most commonly used antibiotic one or two days before surgery is amoxicillin (58.5%),

specifically 750 mg (32.7%) TID (32.2%), followed by amoxicillin/ clavulanic acid (40.1%) at a dose of 875/125 mg (34.1) TID (25.8%).

Table 3: Antibiotic prescription choices in patients with risk conditions. (ATB, antibiotic; ID, dental implant; N, responses; PreOp, preoperative; PostOp, postoperative; PeriOp, perioperative; IE, infective endocarditis).

Risk condition	ATB regimen				
	No ATB prescription	Only PreOp ATB prescription	Only PostOp ATB prescription	PeriOp ATB prescription	I perform this treatment
	N (%)	N (%)	N (%)	N (%)	N (%)
Smokers	107 (35.3)	21 (6.9)	61 (20.1)	109 (36.0)	298 (98.3)
Diabetes mellitus	49 (16.2)	37 (12.2)	66 (21.8)	148 (48.8)	300 (99.0)
Immunodeficiency states	15 (5.0)	51 (16.8)	38 (12.5)	153 (50.5)	257 (84.8)
Psychiatric diseases	131 (43.2)	18 (5.9)	47 (15.5)	77 (25.4)	273 (90.1)
Patients with a history of IE or heart valve prosthesis.	7 (2.3)	83 (27.4)	7 (2.3)	203 (67.0)	300 (99.0)
Patients with hip prostheses.	76 (25.1)	41 (13.5)	48 (15.8)	136 (45.0)	301 (99.3)

Other antibiotics such as azithromycin or clindamycin are only prescribed by 1.4%. In prescribing one hour before or immediately prior to surgery, the most commonly prescribed antibiotic continues to be amoxicillin (87.9%), and the most commonly prescribed dose is 2 g (52.7%), followed by 1 g (27.0%) (Table 4).

Table 4: Preoperative antibiotic prescription (N., responses; QD, once a day; BID, twice a day; TID, three times a day).

		N (%)
Do you routinely prescribe systemic antibiotic with DI placement?	Yes	291 (96.0)
	No	12 (4.0)
If yes, when do you start prophylaxis prior to DI placement?	2 days prior	115 (39.5)
	1 day prior	102 (35.1)
	1 h prior or immediately prior	74 (25.4)
If 1- or 2-day(s) prior is selected	Amoxicillin 500 mg BID	1 (0.5)
	Amoxicillin 500 mg TID	30 (13.8)
	Amoxicillin 750 mg BID	1 (0.5)
	Amoxicillin 750 mg TID	70 (32.2)
	Amoxicillin 1 g BID	18 (8.3)

Table 4: Preoperative antibiotic prescription (N., responses; QD, once a day; BID, twice a day; TID, three times a day).

		N (%)
	Amoxicillin 1 g TID	7 (3.2)
	Amoxicillin/ clavulanic acid 500/125 mg BID	3 (1.4)
	Amoxicillin/ clavulanic acid 500/125 mg TID	10 (4.6)
	Amoxicillin/ clavulanic acid 875/125 mg BID	18 (8.3)
	Amoxicillin/ clavulanic acid 875/125 mg TID	56 (25.8)
	Azithromycin 500 mg QD	1 (0.5)
	Clindamycin 300 mg TID	2 (0.9)
If 1 h or immediately prior is selected	Amoxicillin 750 mg	3 (4.1)
	Amoxicillin 1 g	20 (27.0)
	Amoxicillin 2 g	39 (52.7)
	Amoxicillin 3 g	3 (4.1)
	Amoxicillin/ clavulanic acid 500/125 mg	2 (2.7)
	Amoxicillin/ clavulanic acid 875/125 mg	7 (9.5)

Postoperative antibiotics are prescribed by 92.4% of participants. Of these, the majority use them for 7 (58.6%) or 5 days (31.8%). The most commonly prescribed is amoxicillin (55.7%) 750 mg (38.2%) TID (34.6%), followed by amoxicillin/clavulanic acid (41%) 875/125 mg (32.1%) TID (26.1%). Other antibiotics such as azithromycin (1.1%), clindamycin (1.8%) or erythromycin (0.4%) are prescribed by 3.2%. In penicillin-allergic patients, more than half of the surveyed professionals use clindamycin (58.4%), followed by azithromycin (22.1%) (Table 5).

Table 5: Postoperative antibiotic prescription (QD, once a day; BID, twice a day; TID, three times a day; QID, four times a day).

		N (%)
Do you prescribe antibiotics postoperatively after a routine DI placement?	Yes	280 (92.4)
	No	23 (7.6)
If yes, which antibiotic do you prescribe?	Amoxicillin 500 mg TID	49 (17.5)
	Amoxicillin 750 mg BID	10 (3.6)
	Amoxicillin 750 mg TID	97 (34.6)
	Amoxicillin/ clavulanic acid 500/125 mg BID	7 (2.5)
	Amoxicillin/ clavulanic acid 500/125 mg TID	18 (6.4)
	Amoxicillin/ clavulanic acid 875/125 mg BID	17 (6.1)
	Amoxicillin/ clavulanic acid 875/125 mg TID	73 (26.1)
	Azithromycin 500 mg QD	3 (1.1)
	Clindamycin 150 mg QID	1 (0.4)

Table 5: Postoperative antibiotic prescription (QD, once a day; BID, twice a day; TID, three times a day; QID, four times a day).

		N (%)
	Clindamycin 300 mg TID	4 (1.4)
	Erythromycin (ethylsuccinate) 400 mg QID	1 (0.4)
How many days do you prescribe the antibiotic after the surgery (duration)?	1	2 (0.7)
	2	2 (0.7)
	3	18 (6.4)
	5	89 (31.8)
	7	164 (58.6)
	10	5 (1.8)
Which antibiotic do you prescribe in penicillin-allergic patients?	Clindamycin	177 (58.4)
	Azithromycin	67 (22.1)
	Erythromycin	57 (18.8)
	Clarithromycin	2 (0.7)

When analysing the factors that motivate PA prescribing habits, it is observed that those associated with scientific evidence, such as knowledge acquired in postgraduate courses (4.4 ± 0.86), during dental or medical studies (4.03 ± 1.06), reading scientific material (4 ± 1.13) or knowledge acquired in courses and congresses (3.95 ± 1.07) have a greater weight than those not associated to scientific evidence, such as the use of the antibiotic that the patient has at home (1.18 ± 0.55), recommendations from commercial firms (1.32 ± 0.64), the cost of the antibiotic (1.46 ± 0.92), recommendations from other colleagues (2.66 ± 1.17) or previous experience of the antibiotic in a similar procedure (3.72 ± 1.21) (Table 6).

From the data obtained in this survey it can be deduced that PAs are frequently administered in dental implant treatments; however, there is a great disparity in the guidelines used, reflecting the current lack of protocols on the use of these drugs in Oral Implantology. For this reason, the SEI has prepared this CPG to provide recommendations based on scientific evidence, unifying criteria for action by healthcare professionals in the field of dentistry to rationalise the use of PAs in these cases.

No CPG on PAs in Oral Implantology procedures has been found in the literature, so tackling this work for the first time has been a real challenge. The scope of this CPG is limited, focusing on the antibiotic guidelines recommended for various implant treatments in healthy patients, with an in-depth study of the dosages in those cases where it is possible. The aim is to achieve a concise CPG that will serve as a routine reference for professionals in their clinical practice when making decisions regarding these treatments.

This CPG would not have been possible without the effort and dedication of all the authors. The team has encountered major limitations in some sections to support the evidence-based recommendations, in some cases having to make recommendations based on expert opinion. PAs can be prescribed preoperatively, postoperatively or perioperatively, i.e.,

before and after surgery, to avoid early implant failure and the development of postoperative infections that may jeopardise treatment goals. The ultimate aim of this CPG is responsible antibiotic prescribing and patient re-education in the fight against antimicrobial resistance.

Table 6: Factors determining the prescription of PAs in Oral Implantology treatments (S.D, standard deviation).

Motivation	Mean	S. D
Knowledge acquired during postgraduate training	4.40	0.86
Knowledge acquired during basic university studies (dentistry/ stomatology)	4.06	1.06
Scientific material reading	4.00	1.13
Knowledge acquired in courses and/or congresses	3.95	1.07
Previous experience with the antibiotic in a similar procedure	3.72	1.21
Recommendations from other peers	2.66	1.17
Patient preferences	1.68	0.93
Cost of the antibiotic	1.46	0.92
Recommendations from commercial companies	1.32	0.64
Any antibiotic the patient may have at home	1.18	0.55

**The results of the survey conducted by the SEI can be consulted and were published in: Salgado-Peralvo AO, Kewalramani N, Peña-Cardelles JF, Mateos-Moreno MV, Monsalve-Guill L, Jiménez-Guerra A, Ortiz-García I, Velasco-Ortega E. Preventive Antibiotic Prescribing Habits among Professionals Dedicated to Oral Implantology: An Observational Study. Antibiotics 2021;10:301.*

**Available free of charge by scanning the following QR code.*

4. METHODOLOGY

We understand a CPG as "a set of systematically developed recommendations that aim to help professionals and patients to make the most appropriate healthcare decisions, and to select the most appropriate diagnostic or therapeutic options for a specific health problem or clinical condition". Therefore, they must be based on an extensive literature review, critically appraising the resulting articles.

The project includes the preparation of this CPG entitled "*Clinical Practice Guideline on prescribing preventive antibiotics in Oral Implantology".* A working group of 11 expert dentists and stomatologists, carefully selected for their extensive knowledge of the subject, was set up to prepare it. It also benefited from the assessment of 4 external reviewers who participated as independent evaluators and the validation of the following Scientific Societies:

- **SEI:** Spanish Society of Implants.
- **SEGER**: Spanish Society of Gerodontology.
- **SIOLA**: Society of Latin American Oral Implantology Society.
- **FIIO**: International Federation of Oral Implantology, which includes the following scientific societies:
  - **SOCI: Colombian Dental Implant Association.**
  - **CMIBM:** Mexican College of Oral and Maxillofacial Implantology.
  - **Chilean Society of Oral and Maxillofacial Implantology.**
  - **ABROSS:** Brazilian Academy of Osseointegration.
  - **ASPIOI:** Peruvian Association of Integral Oral Implantology.

Its elaboration took place in 5 consecutive phases that were developed in parallel at certain times:

- **Phase 1: Establishment of the group and tasks.**
  - Duration: From January to February 2020.
  - Landmarks included:
    - Establishment of the Working Group and definition of tasks.
    - Training in:
      - Mendeley bibliographic manager.
      - GRADE methodology.
      - Preparation of questions in PICO format (Patient, Intervention, Comparison and Outcome).
    - Elaboration of clinical questions/doubts.
    - Identifying terms for the bibliographic search.
    - Initial bibliographic search: a first approach to the bibliographic search to define the "Objectives and Scope" of the CPG.
    - Discuss and standardise criteria for the systematic literature review.

- **Phase 2: Search and evaluation of the literature.**
    - Duration: From February to October 2020.
    - Landmarks included:
        - Conducting a second literature search.
        - Reading of the abstracts to select the articles to be included in the review.
        - Definition of criteria for selecting or rejecting studies.
        - A detailed review of the literature and grading of the evidence.

- **Phase 3: Drafting of the Guide.**
    - Duration: From October to December 2020.
    - Landmarks included:
        - Compilation of the documentation produced.
        - Formulation of recommendations.
        - Drafting of the CPG.

- **Phase 4: External review.**
    - Duration: From December 2020 to January 2021.
    - Landmarks included: Evaluation and external review.

- **Phase 5: Final review.**
    - Duration: From January to February 2021.
    - Landmarks included:
        - Incorporation of modifications provided in the external review.
        - Publication and dissemination.

The methodology developed during these 13 months of work has been entirely online, due to the COVID-19 pandemic that we treasured during the aforementioned period. To this end, Google Drive was used throughout the project, as well as the ZOOM® platform for online meetings.

ON THE WORK METHODOLOGY

The document has followed a rigorous methodological process based on the indications of the document "*Elaboración de Guías de Práctica Clínica en el Sistema Nacional de Salud: Actualización de Manual Metodológico*" (Elaboration of Clinical Practice Guidelines in the National Health System: Methodological Update of the Manual) [23] (2016). The scientific literature available up to March 2020 was reviewed, although the review was extended to

December 2020, following the search strategies in Annex 3.2. For each clinical problem raised, a worksheet of our own was prepared in which the following aspects were detailed:

Part 1: Clinical Question

The authors pose the clinical question that arises from the knowledge of the subject area and the professional experience of each expert.

Part 2: PICO Question

Question posing the clinical problem, structured in such a way as to incorporate the target population, the intervention and the expected outcome:

- *Patient:*
  Population targeted by the intervention.
- *Intervention/ Comparison:*
  Intervention measured as a comparison, or not, with another one being performed.
- *Outcome:*
  Expected outcome (Annex 2).

Part 3: Introduction

Explanation of the scientific knowledge that exists concerning the prescription of Preventive antibiotics in the specific implant procedure about which the clinical doubt arises, subsequent PICO question and, finally, the recommendation.

Part 4: Type of question

This consists of categorizing the type of question into (1) epidemiological/ aetiological, (2) diagnostic, (3) therapeutic or (4) prognostic.

Part 5: Methodology used

This section describes the specific methodology of the literature search incorporating the Medline database (via PubMed); the subject heading with search terms and connectors (AND, OR, NOT), as well as keywords and MeSH (Medical Subject Headings) terms and, finally, the search results indexing all bibliographic references. In addition, an ancillary search was performed in Google Scholar and the references of the selected articles were analysed for publications that might be of interest.

Part 6: Evaluation and Evidence Synthesis

The studies referenced in the previous section were evaluated, determining the quality of the scientific evidence on which the recommendations are based, defining the "strength" of the recommendation. The analysis was carried out using **SIGN** checklist templates (to assess meta-analyses, systematic reviews, randomised clinical trials, cohort studies, case-control studies, diagnostic test studies and economic evaluations), the **OSTEBA** template (to assess case series) and the **AGREE** (for CPG).

Part 7: Drawing Conclusions

This section proposes the recommendations that the group makes to the initial [PICO] question, as well as the grading of the recommendation. The SIGN instrument was used to elaborate them.

After having catalogued each of the shreds of evidence that respond to the initial [PICO] question, the recommendation is made by incorporating a Grade of Recommendation with the letters "A", "B", "C" or "D":

- **A**: At least one meta-analysis, systematic review or clinical trial 1++; or a volume of evidence composed of studies classified as 1+ and with high consistency between them.
- **B**: Evidence comprised of studies classified as 2++ directly applicable to the guideline's target population, with high consistency between them; or clinical evidence extrapolated from studies classified as 1++ or 1+.
- **C**: Scientific evidence formed by studies classified as 2+ directly applicable to the guideline's target population and demonstrating high consistency between them; or scientific evidence extrapolated from studies classified as 2++.
- **D**: Level 3 or 4 scientific evidence, or evidence extrapolated from studies classified as 2+.

Therefore, studies are classified according to their level of scientific evidence to assess their quality:

Levels of scientific evidence	
1++	High-quality meta-analyses, systematic reviews of clinical trials or high-quality clinical trials.
1+	Well-conducted meta-analyses, meta-analyses of clinical trials or well-conducted clinical trials with low risk of bias.
1-	Meta-analyses, systematic reviews of clinical trials or clinical trials with a high risk of bias.
2++	High-quality systematic reviews of cohort or case-control studies. Cohort or case-control studies with very low risk of bias and high probability of establishing a causal relationship.
2+	Well-conducted cohort or case-control studies with low risk of bias and with a moderate probability of establishing a causal relationship.
2-	Cohort or case-control studies with a high risk of bias and significant risk that the relationship is not causal.
3	Non-analytical studies, such as case reports and case series.
4	Expert opinion.

**Studies classified as 1- and 2- should ideally not be used in the recommendation process because of their high risk of bias.*

Part 8: Recommendations for Future Research.

This last part aims to establish several future lines of research due to a lack of studies on the subject, to be able to provide evidence on possible gaps in knowledge.

ABOUT THE LITERATURE SEARCH

The initial literature search carried out in January 2020 made it possible to define the "scope and objectives" of the CPG and was conducted through Medline (via PubMed). The references were downloaded in the Mendeley citation manager and then preliminarily reviewed by the panel of experts. In a second search carried out in February 2020, the search criteria were redefined, as well as the scope of the CPG itself.

The criteria by which the PICO questions would be developed were established. The work period from February to October 2020 was subsequently completed with weekly alerts to update the content (December 2020). These references were shared in full text with the expert panel via a shared folder in Mendeley.

Literature that had not been published in English or Spanish was excluded. The titles and abstracts of the articles resulting from the searches were screened to eliminate those that did not meet the search criteria. Finally, a final document was produced with the references included answering each PICO question of the CPG.

5. SUMMARY OF RECOMMENDATIONS

The recommendations for each of the questions asked are summarised below, providing recommendations on the type of antibiotic and dosage when possible:

Q1: In healthy patients to be treated with dental implants without the need for simultaneous guided bone regeneration (GBR), does the prescription of PAs compared to not prescribing PAs modify the rate of implant failure and/or postoperative infection?

> **Antibiotic prophylaxis reduces the rate of early implant failure in healthy patients, but not the risk of infection. Postoperative or perioperative regimens are not justified as they have not shown additional benefit to preoperative prescription and increase the likelihood of adverse drug reactions. Therefore, it is recommended to prescribe PA preoperatively before implant placement, specifically 2 to 3 g of amoxicillin one hour before surgery (Grade of recommendation A). However, not prescribing it could also be considered a wrong approach in certain cases (Grade of recommendation B).**

Q2: In healthy patients to be treated with immediate dental implants, with or without infection of the tooth to be extracted, does the prescription of PAs compared to not prescribing PAs modify the rate of implant failure and/or postoperative infection?

> **Evidence has shown an added benefit of perioperative PAs prescription in reducing early failure of immediate implants. Despite this, studies have failed to recommend a specific type and dose of antibiotic and therefore, pending further research, it is necessary to advise a specific guideline based on the extrapolation of the recommendations established in Endodontics given the nature of the microbiota to be combated, advocating the prescription of PAs with a loading dose followed by a maintenance dose (Grade of recommendation D). It is recommended to administer the loading dose of 2 or 3 g of amoxicillin one hour before surgery (Grade of recommendation B), followed by 500 mg/ 8h, during the 5–7 postoperative days (Grade of recommendation D). In case of confirmed true penicillin allergy, azithromycin 500 mg one hour before followed by 250 mg/ 24 h, 5–7 days; clarithromycin 500 mg one hour before followed by 250 mg/ 12 h, 5–7 days; or metronidazole 1 g one hour preoperatively followed by 500 mg/ 6 h/ 5–7 days (Grade of recommendation D).**

Q3: In healthy patients to be treated by sinus lifts with a transcrestal or lateral window approach, with single or two-stage implant placement, does the prescription of PAs compared to not prescribing PAs modify the rate of implant or graft failure?

> **The evidence suggests that the prescription of PAs does not reduce the failure rate of implants placed at the same time as sinus lifts compared to not prescribing it. There is no evidence of their effect on the prevention of postoperative infections.**

Assuming that PAs do prevent them, their prescription should be based on prior cultivation (Grade of recommendation C), however, it is an impractical approach. Prescription of 2 to 3 g of amoxicillin one hour before surgery would be sufficient in the absence of Schneider's membrane perforation (Grade of recommendation B). In most cases, it is not possible to foresee this complication, so it is recommended to rely on the assumption that such a complication would occur. In this case, amoxicillin/clavulanic acid 875/125 mg/ 12 h starting one day before surgery, followed by the same regimen, every 8 h, 7 days (Grade of recommendation D). In penicillin-allergic patients, ciprofloxacin 500 mg/ 12 h/ 9 days is recommended (Grade of recommendation D).

Q4: In healthy patients to be treated by bone augmentation procedures, with or without simultaneous insertion of dental implants, does the prescription of PAs compared to not prescribing PAs modify the rate of implant failure and/or postoperative infections?

In general, different studies have shown a reduction in the rate of postoperative infections in those cases where antibiotics were prescribed preoperatively compared to perioperatively (Grade of recommendation A). A single dose of 2 or 3 g amoxicillin one hour before surgery is recommended to reduce the failure rate of single-stage implants and to reduce the degree of bacterial contamination of the grafted bone particles in these cases as well as in two-stage implants (Grade of recommendation C).

Q5: In healthy patients starting the implant prosthetic phase, does the prescription of PAs compared to not prescribing PAs decrease the occurrence of infectious complications?

At present, PAs in second implant stages, impression making and/or implant prosthetic placement does not seem to be justified (Grade of recommendation D).

Q6: In healthy patients treated with dental implants and in whom PAs is prescribed, does the prescription of amoxicillin compared to another type of antibiotic modify the rate of implant failure and/or postoperative infection?

The prescription of clindamycin has a significantly elevated risk of implant failure related to osseointegration failure and a risk of infection up to 6 times higher than in patients prescribed amoxicillin. In turn, immediate implants have an increased risk of failure in these cases (Grade of recommendation C). Pending further studies, azithromycin 500 mg, one hour before surgery, is recommended (Grade of recommendation C).

6. SCOPE AND OBJECTIVES

Background

The SEI has entrusted various clinicians and groups of experts in the field of dentistry with the development of a CPG that provides recommendations for good clinical practice on the indications for preventive antibiotic therapy in various implant procedures in healthy patients.

These recommendations are based on the best scientific evidence available, so that this CPG will be a reference for improving the quality of care, unifying the criteria for action by healthcare professionals and reflecting the scientific evidence collected up to the date of its publication.

Rationale

Antibiotic therapy in Oral Implantology can be classified as prophylactic or preventive (to prevent infections) or therapeutic (as a treatment for infections that have already occurred). Dentists are often faced with the dilemma of whether or not to prescribe antibiotics preventively in dental implant treatment, which is currently a controversial issue. Prescription has been accepted to avoid systemic bacteraemia [1], but also to achieve an adequate antibiotic concentration in the blood to prevent bacterial contamination during implant surgery or grafting [2], since the oral cavity per se is a septic cavity. Despite this, the routine prescription of PAs in healthy patients does not present a justified risk-benefit ratio [3-5]. The main reason for this is the growing worldwide development of bacterial resistance to virtually all known antibiotic families, which is causing an increasing number of infections to become more difficult to treat due to the loss of efficacy of these drugs [6], as well as increasing the likelihood of idiosyncratic and dose-dependent adverse reactions that may even compromise the patient's life [7]. It is estimated that for every million patients treated with a single dose of antibiotics, mild, moderate and severe allergic reactions occur in 2,400, 400 and 0.9 patients, respectively [8]. Other problems related to their use are direct toxicity including gastrointestinal problems (nausea, vomiting, diarrhoea and abdominal pain), haematological problems (neutropenia, thrombocytopenia and haemolysis), alterations in the usual bacterial flora of the mucous membranes, which may lead to opportunistic infections or pseudomembranous colitis, nephrotoxicity (proteinuria or renal failure), neuropathies (nerve dysfunction or peripheral neuropathy), hepatobiliary disorders (jaundice or hepatitis) and drug-drug interactions [9].

Antibiotics are drugs used to prevent and treat bacterial infections and resistance to antibiotics occurs when bacteria mutate in response to their use. This is a natural phenomenon, although the unwarranted use of these drugs in humans, in food-producing animals and the environment is accelerating the process. In addition, antibiotic resistance

prolongs hospital stays, increases medical costs and increases mortality, making it a major public health problem. It is therefore imperative that the way antibiotics are prescribed and used is urgently changed because even if new antibiotics are developed and current prescribing patterns remain unchanged, resistance will continue to pose a serious threat. Without urgent action, the world is heading for a post-antibiotic era in which many common infections and minor injuries will once again become life-threatening [6]. Dentists play an important part in raising awareness of this problem as it is estimated that, in Spain, dental infections account for around 10% of antibiotic prescriptions [10,11]. In particular, 72–85.5% of dentists in Finland, India, Sweden, the UK and the USA routinely prescribe PA pre- and/or post-operatively [12-17].

Before the publication of this CPG, there was no other CPG that addressed recommendations on the prescription of PAs in dental implant surgery. Due to the massive number of implant treatments performed worldwide, it has been considered essential to establish clear guidelines in this regard, so that more responsible and effective use of these drugs can be carried out. In this document, the authors define precisely what will and will not be addressed in the CPG. The scope is based on the SEI's request for the assignment.

Target Population

Groups to be considered

This guideline will consider healthy patients who will undergo various implant procedures.

Groups not considered

Patients with pathologies or systemic conditions considered to be at risk are excluded from the CPG:

- Smokers.
- Diabetes mellitus.
- Immunodeficiency states (antineoplastic treatments, lymphopenia, convalescence or recent postoperative periods, etc.).
- Psychiatric diseases.
- Patients with a history of IE or heart valve prosthesis.
- Patients with hip and/or knee prostheses.

Clinical issues to be addressed in the guideline

This CPG will address in which implant dentistry procedures the prescription of PAs is indicated and, in the case of its indication, the most appropriate type and dosage according to the case.

Scope of practice

The SEI has among its members, professionals in Dentistry, Stomatology and Maxillofacial Surgery who practice Oral Surgery and Implantology. These professionals may practice in university centres, dental clinics and/or public or private hospitals.

This CPG is aimed at its members, as well as other dental professionals, stomatologists or maxillofacial surgeons in the private or public sector who carry out these types of treatments. Its consultation is intended to assist in the assessment of indications for PAs in dental implant treatment. The application of the recommendations based on scientific evidence should offer the maximum benefit for all patients.

Description of the process

The CPG will examine the indications for PA in the following procedures:

- Placement of dental implants without the need for simultaneous ROG.
- Placement of immediate implants with or without chronic infection of the tooth to be extracted.
- Transcrestal sinus lifts or with a lateral window approach.
- Bone augmentation procedures with implant placement in one or two stages.
- Implant prosthetic phase, understood as the uncovering of the implants for the connection of a prosthetic abutment, taking impressions and the placement of the prosthesis on implants.
- Risk of implant failure or infection in patients who are prescribed drugs other than amoxicillin, such as those allergic to penicillins.

Type of decisions

This CPG provides users with recommendations for deciding when to prescribe PAs for dental implant treatment, as well as the type of antibiotic and posology of choice depending on the case.

Each section specifies the level of evidence and the degree of recommendation according to the SIGN criteria.

7. CLINICAL PROCEDURES ANALYSED

Q1: IN HEALTHY PATIENTS TO BE TREATED WITH DENTAL IMPLANTS WITHOUT THE NEED FOR SIMULTANEOUS GBR (P), DOES THE PRESCRIPTION OF PAs (I) COMPARED WITH NO PRESCRIPTION OF PAs (C) MODIFY THE RATE OF IMPLANT FAILURE AND/OR POSTOPERATIVE INFECTION (O)?

PAs in Oral Implantology was originally born through its implementation in the first implant therapy protocol described by Branemark et al.[1] These authors routinely prescribed phenoxymethylpenicillin one hour before surgery and for 10 days after to improve early implant survival. This trend was established due to the idiosyncratic characteristics of the oral cavity, which makes it a highly contaminated area that may contribute to postoperative infections. Nowadays, these practices have been questioned and professionals are faced with the dilemma of whether or not to prescribe antibiotics as a preventive measure in implant treatment, which is a controversial issue.

To date, the largest number of publications and the highest level of scientific evidence (systematic reviews and/or meta-analyses) refer to the prescription of PAs in healthy patients without anatomical conditions. Certain indicators such as the NNT ("*number needed to treat*") demonstrate a benefit derived from its use [2,3]. The NNT refers to the number of individuals who must be treated to prevent an adverse event, compared to the expected outcomes in the control group. The NNT is the inverse of the difference between the proportion of events in the control group (CG) and the proportion of events in the test group (TG): NNT= 1/(CG - TG). Therefore, it is a parameter that provides fundamentally clinical information [4]. In this sense, the NNT for preventing implant failure has been estimated at between 24 [5] to 55 [6], which is why its prescription in this type of patient is a source of controversy.

Evaluation and synthesis of the evidence

For the evaluation of the scientific evidence, the articles were reviewed by two authors using the SIGN critical reading template. Disagreements between the two were resolved by the intervention of a third author.

A large number of systematic reviews and/or meta-analyses on the effects of PAs administration on early implant failure and/or postoperative infections have been published in the last 10 years. Specifically, 12 studies were found that answered the established PICO question [2,3,5-13], of which two [8,12] were classified with a level of evidence 1-; [8] [2,5-7,9-11,13] with a 1+; and one 3 with a 1++.

In general, there is great heterogeneity among the different randomised clinical trials (RCTs) on which these investigations are based, as most of them used oral amoxicillin, except for some authors who used other types [3,11]. In addition, the amoxicillin regimens and doses varied widely. All protocols were effective in reducing early implant failure compared to no

PAs prescription or placebo (Odds ratio [OR] $_{medio}$ = 0,08–0,45). More specifically, a significant benefit has been demonstrated in the use of preoperative antibiotics [5,6] (level of evidence 1+). No additional benefit is observed when combining amoxicillin with clavulanic acid [6,10] or amoxicillin postoperatively or perioperatively (level of evidence 1+), but instead, they increase the risk of adverse reactions as the regimens are extended over a longer period. Despite this, patients treated with PAs have only a 1.8% higher risk than those not treated [2] (level of evidence 1+).

Their influence on the prevention of postoperative infections was also evaluated in 6 studies [2,6,7,11-13], of which 4 provided data globally and two specifically on how pre- and/or postoperative administration affects infection rates [6,7]. The various studies were unanimous in determining that, in healthy patients, there is no significant difference between not prescribing PAs or prescribing a placebo compared to prescribing antibiotics [2,6,7,11-14] in the risk of developing early (1–2 weeks) and/or late (3–4 months) infections [7]. The mean NNT for avoiding postoperative infection is 143 (patient-level) [6]. Specifically, the NNT for preoperative amoxicillin prescriptions is 100 [6] and for postoperative amoxicillin prescriptions 143 [6].

In short, there is a tendency to recommend the routine prescription of PAs in these cases, however, a smaller number of authors consider that its use should be avoided in simple cases in healthy patients [2,3,5,8] (level of evidence 1- [n=1], 1+ [n=2]), 1++ [n=1]). These authors base their conclusions on the fact that PAs offer a modest reduction in early implant failure of 1.8–4% [3] (level of evidence 1++).

Only three authors studied the recommended guideline in these cases [6,10,13]. Rodríguez-Sánchez et al.[6] (2018) based on the recommendations of the Cochrane Collaboration [13] (2013) concluded that only preoperative treatment with amoxicillin at a dose of 2 or 3 g 1 hour preoperatively is effective (level of evidence 1+). A year later, Romandini et al.[10] (2019) conducted a network meta-analysis – which allows more than two interventions to be compared simultaneously as the only better alternative would be to conduct an RCT with several thousand participants, which is quite complex – concluding that the most effective protocol in preventing implant failures is the administration of 3 g of amoxicillin one hour before (OR=0.41). The most studied protocol (2 g 1 hour before) has only a 0.2% chance of being the best (level of evidence 1+).

Drawing conclusions

PA reduces the early failure rate in healthy patients, but not the risk of infection. Postoperative or perioperative guidelines are not justified as they have not demonstrated additional benefit to preoperative prescription and increase the risk of adverse drug reactions. Therefore, it is recommended to prescribe 2 to 3 g amoxicillin one hour before implant surgery **(Grade of recommendation A)**. However, not prescribing them could also not be considered a wrong approach in certain cases **(Grade of recommendation B).**

Recommendations for future research

It would be interesting to study the rates of postoperative infection and early implant failure in RCTs with large sample sizes comparing the prescription of 2 and 3 g amoxicillin versus placebo or versus not prescribing PAs in healthy patients without anatomical conditions.

Q2: IN HEALTHY PATIENTS TO BE TREATED WITH IMMEDIATE DENTAL IMPLANTS WITH OR WITHOUT INFECTION OF THE TOOTH TO BE EXTRACTED (P), DOES PAs PRESCRIPTION (I) COMPARED WITH NO PAs PRESCRIPTION (C) MODIFY THE RATE OF IMPLANTATION FAILURE AND/OR POSTOPERATIVE INFECTION (O)?

Immediate implants placed in sites with apical pathology fail up to three times more often than those placed in the absence of pathology [1] because of the potential for implant contamination during the initial healing period due to the presence of pathogenic bacteria [2]. Bacteroides species can colonise periapical lesions while remaining encapsulated in polysaccharides that enhance their virulence and survival in mixed infections [3]. In particular, *Tannerella forsythia* persists asymptomatically in endodontic lesions and survives at the bone level encapsulated after tooth extraction and can infect immediate implants [4]. Therefore, despite extraction of a tooth with apical pathology and thorough curettage of the tooth bed, bacteria persist and can reactivate leading to infection of the implant treatment [5]. Kassolis et al.[6] described the presence of biofilm-forming regions and necrotic alveolar bone in edentulous jaws up to one year after extraction, which is a risk factor for early implant failure. Despite this, acute or chronic endodontic infections are usually of a mixed type, with anaerobic species such as *Fusobacterium, Prevotella, Prophyromonas, Actinomyces, Streptococcus and Peptostreptococcus* predominating, commonly located in the area of the root canals [7] so that, usually after extraction of the contaminated tooth, the microorganisms usually disappear [8].

In the opinion of the authors, immediate implants should always be approached as if the teeth to be extracted were chronically infected, as these are sometimes asymptomatic, which can lead to the loss of the implants [9,10].

Evaluation and synthesis of evidence

For the evaluation of the scientific evidence, the articles were reviewed by two authors using the SIGN critical reading template. Disagreements between the two were solved by the intervention of a third author.

After evaluation of the selected articles, 6 articles with a level of evidence of 2++ were included. All were systematic reviews [2,11-14] and one of them was also a meta-analysis [15].

Cosyn et al [15] (2019) reported immediate implant failure rates of 5.1% compared to 1.1% for delayed placement, i.e. 6 months after extraction (Relative Risk [RR]=0.96, *p*=0.02),

with all failures being early failures. A trend towards lower survival of immediate implants was observed when PAs were not administered postoperatively (RR=0.93). On the other hand, in both implant placement protocols (immediate vs. delayed) healing was adequate, except in one study [16] where they found 5 times higher risk of surgical wound complications in immediate implants (26.1% vs. 5.3%, respectively), which may have been due to the fact that immediate implants often require simultaneous GBRs (level of evidence 2++).

Lee et al.[13] (2015) concluded that there is no specific protocol for antibiotic regimen in these treatments but acknowledged the need to prescribe them (level of evidence 2++).

Chrcanovic et al.[2] (2015) conducted a systematic review including studies that investigated the prognosis of immediate implants in infected beds. They included animal (n=7) and human (n=21) studies, none of which compared immediate placement with and without the prescription of PAs, so there is no control group with which to compare results. If only human studies are considered and all cases of immediate implants are included, without distinction between the previous pathology or not, the failure rate is 1.7%. The total duration of antibiotic therapy in the different studies was 6–14 days. The most frequent regimen was perioperative, although some studies carried out only pre- or postoperative antibiotic therapy (level of evidence 2++).

Álvarez-Camino et al.[14] (2013) highlighted the need to prescribe PAs in immediate implants in infected beds, however, they did not recommend a specific guideline (level of evidence 2++).

Lang et al.[12] (2012) conducted a systematic review including 46 studies, of which 33 prescribed PAs: 4 carried out preoperative prophylaxis (n=244 implants) and in 15 only postoperative prophylaxis lasting 5–7 days (n=935 implants). The remaining 14 studies prescribed perioperative PAs (one preoperative dose followed by 5–7 days postoperatively) (n=665 implants). To determine the implant failure rates associated with each regimen, they performed a multivariate analysis using the fixed-effect Poisson regression model, taking the preoperative prescription as a reference. In this way, they calculated the annual failure rate of implants placed under preoperative prophylaxis at 1.9%; postoperative at 0.5% and perioperative at 0.8% (p=0.002). Therefore, single-dose preoperative prophylaxis alone is not sufficient to maintain bacterial levels below the critical threshold during the healing period but prescribing them 5–7 days post-surgery may help to prevent complications that may lead to implant failure (level of evidence 2++).

Waasdorp et al.[11] (2010) did not elaborate on the recommended antibiotic regimen but, despite stating that there is controversy about its use, they recommend prescribing PAs for immediate implants in infected sites. The regimens were very heterogeneous, with durations ranging up to 31 days. Failure rates ranged from 0–8%. In studies where they were prescribed postoperatively, the failure rate was 0–2.3% (n=4), in those prescribed preoperatively 8% (n=1) and perioperatively 0–2.6% (n=2) (level of evidence 2++).

The type of PA and the guidelines used were not provided by all studies. From those that did provide these data, it can be extracted that they were very heterogeneous [2,11,14] reflecting a lack of consensus.

Drawing conclusions

There is a consensus to prescribe PAs in immediate implants although none of the included studies compared prescribing PAs with a control group given a placebo or no PAs prescription [2,15].

Evidence has shown that administration of a single preoperative dose is not sufficient to maintain antibacterial levels below the critical threshold during the healing period but prescribing them 5–7 days postoperatively may help prevent postoperative complications [12].

There is no evidence to recommend a specific type and dose of PAs in these cases. Therefore, this expert panel considers it prudent to apply the recommendations established by the *European Society of Endodontology* [17] (2018) given the nature of the microbiota to be avoided, which advises the use of antibiotics with a loading dose followed by a maintenance dose. It is recommended to administer the loading dose suggested by a recent network meta-analysis for conventional implant placement [18] which coincides with that suggested by a recent systematic review in GBRs with single or two-stage implant placement [19] **(Grade of Recommendation B)**, of 2 or 3 g of amoxicillin one hour before surgery. The maintenance dose, i.e. 500 mg/ 8 h, would be extended for 5–7 postoperative days **(Grade of recommendation D)**. In the case of confirmed true penicillin allergy, the first-line alternatives are azithromycin 500 mg one hour before followed by 250 mg/ 24 h, 5–7 days; clarithromycin 500 mg one hour before followed by 250 mg/ 12 h, 5–7 days; and metronidazole 1 g one hour preoperatively followed by 500 mg/ 6 h, 5–7 days (**Grade of recommendation D)**. *****Due to the higher failure rates associated with the use of clindamycin it would be prudent to avoid its use until further studies are conducted **(Grade of recommendation C)** *[*See Question 6].*

Recommendations for future research

Future research should be directed towards the validation of the antibiotic guidelines recommended in this CPG. It is also important to investigate the effect of other antibiotics prescribed as an alternative in patients allergic to penicillin given the higher risk of implant failure described in some studies concerning the use of clindamycin, as well as their confirmation by RCTs with larger sample sizes.

Q3: IN HEALTHY PATIENTS TO BE TREATED WITH SINUS LIFTS THROUGH A TRANSCRESTAL APPROACH OR THROUGH A LATERAL WINDOW APPROACH WITH SINGLE OR TWO-STAGE IMPLANT PLACEMENT, (P) DOES THE PRESCRIPTION OF PAs (I) COMPARED TO NOT PRESCRIBING PAs (C) MODIFY THE RATE OF IMPLANT AND/OR GRAFT FAILURE (O)?

Sinus lift surgery is the most performed and predictable surgical procedure for prosthetic rehabilitation of the atrophic posterior maxilla, with median survival rates of 93.6% in over 13,000 implants placed in more than 4,000 patients with follow-up times of up to 144 months [1]. Infections secondary to these procedures are relatively uncommon (2–5.6%), with no distinction between true sinus or bone graft infections. Of these two, the most frequent is graft infection, which does not occur in the maxillary sinus per se, but between the sinus floor cortex and the elevated Schneider's membrane [2]. It is caused by bacterial contamination of the bone graft, the materials used and/or inadequate environmental aseptic measures. True sinus infections are less frequent but cause more complications.

A sinus lift aims to separate the Schneider's membrane lining the floor of the maxillary sinus to introduce a bone graft into this cavity and, after its maturation, to increase the height of the alveolar process allowing the placement of implants. Several studies have analysed the microflora found in the subsinusal cavity. The conclusions drawn are that it is a sterile area that is easily contaminated by oral bacteria during surgery. In this regard, Peleg et al.[3] (2018) analysed the microflora found in the nasal and sinus mucosa in 36 biopsies after Lefort I type osteotomies. 28% of the sinuses were sterile while the remaining 72% had microorganisms. No association with nasal microflora was observed, so that a nasal bacterial culture is not predictive of microorganisms that might be found in the same patient in the subsinus cavity, supporting the theory of oral bacterial contamination during surgery. Other similar studies reported 82% sterile sinuses [4].

Another study showed that about 58% of the bacteria cultured were aerobic and 41.7% anaerobic. The aerobic species were mainly polymicrobial (50%), while 5% were dominated by *S. aureus* and 14% by *Propionibacterium acnes* [3]. Other authors found *Streptococcus* species in 45% (mostly *S. viridans* [62.4%]), *Staphylococci* [25%], in particular, *S. aureus* [80%]), and of the *Enterobacteriaceae* family in another 25% (of which 80% were *Klebsiella oxytoca*) and in 5% *Haemophilus influenzae*. These are found in the oral cavity, nasopharynx, and maxillary sinus, which may be explained by a passage of bacteria between the nasal, paranasal and oral cavity sinuses through the middle meatus [5]. These microorganisms do not normally cause infection, but after surgical trauma, depression of the immune system or migration of bacteria from other regions, they can become virulent and cause subantral graft infection [6].

Evaluation and synthesis of evidence

For the evaluation of the scientific evidence, the articles were reviewed by two authors using the SIGN critical reading template. Disagreements between the two were solved by the intervention of a third author.

The evidence related to PAs in sinus lifts is very limited. After searching one study was found [7] that examined whether PAs prevent failure of implants placed in these procedures (level of evidence 2+). Recommendations on how to prescribe them in these cases could be extracted from two studies (level of evidence 2+ [6] and 4 [2]). No studies were found that

provided information on the effect of these drugs on the prevention of postoperative infections.

Zinser et al.[7] (2013) evaluated risk factors in sinus lifts with 1- or 2-stage implant placement, showing that prescribing PAs does not significantly influence implant or graft failure rates compared to not prescribing PAs (level of evidence 2+). Some authors only recommend prescribing PAs if Schneider's membrane perforation occurs because of the high failure rate due to graft infection [3] (level of evidence 2+) (OR=16.82 [8]). The rate of sinus membrane perforation in these procedures has been estimated at 18.3% [8]–23.5% [9]. Of these, 11.3% will experience sinusitis and infection (compared to 1.4% in the case of no perforation), most likely due to colonisation by native sinus bacteria. These authors recommend applying, in the case of non-perforation, the same protocols applied to the placement of ordinary implants [3], i.e., 2 or 3 g of amoxicillin one hour before surgery [10,11] (level of evidence 1+).

Carreño-Carreño et al.[6] took microbiological samples from subsinusal cavities during 227 sinus lifts with a lateral window approach. They did not prescribe PAs or chlorhexidine preoperatively and in this study amoxicillin, 1 g/ 12 h was administered postoperatively. Once the results were obtained at 48 h, 81.9% of the patients were interrupted on antibiotic treatment because no bacterial species were found, i.e., they presented sterile sinuses at the time of sampling, while in the remaining 18.1% antibiotic treatment was continued when a positive culture was obtained. In the case of a positive culture, the duration of antibiotic treatment was not specified (level of evidence 2+).

The choice of the type of PAs should be made based on the sensitivity of the micro-organisms following an antibiogram. In the case of empirical prescription of antibiotics, which is done in routine clinical practice, amoxicillin/clavulanic acid, ampicillin or ciprofloxacin are recommended as the first choice, since the germs found are sensitive to these antimicrobials, while they have shown greater resistance to macrolides, fosfomycin or penicillin G [6] (level of evidence 2+). Cephalosporins have shown modest efficacy and the use of clindamycin has been associated with an increased risk of graft failure (6%) compared to the group prescribed amoxicillin (0%) [12] (level of evidence 3).

An expert panel recommended amoxicillin/clavulanic acid 875/125 mg every 12 h starting one day before surgery, followed by the same schedule, every 8 h, 7 days. In patients allergic to penicillin, clarithromycin 250 g/12 h together with metronidazole 500 mg/8 h starting one day before surgery, followed by the same regimen for 7 days [2] (level of evidence 4), however, the use of macrolides is not justified in these cases, so ciprofloxacin [6] (level of evidence 2+) is recommended. The recommended doses of this drug for preventive use have not been described; however, in the treatment of chronic sinusitis, its efficacy has been demonstrated at a dose of 500 mg/ 12 h/ 9 days [13] (level of evidence 2++).

Khoury et al.[12] (2018) (level of evidence 3) used in self-declared penicillin-allergic patients (i.e. not diagnosed by specific tests), clindamycin 600 mg one hour preoperatively

followed by 300 mg/ 8h/ 7 days, while in the non-allergic group they prescribed amoxicillin 2 g preoperatively followed by 10 days postoperatively, in sinus lifts with lateral window approach with one or two-stage implant placement. Graft infection occurred in 0.48%, all of whom were "allergic" to penicillin, which accounted for 6% of these patients. Symptomatology started at 4–8 weeks. None of the patients had a history of sinusitis and there were no surgical complications such as sinus membrane perforation, mucosal dehiscence, graft exposure and/or tissue necrosis.

The use of topical antibiotics, such as metronidazole, has also been described. For this, 5 ml of a sterile 0.5% metronidazole solution (25 mg) is applied as follows: 3 ml to irrigate the sinus after membrane elevation and 2 ml to hydrate the graft, which is equivalent to 1/20 of a 200 mg tablet, reducing the possibility of antimicrobial resistance. This results in a significant decrease in the number of inhomogeneous areas of the graft over the next 3 months, leading to a more compact and higher quality graft. These air bubble gaps suggest an anaerobic bacterial activity that increases the risk of graft failure ("septic theory") [14] (level of evidence 2+).

Drawing conclusions

The evidence suggests that prescribing PAs does not reduce implant failure rates in sinus lifts compared to not prescribing it. No information was obtained on their effect on the prevention of postoperative infections. Assuming that PAs prevent postoperative infections, their prescription should be based on prior culture (**Grade of recommendation C**), however, in clinical practice their application is complex. Therefore, to avoid possible infections, the prescription of 2 to 3 g amoxicillin one hour before surgery would be sufficient in the absence of Schneider's membrane perforation (**Grade of recommendation B**). Anticipating this complication is complex, so it is recommended to base PAs prescription on the assumption that it would occur, prescribing amoxicillin/clavulanic acid 875/125 mg every 12 h starting one day before surgery, followed by the same guideline, every 8 h, 7 days (**Grade of recommendation D**). In penicillin-allergic patients, ciprofloxacin 500 mg/ 12 h/ 9 days is recommended (**Grade of recommendation D**).

Recommendations for future research

Further studies investigating the effect of the described guidelines compared to placebo and no prescription are needed to determine the most appropriate antibiotic, as well as the possible benefits of using topical antimicrobials and their influence on the preservation of cellular vitality and bone metabolism.

Q4: IN HEALTHY PATIENTS TO BE TREATED WITH BONE AUGMENTATION PROCEDURES, WITH OR WITHOUT SIMULTANEOUS PLACEMENT OF DENTAL IMPLANTS (P), DOES THE PRESCRIPTION OF PAs (I) COMPARED TO THE NON-PRESCRIPTION OF PAs (C) MODIFY THE RATE OF IMPLANT FAILURE AND/OR POSTOPERATIVE INFECTIONS (O)?

Sometimes, when the amount of residual bone is insufficient, bone augmentation procedures are required at the same time as implant placement, or beforehand, with delayed insertion of the fixtures, known as 1- or 2-stage implant placement, respectively. In other cases, implant surgeries are performed in which GBRs are not planned, however, the appearance of bone dehiscence or fenestrations at the time of implant placement often conditions the implementation of these surgeries.

Whatever the reason, it is certain that the appearance of infections in the grafted areas, whether or not associated with exposure of the barrier membranes, can negatively affect the vascularisation of the graft and jeopardise the success of the bone regeneration [1]. For this reason, PAs were standardised in these cases.

Evaluation and synthesis of the evidence

For the evaluation of the scientific evidence, the articles were reviewed by two authors using the SIGN critical reading template. Disagreements between the two were resolved by the intervention of a third author.

Overall, few studies investigated the effect of PAs on the prevention of postoperative infections after bone augmentation with or without simultaneous implant placement and early implant failure. After evaluation of the selected articles, one systematic review [1] and 4 RCTs were included [2-4]. These articles answered the PICO question. The systematic review [1], rated with a level of evidence 1++, concluded that prescribing PAs improves the rate of postoperative infections, however, they could not clarify whether a single dose is sufficient or whether it is necessary to prolong its administration beyond the day of surgery.

Of the 4 RCTs included, three employed a preoperative antibiotic dose in both the test and control groups. The first [2] (level of evidence 1+) studied treatment with 600 mg clindamycin one hour before surgery and, in the test group, in addition, 300 mg/ 6h/ one day postoperatively versus placebo, in bone augmentations with bone blocks covered with barrier membranes. The second RCT [3] (level of evidence 1+) compared the effect of a preoperative dose of 2 g fenetylline or 600 mg clindamycin in bone blocks covered by barrier membranes. Both studies showed lower failure rates in the group prescribed a single preoperative dose of clindamycin, but no significant differences. The RCT by Lee et al.[4] (level of evidence 1-) studied the effect of 2 g of a first-generation cephalosporin. Post-surgery, they prescribed 1 g/ 8 h, 3 days versus placebo in the test group, with no significant differences. Finally, the multicentre RCT led by Payer et al.[5] (level of evidence 1++) was the only one to compare perioperative PAs administration (2 g amoxicillin one hour before surgery, followed by 500 mg/ 8 h/ 3 days) versus placebo, with no significant differences. However, at the clinical level, suppuration was

higher in the control group. Failure rates of implants placed in one stage were lower in the control group compared to the test group (97.4% vs. 99.2%), although without significant differences. The authors concluded that there is no evidence to recommend the routine prescription of PAs in these interventions. Infection of the grafted material leads to its total loss [2,3] or partial loss (in the case of mucosal opening at 7–8 weeks post-surgery without clinical signs of infection) [3] and, it is suggested that, in the case of placing the implants in one stage, it could be a risk factor for failure of osseointegration as it could lead to an increase in the local inflammatory response [6,7].

Another important factor is that, when using an autologous bone graft, the way it is obtained influences the degree of contamination of the graft. Thus, the methods that produce significantly less bacterial contamination are trephine [8], chisel and gouge forceps [9], compared to bone collector and bone scraper [8]. In the case of combining bone collectors with an aspirator that collects saliva, bacterial counts decrease by 58% [10].

Drawing conclusions

One dose of PA is sufficient to prevent postoperative infections after bone block grafts, while postoperative doses are not justified **(Grade of recommendation A).**

The study of the effect of PAs in healthy patients without anatomical conditions has been extensively studied. In this regard, since in clinical practice a large number of implants require associated GBRs, often unplanned, it would be prudent to prescribe, unless otherwise indicated, the dose recommended by a recent network meta-analysis [11] (level of evidence 1++) of 2 or 3 g of amoxicillin one hour before surgery to prevent early implant failure. In the case of two-stage placement, it could be interesting to adopt the same strategy to reduce bacterial contamination of the grafted bone particles by decreasing the salivary bacterial load **(Grade of recommendation C).**

*The results obtained were published recently (2021) by the working group in a systematic review: Salgado-Peralvo AO, Mateos-Moreno MV, Velasco-Ortega E, Peña-Cardelles JF, Kewalramani N. *Preventive Antibiotic Therapy in Bone Augmentation Procedures in Oral Implantology: A systematic review. J Stomatol Oral Maxillofac Surg* 2021;22:S2468-7855(21)00035-5 [In press].

Recommendations for future research

Future lines of research should aim to conduct RCTs comparing infection rates, the level of bone formation achieved after GBR and, in the case of placing implants in one stage, their failure rates in patients prescribed PAs versus placebo and no PAs prescription. It is also interesting to know the effects of using topical antibiotics mixed with graft biomaterials and/or antibacterial barrier membranes compared to not using them and prescribing oral PAs, as well as their influence on cell vitality and bone metabolism.

Q5: IN HEALTHY PATIENTS WHO ARE ABOUT TO START THE IMPLANT PROSTHETIC PHASE (P) DOES PRESCRIPTION OF PAs (I) COMPARED WITH NO PRESCRIPTION OF PAs (C) DECREASE THE APPEARANCE OF INFECTIOUS COMPLICATIONS (O)?

The prosthetic phase of implants includes (1) second phases, i.e., the uncovering of the implants for the placement of a prosthetic abutment, around which the peri-implant mucosa will heal, (2) the taking of impressions, (3) and placement of the implant-supported prosthesis.

The second stages of implants may present a greater or lesser risk of infection depending on the complexity of the technique used. These procedures can range from making a minimally invasive linear incision in the mucosa to techniques that aim to increase the thickness and/or width of the keratinised mucosa by harvesting autologous soft tissue grafts or using other types of biomaterials.

Evaluation and synthesis of evidence

For the evaluation of the scientific evidence, the articles were reviewed by two authors using the SIGN critical reading template. Disagreements between the two authors were solved by the intervention of a third author.

The search did not find any articles investigating the appropriateness of prescribing PAs for the second stage of implants, so the information obtained from 4 studies on surgical procedures in periodontology was extrapolated. Of these, three [1-3] had a level of evidence 2++, and one had a level of evidence 4. No studies on PAs in implant impression-taking and/or prosthetic placement were found.

Liu et al.[1] (2017) conducted a systematic review of RCTs (level of evidence 2+) in which they analysed the effect of PAs in periodontal access surgeries and/or regenerative periodontal surgeries, excluding mucogingival surgeries. The postoperative infection rate was very low, both in the test group (PAs) 0.073% and in the control (no prescription of PAs) 0.693%, with significant differences. However, only 0.170% of all surgeries experienced infectious complications and the NNT to avoid postoperative infection is 203, so the benefit of using PAs in these cases is considered to be of no clinical significance.

Oswal et al.[2] performed an RCT (level of evidence 2+) in which they analysed the effect of 1 g amoxicillin 1 h preoperatively versus amoxicillin 500 mg/ 8h/ 5 days postoperatively and versus not prescribing PAs in periodontal access surgery, mucogingival surgery, periodontal regeneration, osteoplasty and crown lengthening. No postoperative infections were reported, and they recommend not to prescribe these drugs in healthy patients, except in long surgeries (> 2 h duration) or when biomaterials are grafted extensively. Powell et al.[3] studied the influence of PAs in procedures related to periodontal flap elevation. They observed that when soft tissue grafts are incorporated, the infection rate is 4% compared to 1.9% when they are not used. Specifically, the infection rate after connective tissue grafts is 3.7% and after free gingival grafts 5.9%. However, the infection rate is lower when these drugs are not

administered compared to when they are used pre- and/or postoperatively (1.8% vs. 2.9%), although without significant differences (level of evidence 2+).

An expert panel of the 10th European Workshop on Periodontology [4] (2014) concluded that systemic prescription of peri- or postoperative PAs is not indicated in periodontal plastic surgeries, although in extensive surgeries local or systemic antibiotic therapy might be indicated (level of evidence 4).

Drawing conclusions

At present, PAs in second stage surgeries for implants, taking impressions and/or placing the implant-supported prosthesis does not seem to be justified **(Grade of recommendation D).**

Recommendations for future research

RCTs are recommended to specifically analyse the influence of prescribing PAs in second stage implant surgeries, with and without the use of soft tissue grafts, versus not prescribing them.

Q6: IN HEALTHY PATIENTS TREATED WITH DENTAL IMPLANTS AND IN WHICH PAs (P) IS PRESCRIBED, DOES PRESCRIPTION OF AMOXICILLIN (I) COMPARED WITH ANOTHER TYPE OF PA (C) MODIFY THE RATE OF IMPLANT FAILURE AND/OR POSTOPERATIVE INFECTION (O)?

Most of the studies that investigated the effect of PAs in implant procedures studied amoxicillin, leaving little room for the study of other types of antibiotics and when these were analysed, the patients studied were those with penicillin allergy [1]. For this reason, the effect of other antibiotics has been studied in this population, as well as whether penicillin allergy per se modifies the rate of implant failure and/or postoperative infection.

In this regard, around 10–20% of patients report an allergy or reaction to penicillin, however, these are rarely hypersensitivity or immunoglobulin E-mediated reactions, so these drugs could be used safely [2-4]. Furthermore, 80–99% of patients may no longer be considered allergic after a specific diagnostic test [5-7].

Evaluation and synthesis of evidence

For the evaluation of the scientific evidence, the articles were reviewed by two authors using the SIGN critical reading template. Disagreements between the two were solved by the intervention of a third author.

Five studies were found that answered the PICO question posed. All were observational and, in particular, 4 were cohort studies [8-11] (level of evidence 2+) and one case series [12] (level of evidence 3).

The included studies only evaluated the effect of clindamycin as an alternative to amoxicillin in the placement of implants in native bone with or without the need for simultaneous GBR and/or sinus lifts and immediate implants [8-11]. Of the 4 studies, allergy testing to confirm the diagnosis was performed in only one study [11]. The remaining three studies included patients with self-reported allergy [8-10]. Additionally, an investigation [13] evaluating the effect of azithromycin versus amoxicillin was included (level of evidence 2++).

Salomo-Coll et al.[8] (2018) (level of evidence 2+) described failure rates in non-allergic patients as 4 times lower (RR=3.84) than in allergic patients (8% vs. 24.7%). In allergic patients, 21.1% of implants failed late, while 79% failed early, as a consequence of a failure of the osseointegration process (80%) or uncontrolled infections (20%). At the patient level, failure rates were 5.2% in non-allergic and 18.9% in allergic patients (*p*=0.046) (RR=3.64) [8].

French et al.[11] (2014) (level of evidence 2+) found twice the risk of implant failure in allergic patients treated with clindamycin versus those treated with amoxicillin (Hazard ratio [HR]=2.16), however, these results were not significant due to the low number of allergic patients included and the low failure rates experienced in the whole sample (0.7%). These authors suggest avoiding immediate implant placement if penicillin cannot be administered. The same working group, two years later, published a similar study [9] (level of evidence 2+) in which they described implant failure rates in non-allergic patients of 0.8% (of these, 53.8% were early failures) versus 2.1% in allergic patients (80% failed early) (*p*=0.002), with an OR of 3.10. They also investigated the occurrence of postoperative infections, which was 0.6% in non-allergic and 3.4% in allergic patients, i.e., 6 times higher. 12.3% of the implants were immediate implants (n=687), of which 91.7% (n=630) were placed in non-allergic patients with failure rates of 1%, while 8.3% in allergic patients with failure rates of 10.5%, i.e., 10 times higher. The differences were due to a higher infection rate in "allergy sufferers".

Wagenberg & Froum [10] (2006) conducted a similar investigation in which they described a 5.7-fold increased risk of immediate implant failure secondary to infection in allergy sufferers prescribed clindamycin (8.5%) compared to non-allergy sufferers given amoxicillin (3%; RR=3.34), with significant differences (level of evidence 2+).

Khoury et al.[12] (2018) (level of evidence 3) administered clindamycin 600 mg 1 h preoperatively followed by 300 mg/ 8h, 7 days postoperatively in "allergy sufferers", while in non-allergic patients they administered amoxicillin 2 g preoperatively followed by 10 days postoperatively, in sinus lifts with a lateral window approach, with one- or two-stage implant placement. Subantral graft infection occurred in 0.5%, all in "allergy sufferers", which accounted for 6% of these patients. The infection occurred in the subantral graft and the symptomatology started at 4–8 weeks. None of the patients had a history of sinusitis and no surgical complications such as sinus membrane perforation, mucosal dehiscence, graft exposure and/or tissue necrosis occurred.

A study [13] (level of evidence 2++) evaluated azithromycin 500 mg compared to amoxicillin 2 g, both one hour before implant surgery. On day 6 they found concentrations of 3.4 g/mL (± 0.7) and 2.8 g/mL (± 0.9) in gingival and peri-implant crevicular fluid, respectively, while amoxicillin concentrations were below detectable limits. Furthermore, gingival crevicular fluid levels were significantly lower in the azithromycin group during the initial healing period. Therefore, azithromycin acts on inflammation and early healing by decreasing levels of granulocyte colony-stimulating factor (G-CSF), interleukins 6 and 8, macrophage inflammatory protein 1 (MIP-1) and interferon-induced 10 kDa protein (IP-10), reducing mobilisation of granulocyte precursors and recruitment of immune and inflammatory cells during the healing phase. In addition, its bioavailability is higher compared to amoxicillin and clindamycin.

Drawing conclusions

It is not possible to state that penicillin allergy per se is a risk factor for implant failure because most studies did not test patients for allergy. On the other hand, the PAs used in these cases was clindamycin, which has shown a significant risk of implant failure, related to the failure of osseointegration and a risk of infection up to 6 times higher than in patients administered amoxicillin. Immediate implants have an increased risk of failure in these cases **(Grade of recommendation C)**. Pending further studies, an appropriate alternative is the use of azithromycin 500 mg, one hour before surgery **(Grade of recommendation C).**

Recommendations for future research

Future lines of research should be directed towards RCTs studying the administration of clindamycin and amoxicillin in patients not allergic to penicillin, and the study of clindamycin in comparison to other drugs (such as azithromycin), in allergic patients diagnosed by specific tests. It is recommended to investigate whether there is an association between polymorphisms related to such allergy and alterations at the bone level that may have a negative influence on the osseointegration of dental implants.

8. ANNEXES

ANNEX 1. SURVEY TO COLLECT INFORMATION ON THE PRESCRIPTION OF PREVENTIVE ANTIBIOTICS AMONG PROFESSIONALS DEDICATED TO ORAL IMPLANTOLOGY.

Block I: General variables related to the population surveyed (demographic, academic, professional and experience data of the respondent).

1. **Gender:**
   - Male.
   - Female.

2. **Age (years)**
   - ≤ 30 years.
   - 31–40 years.
   - 41–50 years.
   - 51–60 years.
   - > 60 years.

3. **Education levels:**
   - Graduate in Dentistry.
   - Degree in Dentistry.
   - Stomatologist.
   - Maxillofacial surgeon

4. **Level of postgraduate training achieved:**
   - Non-accredited training courses (clinical placements, commercial firm courses, etc).
   - Postgraduate university courses related to Oral Implantology.
   - Student at any university master's degree related to Oral Implantology (Oral Surgery, Oral Implantology, Periodontics or combinations of these).
   - A completed master's degree course related to Oral Implantology.

5. **Years of experience placing implants:**
   - ≤ 5 years.
   - 6–15 years.
   - 16–20 years.
   - > 20 years.

6. **Approximate average number of implants placed per year:**
   - ≤ 50.
   - 51–100.
   - > 100.

7. **Are you dedicated exclusively to the placement of implants?**
   - Yes.
   - No.

BLOCK II: Frequency of prescription of different antibiotic regimens and regimens of choice according to different scenarios (implant procedures and patients with risk or special conditions).

1. **In healthy patients, do you prescribe preventive antibiotics in dental implant surgeries?**
   - Always.
   - Sometimes.
   - Never.

2. **Please specify whether you prescribe preventive antibiotics in the following procedures in healthy patients:**

2.1. Immediate implants **2.2. Multiple implants** **2.3. Immediate implant placement without the presence of chronic infection in the site of the tooth to be extracted** **2.4. Immediate implant placement in the presence of chronic infection in the site of the tooth to be extracted** **2.5. Transcrestal (atraumatic) sinus lift** **2.6. Sinus lift with lateral window approach** **2.7. Bone augmentation procedures (bone regeneration)** **2.8. Second stage implant surgery (uncovering implants prior to the beginning of the prosthetic phase)** **2.9. Taking impressions for implant-supported prosthesis** **2.10. Placement of implant-supported prosthesis**	**Possible answers for each procedure:** ▪ I do not normally prescribe antibiotics for this procedure. ▪ I prescribe antibiotics preoperatively only. ▪ I prescribe antibiotics postoperatively only. ▪ I prescribe antibiotics preoperatively and postoperatively. ▪ I do not perform this type of treatment.

3. **Mark if any of the following risk factors trigger the prescription of antibiotics:**

3.1. Smokers: **3.2. Diabetes mellitus:** **3.3. Immunodeficiency states (antineoplastic treatments, lymphopenia, convalescence or recent postoperative period, etc.)** **3.4. Psychiatric disorders** **3.5. Patients with a history of bacterial endocarditis or prosthetic heart valves** **3.6. Patients with a hip prosthesis**	**Possible answers for each procedure:** ▪ I do not normally prescribe antibiotics for this procedure. ▪ I prescribe antibiotics preoperatively only. ▪ I prescribe antibiotics postoperatively only. ▪ I prescribe antibiotics preoperatively and postoperatively. ▪ I do not perform this type of treatment.

<u>BLOCK III:</u> Type of antibiotic of choice, dose and dosage of administration in healthy patients without allergies.

1. Do you routinely prescribe antibiotics preoperatively and prior to implant procedures?

- No.
- Yes. If you have chosen this answer:

1.1. How many days before surgery do you start antibiotic prophylaxis?

- 2 days before.
- 1 day before.
- 1 hour before.
- Immediately before.
- I never do preoperative prophylaxis.

1.2. If you have selected "1 or 2 days before", which antibiotic do you prescribe for a patient without allergies? (You can only select one type of antibiotic and one dose)

- I do not perform preoperative prophylaxis "one or two days before".
- *Amoxicillin:*
  - 500 mg, 2 times/day.
  - 500 mg, 3 times/day.
  - 750 mg, 2 times/day.
  - 750 mg, 3 times/day.
  - 1,000 mg, 2 times/day.
  - 1,000 mg, 3 times/day
- *Amoxicillin/ clavulanic acid:*
  - *875/ 125 mg, 2 times/day*
  - *875/ 125 mg, 3 times/day*
  - *500/ 125 mg, 2 times/day*
  - *500/ 125 mg, 3 times/day*
  - *250/ 62.5 mg, 3 times/day*
- *Clindamycin:*
  - *150 mg, 4 times/day*
  - *300 mg, 4 times/day*
  - *300 mg, 3 times/day*
- *Erythromycin:*
  - 400 mg, 4 times/day (ethylsuccinate)
  - 800 mg, 2 times/day (ethylsuccinate)
  - 250 mg, 4 times/day (stearate)
  - 500 mg, 2 times/day (stearate)
- Azithromycin 500 mg, 1 time/day.

1.3. If you have selected "one hour before" or "immediately before", which antibiotic do you prescribe in a patient without allergies? (You can only select one type of antibiotic and one dose).

- I do not perform antibiotic prophylaxis "one hour before" or "immediately before" surgery.
- *Amoxicillin:*
  - 3,000 mg.
  - 2,000 mg.
  - 1,000 mg.
  - 750 mg.
  - 500 mg.

- *Amoxicillin/ clavulanic acid:*
  - 875/ 125 mg.
  - 500/ 125 mg.
  - 250/ 62.5 mg.
- *Clindamycin:*
  - 600 mg.
  - 300 mg.
  - 150 mg.
- *Erythromycin:*
  - 1,600 mg (ethylsuccinate).
  - 800 mg (ethylsuccinate).
  - 1.000 mg (stearate).
  - 500 mg (stearate).
- *Azithromycin:*
  - 1.000 mg.
  - 500 mg.

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2. Do you routinely prescribe antibiotics postoperatively for dental implant treatments in healthy patients?

- No.
- Yes. If you have chosen this answer:

2.1. Which antibiotic do you prescribe in patients without allergies? (You can only select one type of antibiotic and one dose).

- I do not perform prophylaxis postoperatively**.**
- *Amoxicillin:*
  - 250 mg, 4 times/day.
  - 500 mg, 3 times/day.
  - 750 mg, 2 times/day.
  - 750 mg, 3 times/day.
- *Amoxicillin/ clavulanic acid:*
  - 500/ 125 mg, 2 times/day.
  - 500/125 mg, 3 times/day.
  - 875/ 125 mg, 2 times/day.
  - 875/ 125 mg, 3 times/day.
- *Clindamycin:*
  - 150 mg, 4 times/day.
  - 300 mg, 3 times/day.
  - 300 mg, 4 times/day.
- *Erythromycin:*
  - 400 mg, 4 times/day (ethylsuccinate).
  - 800 mg, 2 times/day (ethylsuccinate).
  - 250 mg, 4 times/day (stearate).
  - 500 mg, 2 times/day (stearate).
- Azithromycin 500 mg, 1 time/day.

2.2. Duration of postoperative antibiotic treatment (in days):

- 1.
- 2.
- 3.
- 5.
- 7.
- 10.
- I do not perform postoperative prophylaxis.

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3. **In patients allergic to beta-lactams (such as penicillin), which preventive antibiotic do you usually prescribe?**
    - Clindamycin.
    - Azithromycin.
    - Clarithromycin.
    - Erythromycin.

Block IV: Factors affecting the decision to prescribe antibiotics.

1. **Which of the following factors affect the choice of antibiotic type and dosage of administration?** (mark the degree of influence each factor has on your decision, with 1 being "none" and 5 being "very important")

    - Patient preferences
    - Reading scientific material (articles, books, etc).
    - Knowledge acquired during dentistry/stomatology studies.
    - Knowledge acquired in postgraduate courses (specialisation courses, master's degree or doctorate).
    - Knowledge acquired in courses and congresses.
    - Cost of antibiotics.
    - Recommendations from other fellow professionals.
    - Previous experience with the antibiotic in a similar procedure.
    - Recommendations from a commercial firm.
    - I don't think it makes any difference. Any antibiotic that the patient keeps at home may be useful.

ANNEX 2. PICO QUESTIONS.

Q1

Clinical Problem: PAs prescribing guidelines for implant placement in routine situations in healthy patients.	
Population	Healthy patients to be treated with dental implants without simultaneous GBR.
Intervention	Prescription of PAs.
Comparison	No prescription of PAs.
Outcome	Implant failure. Postoperative infection.
PICO Question	**IN HEALTHY PATIENTS TO BE TREATED WITH DENTAL IMPLANTS WITHOUT THE NEED FOR SIMULTANEOUS GBR (P), DOES THE PRESCRIPTION OF PAs (I) COMPARED WITH NO PRESCRIPTION OF PAs (C) MODIFY THE RATE OF IMPLANT FAILURE AND/OR POSTOPERATIVE INFECTION (O)?**
Question type:	PROGNOSTIC

Q2

Clinical problem: PAs prescribing guidelines in healthy patients for immediate implant placement.	
Population	Healthy patients undergoing immediate implant placement, with or without the presence of chronic infection of the tooth to be extracted.
Intervention	Prescription of PAs.
Comparison	No prescription of PAs.
Outcome	Implant failure Postoperative infection.
PICO Question	**IN HEALTHY PATIENTS TO BE TREATED WITH IMMEDIATE DENTAL IMPLANTS WITH OR WITHOUT INFECTION OF THE TOOTH TO BE EXTRACTED (P), DOES PAs PRESCRIPTION (I) COMPARED WITH NO PAs PRESCRIPTION (C) MODIFY THE RATE OF IMPLANTATION FAILURE AND/OR POSTOPERATIVE INFECTION (O)?**
Question type:	PROGNOSTIC

Q3

Clinical Problem: PAs prescribing guidelines for healthy patients undergoing sinus lifts with single or two-stage implant placement.	
Population	Healthy patients treated with sinus lifts with lateral window or transcrestal approach, with one or two-stage placement of dental implants.
Intervention	Prescription of PAs.
Comparison	No prescription of PAs.
Outcome	Postoperative infection. Failure of implants placed in one stage.
PICO Question	**IN HEALTHY PATIENTS TO BE TREATED WITH SINUS LIFTS THROUGH A TRANSCRESTAL APPROACH OR THROUGH A LATERAL WINDOW APPROACH WITH SINGLE OR TWO-STAGE IMPLANT PLACEMENT, (P) DOES THE PRESCRIPTION OF PAs (I) COMPARED TO NOT PRESCRIBING PAs (C) MODIFY THE RATE OF IMPLANT AND/OR GRAFT FAILURE (O)?**
Question type:	PROGNOSTIC

Q4

Clinical Problem: PA prescribing guidelines in healthy patients in GBR, with single or two-stage implant placement.	
Population	Healthy patients to be treated with bone augmentation procedures, with or without simultaneous placement of dental implants.
Intervention	Prescription of PAs.
Comparison	No prescription of PAs.
Outcome	Postoperative infection. Failure of implants placed in one stage.
PICO Question	**IN HEALTHY PATIENTS TO BE TREATED WITH BONE AUGMENTATION PROCEDURES, WITH OR WITHOUT SIMULTANEOUS PLACEMENT OF DENTAL IMPLANTS (P), DOES THE PRESCRIPTION OF PAs (I) COMPARED TO THE NON-PRESCRIPTION OF PAs (C) MODIFY THE RATE OF IMPLANT FAILURE AND/OR POSTOPERATIVE INFECTIONS (O)?**
Question type:	PROGNOSTIC

Q5

Clinical Problem: PAs prescribing guidelines for healthy patients in the prosthetic phase of dental implants (second stages, impression taking and placement of the implant-supported prosthesis).	
Population	Healthy patients who are about to start the implant prosthetic phase.
Intervention	Prescription of PAs.
Comparison	No prescription of PAs.
Outcome	Infectious complications.
PICO Question	**IN HEALTHY PATIENTS WHO ARE ABOUT TO START THE IMPLANT PROSTHETIC PHASE (P) DOES PRESCRIPTION OF PAs (I) COMPARED WITH NO PRESCRIPTION OF PAs (C) DECREASE THE APPEARANCE OF INFECTIOUS COMPLICATIONS (O)?**
Question type:	PROGNOSTIC

Q6

Clinical Problem: Prescription of antibiotics other than amoxicillin for implant placement in healthy patients.	
Population	Healthy patients treated with implants undergoing antibiotic prophylaxis.
Intervention	Amoxicillin prescription.
Comparison	Antibiotics different from amoxicillin.
Outcome	Implant failure Postoperative infection
PICO Question	**IN HEALTHY PATIENTS TREATED WITH DENTAL IMPLANTS AND IN WHICH PAs (P) IS PRESCRIBED, DOES PRESCRIPTION OF AMOXICILLIN (I) COMPARED WITH ANOTHER TYPE OF PA (C) MODIFY THE RATE OF IMPLANT FAILURE AND/OR POSTOPERATIVE INFECTION (O)?**
Question type:	PROGNOSTIC

ANNEX 3. REFERENCES.

ANNEX 3.1. GENERAL REFERENCES.

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ANNEX 3.2. REFERENCES OF PICO QUESTIONS AND SEARCH STRATEGY.

Q1: In healthy patients to be treated with dental implants without the need for simultaneous GBR (P), does the prescription of PAs (I) compared with no prescription of PAs (C) modify the rate of implant failure and/or postoperative infection (o)?

PubMed Strategy:

(dental implant OR dental implants OR dental implantology OR oral implantology) AND (antibiotics OR preventive antibiotics OR antibiotic prophylaxis).

Filters applied:

- Temporal: 2010 a 2020.
- Human studies
- Meta-analyses and systematic reviews.
- Articles published in English and/or Spanish.

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Q2: In healthy patients to be treated with immediate dental implants with or without infection of the tooth to be extracted (P), does PAs prescription (I) compared to no PAs prescription AP (C) modify the rate of implant failure and/or postoperative infection (O)?

PubMed Strategy:

(immediate implant OR immediate implantation OR fresh extraction socket) **AND** (dental implant OR dental implants OR dental implantology OR oral implantology) **AND** (antibiotics OR antibiotic prophylaxis OR clindamycin OR amoxicillin OR azithromycin OR erythromycin).

Filters applied:

- Temporal: 2010 a 2020.
- Human studies.
- Meta-analyses and systematic reviews.
- Articles published in English and/or Spanish.

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Q3: In healthy patients to be treated with sinus lifts through a transcrestal approach or through a lateral window approach, with single or two-stage implant placement (P), does the prescription of PAs (I) compared to not prescribing PAs (C) modify the rate of implant and/or graft failure (O)?

PubMed Strategy:

(maxillary sinus lift OR maxillary sinus augmentation OR sinus lift elevation) AND (antibiotics OR antibiotic prophylaxis OR clindamycin OR amoxicillin OR erythromycin OR azithromycin OR metronidazole)

Filters applied:

- Temporal: no temporal restrictions and the search was updated to December 2020.
- Human studies
- No filters by study type
- Articles published in English and/or Spanish

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Q4: In healthy patients to be treated with bone augmentation procedures, with or without simultaneous placement of dental implants (P), does the prescription of PAs (I) compared to the non-prescription of PAs (C) modify the rate of implant failure and/or postoperative infections (O)?

PubMed Strategy:

(bone grafting OR alveolar ridge augmentation OR alveolar bone grafting OR bone graft augmentation OR guided bone regeneration OR bone block) **AND** (dental implants OR dental implant OR oral implantology OR dental implantology) **AND** (antibiotic prophylaxis OR antibiotics).

Filters applied:

- Temporal: 2005 to 2020.
- Human studies
- Meta-analyses, systematic reviews and randomised clinical trials.
- Articles published in English and/or Spanish.

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Q5: In healthy patients who are about to start the implant prosthetic phase (P), does the prescription of PAs (I) compared with no prescription of PAs (C) decrease the appearance of infectious complications (O)?

PubMed Strategy:

(periimplant plastic surgery OR periodontal plastic surgery OR free gingival graft OR connective tissue graft OR graft OR second stage surgery OR prosthetic phase OR implant-

supported prosthesis) **AND** (antibiotics OR antibiotic prophylaxis) **AND** (dental OR dental implant OR dental implants OR oral implantology OR dental implantology)

Filters applied:

- Temporal: 2000 to 2020.
- Human studies
- Meta-analyses, systematic reviews, randomised clinical trials, observational studies, multicentre studies, randomised clinical trials, comparative studies, clinical studies.
- Articles published in English and/or Spanish

References

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Q6: In healthy patients treated with dental implants and in which PAs (P) is prescribed, does the prescription of amoxicillin (I) compared with another type of PAs (C) modify the rate of implant failure and/or postoperative infection (O)?

PubMed Strategy :

(penicillin allergy OR clindamycin) AND (dental implant OR dental implant failure).

Filters applied:

- Temporal: the search was not temporally restricted, and the search was updated to December 2020.
- Human studies
- Human studies.
- Meta-analyses, systematic reviews, RCTs, cohort studies, observational studies, comparative studies and multicentre studies.

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ANNEX 4. QUICK REFERENCE SUMMARY TABLE OF RECOMMENDATIONS

Clinical Situation		Preoperative Regimen	GR*	Postoperative Regimen	GR
Ordinary DI†	NA‡	Amoxicillin 2 or 3 g, 1h before	A	No	-
		No antibiotic prescription	B	No	-
	A§	Azithromycin 500 mg, 1h before	C	No	-
Immediate DI with/without chronic infection of the tooth to be extracted	NA	Amoxicillin 2 or 3 g, 1h before	B	500 mg/ 8h, 5–7 days	D
	A	Azithromycin 500 mg, 1h before	D	250 mg/ 24h, 5–7 days	D
		Metronidazole 1 g, 1h before	D	500 mg/ 6h, 5–7 days	D
		Clarithromycin 500 mg, 1h before	D	250 mg/ 12h, 5–7 days	D
Sinus Lifts (Transcrestal and/or lateral approach)	NA	Amoxicillin/ clavulanic acid 875/ 125 mg/ 12 h, 1 day before	D	Same regimen, 7 days	D
	A	Ciprofloxacin 500 mg/ 12h, 1 day before	D	Same regimen, 9 days	D
Bone regeneration	NA	Amoxicillin 2 or 3 g, 1h before	C	No	-
	A	Azithromycin 500 mg, 1h before	D	No	-
Prosthetic phase**	NA/ A	No	D	No	D

* GR., grade of recommendation.

† DI., Dental Implant

‡ NA., patients non-allergic to penicillin.

§ A., patients allergic to penicillins.

** Prosthetic phase: includes the uncovering of implants for the connection of a prosthetic abutment, taking impressions and/or placing the implant-supported prosthesis on the implants.

ANNEX 5. ABBREVIATIONS

AGREE., Appraisal of Guidelines Research and Evaluation.
PA., preventive antibiotics/antibiotic prophylaxis
ATB., antibiotics.
BID., twice a day
CMBD., Minimum Basic Data Set Registry
DT., desviación típica.
IE., infective endocarditis
G-CSF., granulocyte colony-stimulating factor.
CPG., Clinical Practice Guideline
GRADE., Grading the Quality of Evidence and the Assessment of Recomendations.
HR., hazard ratio.
DI., dental implant
MESH., Medical Subject Headings.
MIP-1ß., macrophage inflammatory protein 1ß.
N., answer/response
NNT., ("number needed to treat"). Number of individuals who must be treated to prevent an adverse event compared to the expected outcomes in the control group.
OR., odds ratio.
OSTEBA., Basque Office for Health Technology Assessment.
p., statistical significance
PeriOp., perioperative
PICO., Patient, Intervention, Comparison and Outcome.
PostOp., postoperative.
PreOp., preoperative.
QD., once a day
QID., four times a day.
RCT., randomised controlled trial.
GBR., guided bone regeneration
RR., relative risk.
SEI., Spanish Society of Implants
SEGER., Spanish Society of Gerodontology
SIGN., Scottish Intercollegiate Guidelines Network.
SIOLA., Latin American Oral Implantology Society.
TID., three times a day.

6. CONFLICT OF INTEREST.

None of the authors declare any conflict of interest.

Sociedad Española de Implantes

Together for a responsible use of antibiotics!