Systematic Review and Meta-Analysis

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Use or abuse of antibiotics as prophylactic therapy in oral surgery

A systematic review

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Abstract

Backgroud: Antibiotics are a type of medication routinely prescribed by dental professionals; however, it is very common that the administration is not justified. Around 15% of dentists admit that they have administered antibiotics unnecessarily more than once a week. The objective of this project is to identify the effectiveness of the use of antibiotics as prophylactic therapy in oral surgery, and to carry out an analysis of the alternatives to pharmacological therapy.

Methods: The search strategy was carried out in the PubMed, Scopus, and ScienceDirect databases. For study selection, a first filter was carried out by title and abstract, which mentioned the use of prophylactic antibiotics in some type of oral surgery. To establish the risk of bias, the JBI Critical Appraisal Checklist for Randomized Controlled Trials was utilized.

Results: The type of antibiotics most prescribed as prophylactic therapy were beta-lactams, which were indicated in 100% of the studies. Penicillins predominated, observing amoxicillin as the most indicated drug in 54.1% of the studies (n = 13) followed by the use of amoxicillin in conjunction with clavulanic acid in 33.3% of the studies (n = 8). Of the 21 studies included, 17 mention that there is insufficient evidence to support the use of antibiotics as prophylactic therapy in patients who will undergo some type of oral surgery.

Conclusions: Without a doubt, the biggest challenge is to develop academic update strategies aimed at dentists with active clinical practice and dental students from educational and government institutions to provide updated information about the correct use of prescription drugs.

Keywords: oral surgery, systematic review, use or abuse of antibiotics

1. Introduction

Antibiotics are a type of medication routinely prescribed by the dental professional, which focus on 2 needs: for therapeutic purposes to treat already established infectious processes; or for prophylactic purposes to prevent the spread of oral microflora in the human body.[1] Among the procedures that most demand the use of this type of therapy is oral surgery; various publications mention that the development of complications ranges from 1.28% to 3.57%.[2,3]

Several research groups have undertaken the task of analyzing perceptions and experience of dental professionals and students about the prescription of antibiotics. An analysis carried out on dental students from 3 different countries, shows that students have a moderate level of confidence in the prescription of antibiotics, however, the level of confidence decreases when they have to choose a specific antibiotic scheme. Another noteworthy data is that their level of confidence is moderate when students make a diagnosis of infection as well as their association with systemic diseases.[4] This data is especially important to our study, since the foundation for the management of antibiotics are obtained in university.

The practice of prescribing antibiotics is very common, and such administration is often not justified. Around 15% of dentists in Jordan admit that they have unnecessarily administered antibiotics at least once a week.[5] This fact is worrying for 2 reasons: the high risk of patients developing bacterial resistance, and it is a challenge for the dentist to be well informed of the updated indications for the correct prescription of antibiotics; the

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use of antibiotics as prophylactic therapy in oral surgery; and to carry out an analysis of alternatives to pharmacological therapy. A systematic review was carried out in which 3 databases were reviewed (PubMed, ScienceDirect, and Scopus) to identify the studies that researched the efficiency of antibiotics in oral surgery.

2. Methods

2.1. Research question

What is the evidence related to the effectiveness of prophylactic antibiotics in oral surgery?

2.2. Selection criteria

2.2.1. Inclusion criteria.

- Clinical trial type studies
- Studies whose main objective was to analyze the effectiveness of antibiotics as prophylactic therapy.
- Studies in which third molar surgery, implant surgery, periodontal surgery, tooth extractions, among others have been performed.
- Studies conducted in humans.

2.2.2. Exclusion criteria.

- Reviews.
- Studies whose main objective was other than to measure the effectiveness of antibiotics as prophylactic therapy.
- Studies that did not specify the dose of antibiotic administration.
- Studies in a language other than Spanish or English.

2.3. Search strategy

2.3.1. Selection of studies. The search strategy was carried out in the PubMed, ScienceDirect, and Scopus databases using the keywords "Oral surgery," "antibiotic," "Antimicrobial," "antibacterial," and "Prophylactic." The Boolean operators

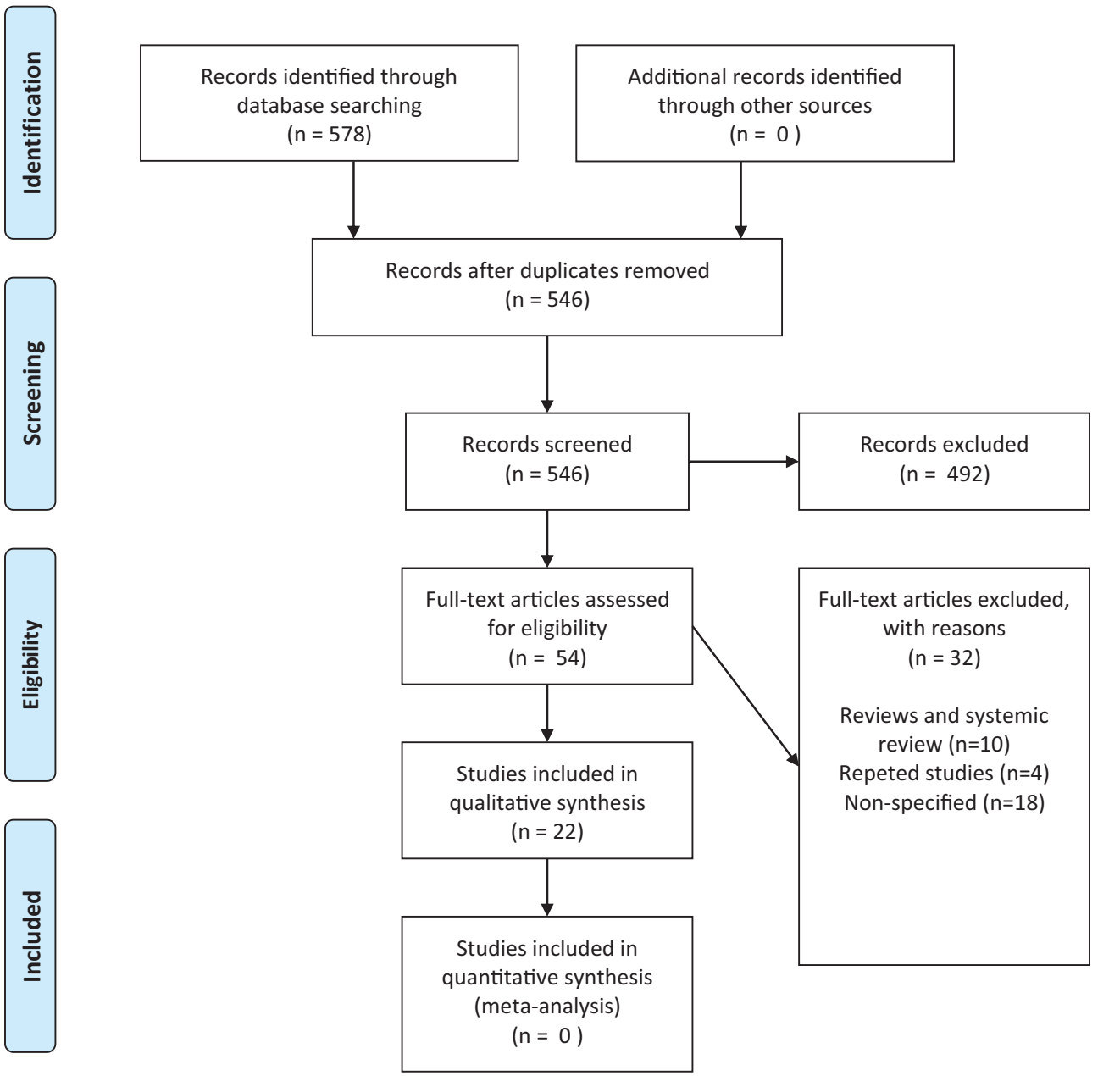

Figure 1. Search strategy used in the methodology.

Table 1

Descriptive statistics of the data founded in the literature included in the study.

					Main results					
Author (year)	Type of study	Number of study subjects	Type of oral surgery	Antibiotic	Dose per day	Medication routes of administration	Use time	Use (prophylactic or infection already established)	Specific recommendation of the author	References
Kirnbauer B (2022)	Clinical trial	50	Third molar surgery	Amoxycillin	2 g	Oral	3 d	Prophylactic	This study demonstrated that prophylactic perioperative antibiotic treatment is not preferable to a placebo medicine	[7]
Tabrizi R (2022)	Clinical trial	450	Implant surgery	Amoxycillin	2 g/500 mg	Oral	Single dose or 5 d	Prophylactic	Prophylactic single-dose should be preferred to longer antibiotic administration protocols, whenever appropriate	[8]
Donmezer CM (2021)	Clinical trial	75	Third molar Implant surgery	Amoxicillin + clavulanic acid	1.75 G/250 mg	Oral	5 d	Prophylactic	Local and systemic antibiotic administration with the use of PRF after mandibular third molar surgery were similar,	[9]
				PRF with amoxicillin/ clavulanic acid	0.5 cc PRF 1000/200 mg	Applied to the socket				
Pietruska M (2021)	Clinical trial	41	Periodontal surgery	Amoxycillin	2 g	Oral	7 d	Prophylactic	Clinical improvement	[10]
Mariscal-Cazalla M (2021)	Clinical trial	92	Third molar surgery	Amoxycillin	2.25 g	Oral	7 d	Prophylactic	The use of antibiotics to avoid postoperative complications shows that their administration both before and after this surgery offers no advantage over their administration only after its performance	[11]
Yanine N (2021)	Clinical trial	154	Third molar surgery	Amoxycillin	2 g	Oral	1 h before surgery	Prophylactic	Amoxicillin before surgery was not effective in significantly reducing the risk of postoperative infectious complications from extraction, when compared to placebo	[12]
Ristow O (2021)	Clinical trial	1420	Orthognathic surgery	Ampicillin + Sulbactam	4 g + 2 g	IV	4 d	Prophylactic	The use of prophylactic antibiotics may reduce the postoperative infection rates	[13]
Momand P (2021)	Clinical trial	474	Implant surgery	Amoxycillin	2 g	Oral	1 h before implant surgery	Prophylactic	The effect of antibiotic prophylaxis in conjunction with dental implant surgery in preventing implant loss is small and may not be clinically relevant	[14]
Cinquini (2020)	Clinical trial	159	Tooth extractions	Amoxicillin + clavulanic acid	2 g	Oral	6 d	Prophylactic	Do not support the routine administration of antibiotics for non-impacted tooth extraction both in healthy and in medically compromised patient	[15]
Payer M (2019)	Clinical trial	236	Periodontal surgery	Amoxycillin	2 g unique dose + 1.5 g	Oral	1–3 d	Prophylactic	Systemic antibiotics do not provide any improvement in healthy patients undergoing oral implant therapy	[16]
Rabi A (2018)	Clinical trial	60	Third molar surgery	Amoxicillin + clavulanic acid or Amoxicillin clavulanic without metronidazole	650 mg	Oral	5 d	Prophylactic	No significant differences	[17]
Sidana S (2017)	Clinical trial	171	Tooth extractions	Amoxycillin	1.5 g	Oral	3 d	Prophylactic	There is no justification for routine antibiotic prophylaxis for dental extractions in healthy patients	[18]
Limeres Posse (2016)	Clinical trial	266	Tooth extractions	Amoxicillin/clavulanate	1000/200 mg	IV	1–2 h before surgery	Prophylactic	Amoxicillin/clavulanate is highly effective in reducing bacteremia following dental extractions	[19]
Gbotolorun OM (2016)	Clinical trial	171	Tooth extractions	Amoxycillin + metronidazole	1.5 g + 1.2 g	Oral	5 d	Prophylactic	Antibiotics after routine intra-alveolar dental extraction in healthy patients may not play any significant role in preventing wound healing complications	[20]
Arduino PG (2015)	Clinical trial	490	Implant surgery	Amoxycillin	2 g	Oral	2 h before implant surgery	Prophylactic	No statistically significant differences were observed	[21]
Iciar Arteagoitia (2015)	Clinical trial	118	Third molar surgery	Amoxicillin + clavulanic acid	4000/250 mg	Oral	2 d after surgery 4 d	Prophylactic	Antibiotic therapy has been more effective for pain relief, reduction in edema and enabling mouth opening than placebo, but not for the prevention of postoperative infections.	[22]

(*Continued*)

Table 1

(Continued)

Author (year)	Type of study	Number of study subjects	Type of oral surgery	Main results						References
				Antibiotic	Dose per day	Medication routes of administration	Use time	Use (prophylactic or infection already established)	Specific recommendation of the author	
Hosseini (2015)	Clinical trial	20	Implant surgery	Amoxicillin or clindamycin	2g or 600 mg	Oral	7 d	Apical infection	The use of perioperative antibiotics has little influence on replacing a tooth with apical pathology with an immediate implant in the esthetic zone	[23]
Crincoli V (2014)	Clinical trial	27	Third molar surgery	Amoxicillin + clavulanic acid Sodium cefazolin	2 g 1 g	Oral IM	5 d	Prophylactic	Oral and intramuscular antibiotic therapies almost overlap in preventing postoperative complications in dental surgery	[24]
Wah Ching Tan (2013)	Clinical trial	329	Implant surgery	Amoxycillin	2 g	Oral	For 4 d or after surgery	Prophylactic	The study questions the necessity of applying peri-surgical antibiotic prophylaxis either before, at the time of or after implant installation	[25]
Adde (2012)	Clinical trial	71	Third molar surgery	Amoxicillin or clindamycin	1.5 g or 1.2 g	Oral	8 d	Prophylactic	Antibiotic prophylaxis should not be indicated in all cases of third molar surgery	[26]
Sixou M. (2012)	Clinical trial	250	Oral surgery	Amoxycillin	3 g	Oral	1 h before implant surgery	Prophylactic	Amoxicillin prophylaxis seems to be effective in preventing postoperative infection in complex oral surgery	[27]

PRF = platelet-rich fibrin.

"AND" and "OR" were used. The search was performed continuously and independently with these terms.

2.3.2. Analysis of results. For the selection of the studies, a first filter was carried out by title and abstract, which mentioned the use of prophylactic antibiotics in oral surgery (performed third molar surgery, implant surgery, periodontal surgery, tooth extractions). All the identified studies were placed in a database to then carry out a second filter by reading the full text. This was done independently by 2 evaluators; in case of discrepancy, a third evaluator participated.

Information was collected, such as type of study, type of oral surgery, type of antibiotic, dose, and route of administration, as well as the author's recommendations on the use of antibiotics as prophylactic therapy.

The data was analyzed descriptively, reporting measures of central tendency and dispersion, as well as frequencies, using the IBM SPSS Statistics for Windows (Version 28.0, Released 2021; IBM Corp., Armonk, NY) program.

2.3.3. Risk of bias. To establish the risk of bias, the JBI Critical Appraisal Checklist for Randomized Controlled Trials were used.[6]

3. Results

In the initial search strategy, 578 studies were identified. The first filtering by title and abstract resulted in 54 potential studies; of these, 21 studies were selected[7–27] after carrying out the extensive review (the second filter), which are shown in Figure 1.

The sample size obtained in each of the included studies was diverse, being the smallest of 20 subjects[23] and the biggest of 1420 subjects.[13] The most common type of oral surgery was the removal of third molars in 38% of the selected studies (n = 8),[7,9,11,12,17,22,24,26] followed by implant placement in 23.8% (n = 5).[8,14,21,23,25] All the other studies[10,13,15,16,18–20,27] identified procedures such as periodontal surgery, unspecified oral surgery, and osteotomies (Table 1).

The antibiotics most prescribed as prophylactic therapy were beta-lactams, which were indicated in 100% of the studies.[7–27] Of these, the penicillin group predominated with amoxicillin being the most indicated drug in 52.3% of the studies (n = 11).[7,8,10–12,14,16,18,21,25,27] Amoxicillin in conjunction with clavulanic acid had the next highest uptake in 33.3% of the studies (n = 7).[9,15,17,19,22,24,26] A lower percentage of studies were those that indicated the use of antibiotics in combination with metronidazole, sulbactam, cefazolin, and unspecified penicillins. The prevailing doses per day were 2 g,[7,8,10–12,14,15,21,23,24] for a period of 5 days,[8,9,17,20,24] followed by for 1 hour before the procedure.[12,14,19,27] Finally, the main route of administration of the antibiotics was oral in 85.7% of the cases (n = 18).

Of the 21 studies included in this review,[7–27] 5 support the use of antimicrobial therapy as an effective prophylactic treatment for oral surgery procedures,[8,10,13,20,27] and 16 studies mention that there is insufficient evidence to support the use of antibiotics as prophylactic therapy in patients who will undergo some type of oral surgery.[7,9,11–18,20–27]

3.1. Risk of bias

The risk of bias analysis was done with the JBI Checklist for randomized controlled trials tool, in which 13 methodological aspects related to the randomization of study subjects were evaluated. The initial characteristics of the groups, the administration of double-blind treatments, the follow-up that was given to the study groups, and the type of statistical analysis according to the objectives of the study were evaluated too among other aspects. Thus, we identified that 100% of the studies had a low risk of bias (Table 2).

Table 2

JBI critical appraisal checklist for randomized controlled trials studies.

	Risk of bias													
	Clinical trial													
Author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Risk of bias
Kirnbauer, B (2022)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Tabrizi R (2022)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Donmezer CM (2021)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Pietruska M (2021)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Mariscal-Cazalla M (2021)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Yanine N (2021)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Ristow O (2021)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Momand P (2021)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Cinquini (2020)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Payer M (2019)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Tripathi S (2019)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
A Rabi (2018)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Sidana S (2017)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Limeres Posse (2016)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Gbotolorun O.M. (2016)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Arduino PG (2015)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Iciar Arteagoitia (2015)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Hosseini (2015)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Crincoli V. (2014)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Wah Ching Tan (2013)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Adde (2012)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Sixou M. (2012)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low

4. Discussion

The use of antibiotics has grown in recent years. The general use per capita has increased by 26.2% in drugs used as first- or second-line treatment and by 90.9% in the consumption of drugs used specifically in cases of bacterial resistance.[28] In dentistry, it is difficult to determine the amount of antibiotics prescribed; however, it has been estimated that from 1996 to 2013 the prescription of antibacterial agents has increased by 62.2%.[29]

As already mentioned, the use of prophylactic therapy has been related to invasive procedures in order to prevent the development of bacteremia, because after the treatment the bacteria that enter the bloodstream are eliminated thanks to the cells of the immune system.[30] Therefore, the use of prophylactic antimicrobial therapy is emphasized in subjects with a high risk of bacterial endocarditis; immunocompromised patients; patients with ASA 3,4,5; patients undergoing radiotherapy; or patients undergoing prolonged procedures or with infection in the surgical area.[1,31]

Although the indications for prophylactic antimicrobial therapies are very clear and specific, the use of antibiotics continues to be present among dental professionals towards patients with no evidence of systemic or immunocompromised diseases or without clinical signs of infection, according to the most recent evidence found in the scientific reports. In a study by Kirnbauer et al,[7] demonstrated that the use of prophylactic antibiotics in third molar removal procedures without evidence of inflammation did not show clinical or statistical differences in the prevention of infections secondary to the surgical procedure compared to the control group when giving amoxicillin treatment 2 g a day for 3 days. In fact, Gbotolorun et al[20] mentioned in their study that, the use of prophylactic antibiotics can increase the risk of developing post-extraction complications by 16%.

In surgical procedures related to the placement of implants, antibiotic administration has been recommended 1 hour before the procedure, which can be extended for several days after the procedure. In a recent study by Momand et al[14] a multicenter clinical trial was carried out in which the effectiveness of amoxicillin 2 g 1 hour prior to the surgical procedure was evaluated, reporting a 0.46% reduction in the risk of developing postoperative complications. They concluded that the use of antimicrobial therapy is not justified due to its very low benefit. In contrast, in an interesting study carried out by Kim et al,[32] they mention that the best prophylactic therapy is based on a single dose of antibiotics because this type of therapy helps to avoid the mechanisms of bacterial resistance. In contrast, long-term treatments give bacteria the opportunity to adapt and resist the therapy through the activation of different molecular pathways. And finally, Tabrizi et al[8] reports that the most widely used antibiotics are either amoxicillin or clindamycin if patients are allergic to penicillin.

The treatment modalities of a single, second or third dose, have gained popularity; however, factors related to the infection site must be taken into consideration. For example, if the infectious process does not have any clinical signs of an abscess, anatomical permeability exists for the antibiotic, and pathogens are found in an extracellular environment. The antibiotic, which has a rapid mechanism of action, can be effective against microorganisms that are in a cell cycle phase other than mitosis, and the drug must maintain its active function in the environment of the infectious process, such as changes in pH, anaerobiosis, and more. Another essential factor to consider is that the free fraction of the drug in plasma must be over 50% during the treatment time.[33] It must be considered that one of the objectives of short-term antimicrobial therapy prior to invasive surgical treatment is to have a free fraction of the antibiotic circulating in order to decrease the bacterial load originated from the surgical procedure.

The oral cavity is the area with the greatest abundance of microorganisms throughout the body; however, it is also the area where there is a better access for the use of antimicrobial elements that allow the use of alternatives such as antimicrobial mouth rinses such as chlorhexidine which is an antiseptic that has shown to be effective in controlling the local bacterial load, preventing the development of the infection process; on the other hand, a recent proposal is the use of antimicrobial peptides, which can modulate their action against microorganisms depending on their structure, hydrophobicity, or amphiphilic characteristics. Their mechanism of

action can be divided into those related to the direct effect on the structure of the microorganism or those related to the immune system. In the mechanism related to bacterial structure, the peptides have the ability to make a bacterial cell membrane porous by disruption of the cell membrane, or through permeabilization, generating alterations at different levels of the cell structure. Also, the peptides can stimulate the defense system through the recruitment of pro- and anti-inflammatory cytokines Clinically, this alternative is attainable. Currently, the main challenges are commercial development and the analysis of the side effects in host cells that could develop over a long period of time.[30,34–36]

5. Conclusion

As it has been demonstrated, the evidence that is currently available about the use of antibiotics in different types of oral surgery, like tooth extraction dental extractions, periodontal surgery, among other procedures, are not substantiated, unless its use is justified due to a particular health condition of the patient. The unjustified excessive use of antibiotics by dentists is generating serious problems related to the resistance of microorganisms. This makes it more difficult to establish treatments against conventional infection processes because they do not respond favorably to the usual medications.

Undoubtedly, the biggest challenge is to convince educational and governmental institutions to develop academic updating strategies that will provide updated information on the correct use of antibiotics, which should be aimed at dentists with active clinical practices and students undergoing training in dentistry, as well as emphasizing which surgical procedures have the highest risk of developing bacteremia.

Author contributions

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