REVIEW

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SYSTEMIC ANTIBIOTIC THERAPY FOR DENTAL TREATMENTS: SIDE EFFECTS VERSUS ANTIBIOTIC RESISTANCE

S. Heta[1], D. Mingomataj[2], V. Ostreni[1], I. Robo[3], D. Zazaj[3], A. Shqerra[3], L. Cupa[2]

[1]University of Medicine, Faculty of Medicine, Tiranë, Albania
[2]Albanian University, Faculty of Medical Sciences, Tiranë, Albania
[3]University of Medicine, Faculty of Dental Medicine, Tiranë, Albania

Abstract. *Treatment of periodontal pathologies has a local but also systemic nature in cases where it is indicated after complete scaling performed in several stages. Seen from this perspective, it is very important to note that the administration of systemic antibiotics should be carried out only after the final stage of local periodontal scaling, taking into account that any remnants of periodontal calculus on the surface of the teeth where periodontal therapy is being performed must be removed. About 52% of the selected articles in this review emphasize that antibiotics are given for prophylactic treatment before dental interventions; in 20% of cases the systemic administration of antibiotics is indicated for periodontal pathologies, while in 12% of cases it is indicated for endodontic pathologies. If we review these values again so that both antibiotics and alternative treatment are applied, it is noted that systemic treatment is performed in 36% of cases, while local treatment with both antibiotics and alternative treatment is performed in 20% of cases. The systemic dosage of antibiotics for dental prophylaxis is still the most common, reaching a value of 28%. Systemic antibiotics are most frequently indicated for administration in prophylactic dental treatment and periodontal pathologies – much more frequently than in cases of endodontic pathologies. For periodontal pathologies, scientific research is oriented towards alternative treatment methods instead of systemic administration of antibiotics effective against the specific pathogen of the pathologies. There are no articles that juxtapose two alternative treatment methods with one another, since all articles emphasize the well-known facts that there is bacterial resistance and there are side effects of antibiotics and the alternative treatment method is compared with the basic methods of non-surgical periodontal treatment.*

Key words: *systemic antibiotics, prophylactic dental treatment, periodontal pathology, bacterial resistance, side effects*

Corresponding author: *Ilma Robo, Faculty of Dental Medicine, University of Medicine, Tiranë, Albania, email: ilmarobo@yahoo.com*

ORCID: *0000-0002-8328-375X*

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INTRODUCTION

Even the smallest surface covered with periodontal calculus, or even the minimal presence of periodontal calculus on the surface of an untreated tooth can serve as an adhesion zone for the "spattered" bacterial flora of the patient's saliva [1, 2]. This can lead to a vicious circle, which can be avoided if the logic of the indications for administering systemic antibiotics is understood [3]. If periodontal calculus is present and bacterial plaque adheres to its surface, the bacteria that survive from the intermediate cooperation of different components of bacterial plaque on the surface of improperly cleaned teeth create antibiotic resistance that makes the treatment of existing periodontal pathology even more difficult [4-7]. There are several antibiotics indicated for patients suffering from periodontal pathologies. They can also be called "periodontal" antibiotics, to distinguish them from antibiotics indicated for other dental pathologies or specialties [3, 8-10]. The characteristic phases of activation and inactivation of some specific pathologies allow the patient to coexist with periodontal pathologies throughout their life, without the need to destroy the periodontal bacterial pathogen causing the said pathology [11-13].

This demonstrates that periodontal pathologies are not curable. In other words, it is not possible to fully remove the pathogenic flora and protect the patient from another reinfection, which can happen through the transmission of salivary quantities, either from habits or from the habits of the patient's daily life [5, 14].

Even in cases where systemic therapy with antibiotics is indicated, the complete destruction of the pathogen of the pathology is not ensured [16]. A good example of this is the last stage of periodontal curettage, when the dentist is sure of the complete moistening of the periodontal plaque. In cases where the patient suffers from periodontal pathologies caused by infection with Actinomyces actinomycetemcomitans, the antibiotic, which fights this bacterium, is only bacteriostatic [17-20]. Seen from this perspective, the administration of a systemic antibiotic (in this case tetracycline) reduces the microbial load of the salivary flora of the patient, but there is no guarantee that the patient will no longer suffer from chronic periodontal pathology [3, 21]. Do these antibiotics have side effects that should be seen and evaluated in terms of clinical outcome versus clinical benefit in curing periodontal pathology and the recently increasing antibiotic resistance?

Antibiotics are among the class of chemotherapeutics, with the only difference being that they are products of biological elements, such as fungi or bacteria. Therefore, it is considered that chemotherapeutics are products of fermentation, while antibiotics are products of chemical synthesis [12, 22]. This still stands today despite the fact that although fermentation is used in the production of some antibiotics, the compound is then produced by chemical synthesis, resulting in semi-synthetic antibiotics. Most antibiotics are produced by biosynthesis, and then the final product is modified chemically [23-25].

The classification of antibiotics as broad-spectrum or narrow-spectrum is based precisely on the fact that they act on different types of bacteria. In the case of chemotherapeutics, the cause of the disease must be precisely identified in order to find a chemotherapeutic that can effectively destroy the pathogenic bacteria [26]. In that regard, the notion of resistance appears. There are types of bacteria that were originally sensitive to an antibiotic, but have become resistant to it due to the transformation they have undergone. In case of resistance, the technique of seeding bacteria and placing them under the sensitivity test against several antibiotics simultaneously also helps [27-29]. There is also the notion of multi- or pluri-resistance, since a type of bacteria can be resistant to several antibiotics simultaneously [30-31]. A list of some of the antibiotics and the resistance to them demonstrated by several different types of bacteria is given below [12, 25].

MATERIALS AND METHODS

This review aims to analyze the side effects of antibiotics, which are used systemically for the treatment of oral pathologies at a time when reports on bacterial resistance have increased in published literature.

The review of literature was carried out on the PubMed page, with the primary goal of finding the initial articles that included both side effects and bacterial resistance in cases of systemic antibiotic dosing. The second review was performed with the more specific goal of finding articles in PubMed on both periodontal diseases and the indications for the administration of systemic antibiotics according to dosages and the predefined periodontal protocol, based on clinical indications of the same periodontal pathologies.

If initially there were about 371,193 articles about antibiotics, the combination with the topics of side effects and bacterial resistance reduced this number to almost 50 times less, to 8,652 articles. The main aim of the study is to assess professional attitudes towards systemic antibiotic dosing for endo-periodontal pathologies.

Other specific aims of the study are:

- To clarify the relationship between the reason or indication for the administration of systemic antibi-

otics for endo-periodontal treatments and, specifically, for the endo-periodontal diagnosis.

- To establish data on the reason for taking systemic antibiotics and the dental treatment, for which systemic antibiotics were indicated.
- To establish data on alternative methods of treating periodontal pathologies versus systemic administration of antibiotics for the treatment of periodontal pathologies.
- To establish data on systemic administration of antibiotics versus endodontic pathologies.
- To establish data discussing the administration of systemic antibiotics for prophylactic reasons, protection against the appearance or aggravation of existing systemic pathologies before dental interventions.
- To establish data from selected articles on the application of new technologies as an alternative method to antibiotics.
- To establish data from articles on indications of systemic pathologies for systemic administration of antibiotics before dental interventions.
- To establish data on side effects of selected antibiotics for the treatment of endo-periodontal pathologies.

Some of the points that attracted attention on this topic were: the way of evaluating the effects of antibiotics, the way of categorizing side effects and the perspective of side effects against the already known presence of bacterial resistance.

The chosen keywords had to do with the more specific combination of side effects with periodontal and endodontic dental treatments.

This combination from the initial search highlighted about 197 articles, which were reduced about 5 times, to 41 articles, when the last year of publication was also included in the combination of keywords. The articles found in this way were also filtered for 1 year of publication, precisely with a predetermined time interval from 1 January 2024 to 1 January 2025, resulting in a total of 30 articles included for further analysis in this study.

The filters or selected criteria were: abstract and full text, English language, and publications within a time interval of 1 year. Out of 41 articles selected for the purpose of our study, about 30 articles were taken for further analysis based on the inclusion and exclusion criteria during the selection of the study sample.

11 of the studies selected in the first phase were excluded because their purposes did not match the purpose of our study. After analyzing the abstracts and articles collected up to this stage, inclusion and exclusion criteria were selected for the analysis.

Inclusion criteria

The inclusion criteria in the analysis were the articles that directly assessed the impact of systemic antibiotics for the treatment of both periodontal and endodontic pathologies, regardless of the specific diagnosis and classification of the pathologies according to clinical signs, for the occurrence of side effects or the aggravation of bacterial resistance. The articles that evaluated the direct effect of systemic antibiotic therapy for the treatment of dental pathologies on the occurrence or aggravation of side effects or bacterial resistance were mainly included.

Exclusion criteria

The exclusion criteria were:

- Studies that aimed to analyze specific medical pathologies that have an impact on the occurrence of oral pathologies, for which the systemic administration of antibiotics is indicated.
- Studies that analyze the protocol treatment of systemic pathologies, for which antibiotics are taken with an impact on the existing oral flora.

After analyzing the selected articles, it was concluded that: out of a total of 30 articles, through the second phase of selecting articles, which are of interest but not in accordance with the purpose of our study, 5 articles [4, 10, 11, 19, 28] were selected based on the following:

- Systemic pathologies and antibiotic treatment of specific flora of these pathologies that are actually outside the scope of our study are analyzed – 2 articles [4, 10]
- Treatment phases of systemic pathologies are analyzed – 3 articles [11, 19, 28]

Twenty-five articles left to be analyzed further, which will initially be classified depending on the method of data analysis in the review or in vitro categorization, and then depending on the publication years. This is the group of articles selected by the secondary combination of keywords.

No duplicate articles were found.

Research on this topic took 1 year and the combination of keywords resulted in 25 selected articles.

Figure 1 shows the methodology flow chart applied in this study.

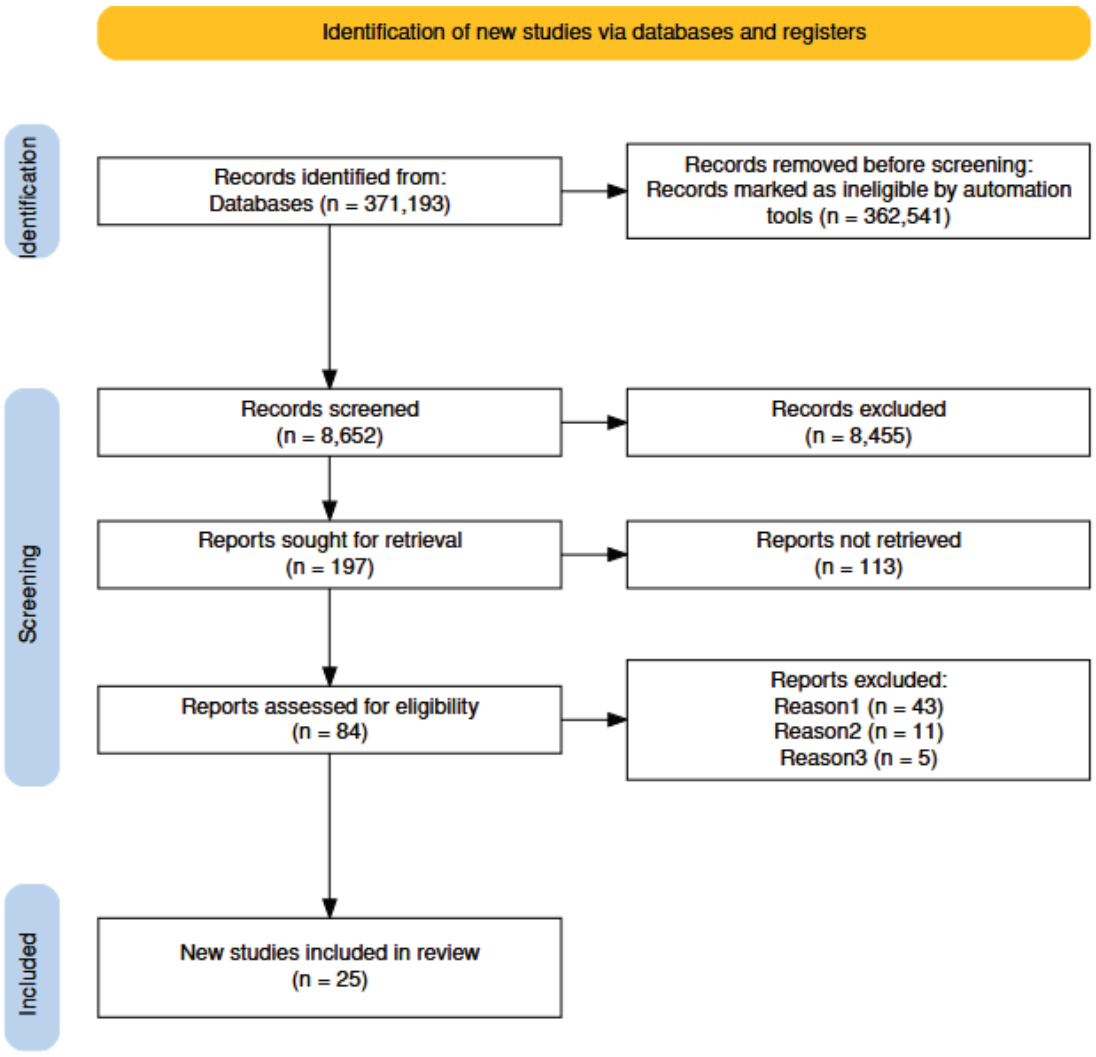

Fig. 1. The methodology flow chart is presented according to the PRISMA Diagram-Flow

RESULTS

After analyzing the information in the selected articles, the following tables and graphs with numerical values about the study have been created. After processing the data collected from the selected articles in the manner explained above, the following tables showing quantitatively and qualitatively the conclusions classified according to specific sub-divisions of the selected articles, were composed.

Figures 2 and 3 show the distribution of articles based on the reason for systemic antibiotic administration and the pathology or dental treatment, for which systemic antibiotics are indicated.

The data collected on the method of administration or dosage of antibiotics indicated for prophylactic dental treatment, classified as local or systemic, are graphically presented in Figures 4 and 5.

Table 1 shows the data collected from selected articles on the side effects of antibiotics indicated for oral pathologies.

Figure 6 shows the data of Table 1 – the proportions of the side effects of applying antibiotics for the treatment of endo-periodontal pathologies in published literature.

Table No. 2 shows data on the dosage of the most recommended antibiotics for periodontal and endodontic pathologies, based on the specifics of studies found in the literature.

DISCUSSION

From the data and its graphical presentations in Figures 2 and 3, it is noted that scientific research is more oriented towards new technologies and new alternative treatment methods for endo-periodontal pathologies instead of treatment with systemic doses of antibiotics. This fact is expressed in 40% of the articles included in the category of new treatment technology/drug [3, 5, 9, 24, 25].

On the other hand, the data in Figure 2 shows that in about 52% of the articles it is emphasized that an-

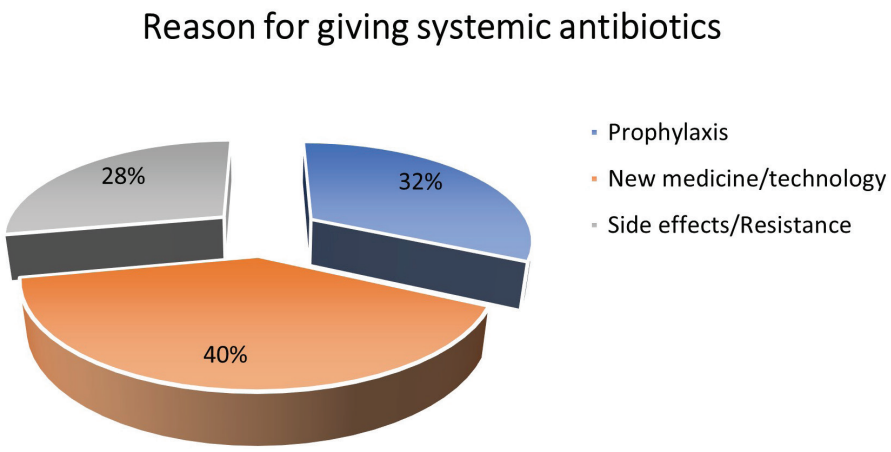

Fig. 2. Distribution of articles based on the reason or issue requiring the systemic administration of antibiotics for dental treatments

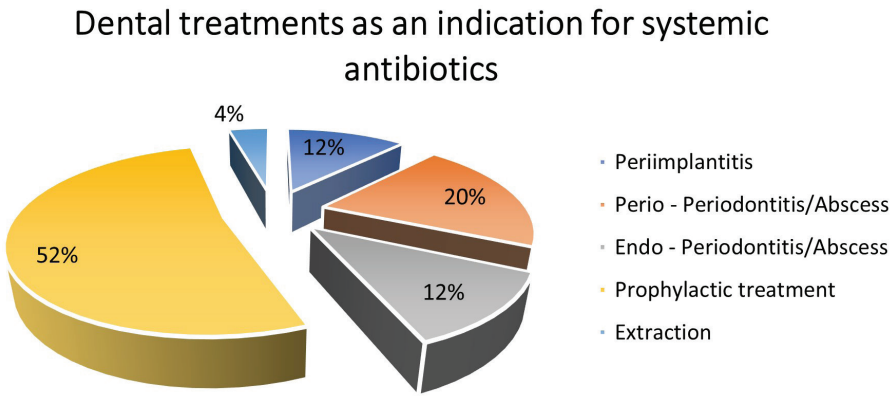

Fig. 3. Graphical representation of dental treatments, for which systemic antibiotic administration is indicated, according to the proportion of articles, which had them listed, as a guide in determining the purpose and methodology of the published articles

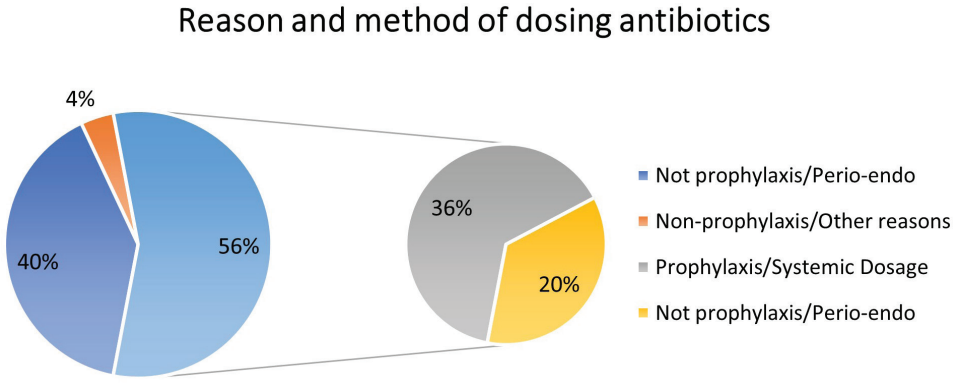

Fig. 4. Data on the proportions of articles analyzing the method of administration or dosage of antibiotics indicated for prophylactic dental treatment, classified as local or systemic

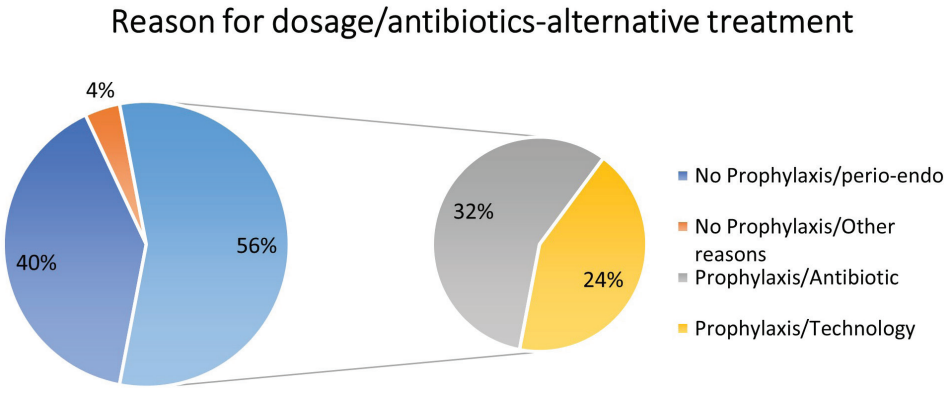

Fig. 5. Graphical representation of the percentage distribution of articles based on the processed data regarding the mode of administration of specific antibiotics or alternative local interventions for prophylactic reasons

Table 1. Data on the side effects of selected antibiotics for the treatment of endo-periodontal pathologies

Side effects		Article	Subjects		Conclusion	Total
Nausea	Riben Grundstrom C et al. (2024) [2].	76 patients – 104 implants	Implant stability and clinical success were higher in the group of patients treated with amoxicillin and metronidazole [2]	4 articles (16%)		
	Review Narwal E et al. (2024) [12].		Antimicrobial agents of botanical origin are effective, cost-effective, and safe [12]			
	Khan H et al. (2024) [20].	364 healthy children	Gastrointestinal disorders are most commonly encountered with penicillin, followed by macrolides and then cephalosporins [20]			
	Pedrolongo DA et al. (2024) [29].	400 patients	Self-medication with non-steroidal anti-inflammatory drugs in 89.5% of the Brazilian population affects the occurrence of side effects [29]			
Diarrhea	Cope AI et al. (2024) [6].	134 patients	Preoperative clindamycin for symptomatic apical periodontitis resulted in no significant difference in patient-reported pain and swelling [6]	2 articles (8%)		
	Review Narwal E et al. (2024) [12].		Herbals must be in a suitable combination to suppress pathogenic microbes in order to adapt them to the oral cavity [12].			
Teeth staining	Review Narwal E et al. (2024) [12].		Photochemical plant extracts suppress the growth of oral bacteria by preventing their attachment to tooth surfaces and inhibiting the formation of biofilm [12]	1 article (4%)		
Allergies	Khan H et al. (2024) [20].	364 healthy children	Most commonly seen with penicillin class [20]	2 articles (8%)		
	Review Lockhart PB et al. (2024) [30].		About 10% of patients in the USA self-report penicillin allergy, which can be eliminated using its classification as low-, medium- or high-risk [30]			
Bacterial resistance	Khan H et al. (2024) [20].	364 healthy children	The proportion of bacterial resistance to antibiotics in children fluctuates depending on the age and sex [20]	3 articles (12%)		
	362 Questionnaires Carbone M et al. (2024) [26].		Overuse of antibiotics for prophylaxis against systemic pathologies contributes to bacterial resistance. However, the tendency to write prescriptions does not differ depending on the sex of the professional [26]			
	Pedrolongo DA et al. (2024) [29].	400 patients	Self-medication with antibiotics among the Brazilian population reached 32.2% [29]			

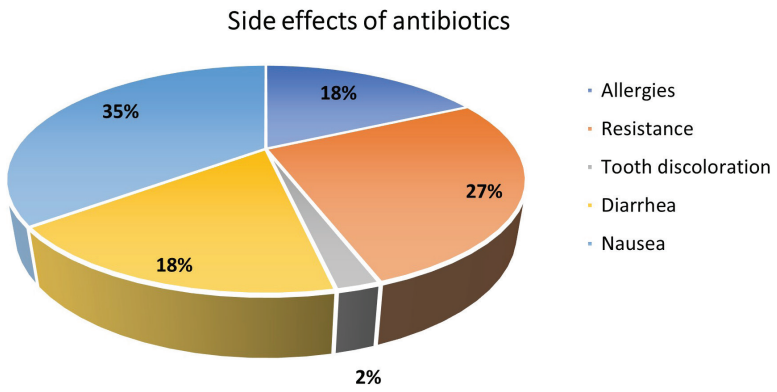

Fig. 6. Data on the side effects of antibiotics used for the treatment of endo-periodontal pathologies

Table 2. Data on the dosage and the most recommended antibiotics for endo-periodontal pathologies based on data published in the literature

Specific antibiotic in absence of allergy	Supporting studies
Amoxicillin	Amoxicillin 500 mg was the first antibiotic of choice for 43.7% of non-allergic patients – Abraham S et al. (2020) [31]. 13.5% of dental students support prescribing amoxicillin – Salvadori M et al. (2019) [32]. Amoxicillin is the primary choice for dentists in Colombia – Dias NM et al. (2022) [33]. Amoxicillin was the primary choice for 97.1% of endodontic specialists in Spain – Lopez-Marrufo-Medina A et al. (2022) [34] It was the primary choice for 40% of post-graduate dentists specializing in endodontics in Spain – Alonso-Ezpeleta O et al. (2018) [35]. In 47% of cases it was the first choice in the absence of allergies for dental students – Martin-Jimenez M et al. (2018) [36]
Amoxicillin is mainly indicated alone at a dose of 500 mg 3x1, or combined with tetracycline or metronidazole at a dose of 250 mg 3x1 each!	
Clarithromycin	0.3% of dental students in Italy support it as their first choice of antibiotic – Salvadori M et al. (2019) [32].
Augmentin	With the increasing practitioner's age and experience, Augmentin is preferred over Amoxicillin – Mende A et al. (2020) [37]. 83.6% of clinicians have it as their primary choice with the diagnosis of acute apical abscess – Yaqoob H et al. (2024) [38]. 85.2% of dental students in Italy support antibiotics as the first choice – Salvadori M et al. (2019) [32]. 90% of clinicians had Augmentin as their first choice in Turkey – Deniz-Sungur D et al. (2020) [39]. It was the primary choice in the absence of allergy for 60% of endodontic specialists in Spain – Alonso-Ezpeleta O et al. (2018) [35]. In 53% of cases it was the first choice for dentistry students – Martin-Jimenez M et al. (2018) [36].

tibiotics are given for prophylactic treatment before dental interventions; in 20% of cases the systemic administration of antibiotics is indicated for periodontal pathologies [3, 5, 9, 12, 24], while in 12% of cases the administration of antibiotics is indicated in cases of endodontic pathologies [6, 14, 25].

From the data in Figure 4 it is noted that the five articles presented in this table specifically indicate an alternative method of replacing the administration of systemic antibiotics with other effective ways of treating periodontal pathologies. What is also noted is the fact that alternative treatment methods are sought since antibiotics have side effects and can cause bacterial resistance. Therefore, it has now been accepted that if there is no absolute indication for the administration of systemic antibiotics, then it should not be performed. It is considered that every article that starts to present a new method also contains an advertisement for this product. Out of these 5 articles only 2 are of the in vivo application type with concrete results in patients [9, 24]. And again these in vivo studies were performed on small patient samples – 50 patients [9] and 36 patients, respectively [24]..

All new treatment methods are studied in regard to periodontal curettage and tooth surface polishing, indicating the administration of systemic antibiotics after these two procedures, but there are no articles comparing the two new methods with one another. Therefore, it is the clinicians' decision whether to apply the methods or not. A grouping within the pool of articles on treatment alternatives presented also the stage of the pathology during which they act [3, 5, 12].

New alternative treatment methods for periodontal pathologies aim to prevent the formation of biofilm in the initial stages by acting on specific pathogenic bacteria – which re-emphasizes that biofilm is the main cause of periodontal pathologies. Based on the data in Figure 6, it is noted that for endodontic pathology, the best intervention with antibacterial agents is at the stage of biofilm formation. In this stage root canal treatment is more effective than systemic antibiotics [6, 14, 25]. Based on the data in Figure 5 and the graphic presentation, the trends in scientific research regarding the dosage of antibiotics for prophylactic reasons and the trends in the search for alternative treatments are clearly distinguished. According to these data, prophylactic dental treatment using the conventional method stands out, comprising 32% of scientific research in this field [7, 16, 18, 20, 26, 29, 30], while the juxtaposition of conventional with alternative or new alternative treatments is 24% [15, 17, 21, 22, 27].

If these values are reviewed again with focus on the way, in which both antibiotics and alternative treatments are applied, it is noted that systemic treatment is preferred in 36% of cases [7, 16, 17, 18, 20, 21, 26, 29, 30], while local treatment with both antibiotics and alternative treatments is preferred in 20% of cases [15, 18, 22, 23, 27]. The systemic dosage of antibiotics for dental prophylaxis has the highest proportion (28%) [7, 16, 18, 20, 26, 29, 30]. The local applica-

tion of antibiotics remains at a lower proportion – 4%, based on the reference source, Ozcan M et al. (2024) [18]. This source is mentioned twice in figure 5, as it refers to both local and systemic application of antibiotics.

A significant decrease in the local application of antibiotics is observed, replacing them locally with alternative treatments where the application with nanoparticles prevails. An interesting datum of Table 1 was that, according to a source in the selected literature [20], bacterial resistance to the type of antibiotic differed significantly depending on gender and age. According to Khan H et al. [20], resistance to penicillin was 18% among children aged 7-9 years, while the resistance to macrolides was 14%. Among the children aged 10-13 years these values increased and decreased to 23% and 13%, respectively [20]. According to this source, women were more affected by resistance to cephalosporins and penicillins and less affected by resistance to macrolides. This type of study was also geographical, since it referred to the area of Pakistan. Based on the data in Table 1 and the graphic presentation in Figure 6, it is noted that nausea is the most common side effect (35%), followed by allergy and diarrhea at 18% each. The share of tooth discoloration is 2%, while the share of bacterial resistance – 27%.

The data in Table 2 also show the trends of worldwide specialists regarding the indications and selection of the first antibiotic in the absence of allergy on the part of the patient. It has been agreed that if an antibiotic must be given, it should be broad-spectrum, with the primary one being amoxicillin, which can be applied alone in doses of 500 mg three times a day or in doses of 250 mg three times a day, accompanied either by tetracycline or by metronidazole, also in doses of 250 mg three times a day.

CONCLUSIONS

The most frequent indications for administration of systemic antibiotics are in cases of prophylactic dental treatment and periodontal pathologies, much more than in cases of endodontic pathologies. For periodontal pathologies, scientific research is oriented towards alternative treatment methods instead of systemic administration of antibiotics effective against the specific pathogen of the pathologies. There are no articles that juxtapose two alternative treatment methods with one another, since all sources emphasize the well-known fact that there is bacterial resistance and there are side effects of antibiotics, therefore, the alternative treatment method is compared with the basic methods of non-surgical periodontal treatment. For the treatment of endodontic pathologies, the aim is to achieve antibacterial effect in the stages of biofilm creation and then mechano-chemical endodontic treatment will be performed in case the primary pathologies are not successfully treated. Antibiotics are still indicated in cases of dental prophylaxis more than in all other treatments. For local treatment of dental pathologies, alternative treatments are preferred over the administration of local antibiotics. As for side effects, the most common ones are gastrointestinal problems, followed by allergies. Bacterial resistance reaches 27% in cases of application of antibiotics for the treatment of endo-periodontal pathologies.

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Authors' contributions: *IR, LC, ASh and SH collected the scientific data and wrote the manuscript. SH, DM and VO revised and edited the manuscript. IR and DZ conducted literature research. All authors read and approved the final manuscript.*

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