UNIVERSIDADE FERNANDO PESSOA

EFFECTIVENESS OF ANTIBIOTICS IN TREATMENT OF DENTAL INFECTIONS : A SYSTEMATIC REVIEW

[Eficácia dos antibióticos no tratamento de infeções dentárias: Uma revisão sistemática]

Dissertação de Mestrado Integrado em Medicina Dentaria

Sabien van Straaten

Orientador:

Ricardo Jorge Afonso Costa Magalhães

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To my wonderful paternal grandmother, a special and incredibly courageous woman.
Thank you for inspiring me.

Acknowledgments

I would like to express my deepest gratitude to everyone who has supported me throughout this journey.

First, I would like to thank my coordinator, Professor Ricardo Magalhães, for guiding me throughout this process.

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To everyone who has been part of this journey, thank you. This achievement is as much yours as it is mine.

Resumo

Os antibióticos têm sido essenciais no tratamento de infeções bacterianas desde a descoberta da penicilina em 1928. Na medicina dentária, os antibióticos são prescritos para fins profiláticos ou terapêuticos e representam cerca de 10% das prescrições globais de antibióticos. A utilização de antibióticos em medicina dentária, particularmente para o tratamento de infeções dentárias, tem sido generalizada. No entanto, as preocupações com o uso excessivo e a resistência aos antibióticos exigem uma avaliação crítica da sua eficácia em comparação com outras opções terapêuticas. O objetivo desta revisão sistemática é avaliar a eficácia dos antibióticos no tratamento de infeções dentárias em comparação com outras opções terapêuticas. Além disso, o estudo visa obter informações sobre as motivações subjacentes às prescrições de antibióticos na área da medicina dentária, com o objetivo de promover a utilização adequada destes medicamentos e melhorar a educação dos pacientes sobre a importância de aderir aos regimes prescritos. Foi efetuada uma pesquisa exaustiva em bases de dados, incluindo PubMed, Cochrane Library, B-On e Scielo, para estudos publicados entre 2013 e 2024. Os critérios de inclusão foram baseados na estrutura PICO: População - pacientes com infeções dentárias; Intervenção - terapia antibiótica sistémica; Comparação - outras opções terapêuticas; Resultado - melhoria das práticas de prescrição de antibióticos. A ferramenta Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) foi utilizada para avaliar o risco de viés nos estudos incluídos. Dos 384 registos identificados, foram incluídos 12 estudos na revisão sistemática. Estes estudos são geograficamente diversos, incluindo populações da Europa, do Médio Oriente, do Sul da Ásia, da América do Sul e dos Estados Unidos. Os resultados destacam as indicações limitadas para a utilização de antibióticos em medicina dentária, sendo os antibióticos sistémicos frequentemente prescritos de forma inadequada para condições que não os requerem, como a pulpite e o abcesso crónico. Em vez disso, a atenção deve centrar-se em métodos não medicamentosos e na educação do paciente para prevenir infeções e reduzir a dependência de antibióticos. A revisão salienta a necessidade de um cumprimento mais rigoroso das diretrizes para a utilização de antibióticos nas infeções dentárias, a fim de combater a resistência aos antibióticos. É da maior importância fornecer aos profissionais de medicina dentária e aos doentes a educação necessária para garantir a utilização adequada de antibióticos. A investigação futura deve centrar-se no desenvolvimento e implementação de estratégias para melhorar a gestão de antibióticos na prática dentária.

Palavras-chave: medicina dentária; antibióticos; terapia antimicrobiana; infeção dentária; intervenção operatória; drenagem

Abstract

Antibiotics have been integral in managing bacterial infections since the discovery of penicillin in 1928. In dentistry, antibiotics are prescribed for either prophylactic or therapeutic purposes and this represent around 10% of global antibiotic prescriptions.The use of antibiotics in dentistry, particularly for the treatment of dental infections, has been widespread. However, concerns about overuse and antibiotic resistance necessitate a critical evaluation of their effectiveness in comparison to other therapeutic options. The objective of this systematic review is to evaluate the effectiveness of antibiotics in the treatment of dental infections in comparison to other therapeutic options. Furthermore, the study aims to gain insight into the motivations behind antibiotic prescriptions in the field of dentistry, with the objective of promoting the appropriate use of these medications and enhancing patient education on the importance of adhering to the prescribed regimens. A comprehensive search was conducted in databases including PubMed, Cochrane Library, B-On, and Scielo for studies published between 2013 and 2024. The inclusion criteria were based on the PICO framework: Population - patients with dental infections; Intervention - systemic antibiotic therapy; Comparison - other therapeutic options; Outcome - improved antibiotic prescription practices. The Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool was used to assess the risk of bias in the included studies. Out of 384 identified records, 12 studies were included in the systematic review. These studies were geographically diverse, including research from Europe, the Middle East, South Asia, South America, and the United States. The findings highlight the limited indications for antibiotic use in dentistry, with systemic antibiotics often prescribed inappropriately for conditions that do not require them, such as pulpitis and chronic abscess. Instead, the focus should be on non-medicated methods and patient education to prevent infections and reduce reliance on antibiotics. The review highlights the necessity for more rigorous compliance with guidelines for antibiotic utilisation in dental infections, to combat antibiotic resistance. It is of the utmost importance to provide both dental professionals and patients with the necessary education to ensure the appropriate use of antibiotics. Future research should focus on developing and implementing strategies to improve antibiotic stewardship in dental practice.

Keywords: dentistry; antibiotics; antimicrobial therapy; dental infection; operative intervention, drainage

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List of Abbreviations, Acronyms, Symbols, or Initialisms

AAE	American Association of Endodontics
DI	dental infection
ESE	European Society for Endodontology
GDP	Gross Domestic Product
G+	Gram-positive
G-	Gram-negative
MRSA	Methicillin-Resistant Staphylococcus Aureus
S.	Staphylococcus
TetR	tetracycline repressor protein
UAE	United Arab Emirates

1. Introduction

In 1928, British physician Sir Alexander Fleming discovered that a mould, *Penicillium* genus, prevented bacterial cultures from proliferating. The bactericidal substance secreted by this mould is named penicillin and becomes available as a medicine in the 1940s becoming the first antibiotic. Since that time, numerous additional substances with antibacterial activity have been identified.

"An antibiotic is defined as "a substance produced by microorganisms that can act on other microorganisms (or living cells) by inhibiting their growth or destroying them (antibiotic action)". Indeed, the term, coming from the Greek and meaning "against life", is thus used to refer to drugs that can inhibit or slow down the multiplication of bacteria, either by inhibiting one or more specific metabolic pathways essential to the bacterium or by acting on a specific target of the bacterial cell" (Ardila et al., 2023, p.1).

Antibiotics are the most important type of antibacterial agent for fighting bacterial infections. Antibiotics have saved countless lives since their discovery and have also contributed to a longer life expectancy. "The use of antibiotics has revolutionized healthcare by saving lives and preventing serious health complications, yet their overuse has serious adverse effects on the health of people and communities" (Stein et al., 2018, p.1).

There are several dozen antibiotics available, which can be categorised into more than ten families. The main families include aminoglycosides, beta-lactams (penicillins and cephalosporins), macrolides, nitroimidazoles, quinolones, and tetracyclines. The mechanism of action of these antibiotics is to inhibit the synthesis of the bacterial cell wall or to inhibit nucleic acids or protein synthesis.

Each antibiotic possesses a few distinctive characteristics. The term 'spectrum of activity' is used to describe the range of bacteria that a given antibiotic is capable of targeting. An antibiotic is broad-spectrum if it is effective against a large array of bacteria, whereas a narrow-spectrum antibiotic is one that is only effective in reduced groups. Bacteria that are not affected by a particular antibiotic are referred to as resistant, which can be due to natural or acquired resistance. The terms 'bacteriostatic' and 'bactericidal' are used to describe the effect of an antibiotic on bacterial multiplication. An antibiotic is classified

as bacteriostatic if it stops bacterial multiplication, whereas it is classified as bactericidal if it destroys the bacteria.

In cases where this is required, a local sample containing the bacteria can be sent to a laboratory for an antibiogram. The objective of this test is to evaluate the efficacy of different antibiotics on the bacteria in question, thereby allowing for the formulation of an appropriate treatment plan.

“The oral cavity has the second largest and diverse microbiota after the gut harboring over 700 species of bacteria. It nurtures numerous microorganisms which include bacteria, fungi, viruses and protozoa.” (Deo & Deshmukh, 2019, p.1) The normal microflora of the oral cavity is made up of aerobic G+ and anaerobic G+ and G- from which the anaerobic bacteria represent three fourth of the oral microflora. The terms ‘aerobic’ and ‘anaerobic’ describe whether a bacterium needs oxygen to live or multiply or not, respectively.

Bacterial infections of the dental and periodontal origin are a common occurrence in clinical practice. By the 1950s, antibiotics were being prescribed routinely for dental infections and as a prophylactic measure in patients with certain conditions.

“Antibiotic prescribing in dentistry, whether for prophylactic or therapeutic purposes, accounts for approximately 10% of antibiotic prescriptions worldwide.” (Ardila et al., 2023, p.2)

Dentists may prescribe antibiotics for either prophylactic or therapeutic reasons. In the context of prophylactic prescription, the prevention of infective endocarditis represents a significant rationale for the prescription of antibiotics. However, over time, the recommendations have undergone a series of modifications, “Additionally, prophylactic use is no longer recommended routinely for dental procedures.” (Bhuvaraghan et al., 2021, p.2)

In the context of therapeutic prescription, there are several situations in which antibiotic prescription is not recommended; however, antibiotics are frequently prescribed, for instance, in the case of alveolitis. Dry socket, or alveolitis, is a condition that presents as inflammation of the alveolar bone following tooth extraction. It is important to note that

this is not an infection; therefore, there is no reason for antibiotic prescription in this context.

It is a well-established fact that antibiotics should be used only in exceptional circumstances within the field of dentistry. There are many more bacteraemia resulting from everyday activities, such as dental brushing and chewing, than those associated with dental care. The most common approach to treat an infectious focus is through non-medicated methods. The use of antibiotics can neither compensate for insufficient oral hygiene nor replace the universal rules of hygiene and asepsis inherent to all healthcare practices. It is very important to maintain good oral hygiene to prevent infections in the field of oral medicine. Patients must receive appropriate information in this regard.

The selection of an appropriate antibiotic treatment is essential. It is of the utmost importance to conduct a comprehensive medical history of the patient. Indeed, the use of antibiotics in inappropriate circumstances can be fatal. “Antibiotics produce adverse drug reactions ranging from minor and reversible to severely debilitating or fatal” (Stein et al., 2018, p.1).

It is beyond dispute that antibiotics have transformed the practice of medicine, significantly improving the health and survival rates of patients with serious infections. However, it is also clear that they have the potential to cause adverse effects, including intestinal dysbiosis, antimicrobial resistance, and the subsequent impact on public health and healthcare costs. (Ardila et al., 2023).

However, a broader concern is the emergence of antibiotic resistance in bacteria, which can be defined as acquired resistance. This phenomenon occurs when bacteria develop a strategy that neutralizes the antibiotic's effect. To illustrate, Beta-lactamases, produced by S. aureus, can neutralize the effects of beta-lactam antibiotics. The emergence of antibiotic resistance in a bacterial strain within a patient may, in certain circumstances, lead to selection and transmission of those genes to the individual normal flora. The process is facilitated by the overuse and misuse of antibiotics.

The concept of antibiotic resistance emerged shortly after the discovery and use of antibiotics. Alexander Fleming, who discovered penicillin in 1928, warned of the potential for bacteria to develop resistance as early as 1945. He noted that misuse or overuse of antibiotics could lead to the evolution of resistant bacterial strains.

“According to National Centre for Disease Control and Prevention it is estimated that around one-third of the out-patient antimicrobial prescriptions are inappropriate” (Saadat et al., 2013, p.1). Unnecessary, inappropriate or prolonged use of antibiotics is the main factor in the development of resistance. The growing prevalence of resistance issues in recent years is likely attributable to the over- or misapplication of broad-spectrum agents. (Oberoi et al., 2015)

Bacterial resistance to antibiotics is a global problem that is now being compared with other issues of worldwide concern. “Consequently, in May 2015, the World Health Organization endorsed a global action plan to combat this issue, with a specific emphasis on antibiotic resistance” (Stein et al., 2018, p.1).

The statistics are alarming. It is estimated that at least 700,000 deaths per year are caused by infections resulting from antimicrobial-resistant organisms. This figure could reach 10 million by 2050, with a projected loss of 100 trillion US dollars to the global economy and a reduction in the world's GDP of 2–3.5%. These projections are based on the assumption that the current trajectory of antimicrobial resistance is unchecked. (Bhuvaraghan et al., 2021)

The clinical situations that necessitate the administration of antibiotics on an empirical basis are restricted to instances of oral infection accompanied by indications of systemic dissemination of infection, such as elevated body temperature, lymphadenopathy, and osteomyelitis. Consequently, antibiotics are not recommended for all odontogenic infections and should not be employed as a substitute for the eradication of the underlying cause of infection. (Ardila et al., 2023)

Indications are available for the use of systemic antibiotics in dentistry but unfortunately dentists are prescribing in situations where they should not prescribe. In endodontics, acute apical abscess is the only situation in which the dental surgeon must prescribe an antibiotic.

Once the necessity for antibiotic therapy has been established, the treatment should be administered for the shortest feasible period until the patient has achieved a clinical cure. (Martins et al., 2017)

Although odontogenic infections are quite common, there are no consistent guidelines for the use of antibiotics in their treatment. Many dental pain cases stem from acute and chronic infections of the pulp, which typically require operative procedures rather than antibiotics. Dentists often prescribe antibiotics for conditions where they are not needed, such as acute periapical infections, dry sockets, and pulpitis. (Oberoi et al., 2015).

In cases like toothache stemming from pulpal or periapical inflammation, the use of systemic antibiotics is not indicated, given that these are localised conditions. Instead, dental intervention, such as tooth extraction or the removal of the dental pulp, represents the optimal course of action for their management. (Bhuvaraghan et al., 2021)

Endodontic treatment is the only effective way to relieve symptoms and eradicate the infection. Despite this, dentists worldwide continue to prescribe antibiotics for localized infections that do not involve systemic symptoms. (Ardila et al., 2023). The key to treating dental infections lies in removing the source and performing surgical drainage when necessary. While antibiotics are sometimes needed, it is a misconception that all infections require them. In fact, there are cases where their use is unnecessary or even counterproductive. (Martins et al., 2017)

The selection of an antibiotic is depending on the characteristics of the infection, including its location and severity, as well as the patient's medical history, which may include allergies, renal or hepatic disease. In certain instances, it may be necessary to combine multiple pharmaceutical agents, such as in the case of a severe infection. The optimal therapeutic strategy is based on the identification of the microorganism and demonstration of susceptibility to antibiotics. “Patient adherence to antibiotic therapy is paramount in achieving therapeutic success and reducing the development of resistant bacterial strains” (Ardila et al., 2023, p.18).

It is of the utmost importance that patients adhere to the prescribed treatment regimen. Consequently, any antibiotic prescription must be explicitly communicated to the patient, including the dosage and the length of the treatment period. Indeed, the prescribing strategy is based on a comprehensive understanding of the patient. It is imperative that patients are informed that they must seek medical attention if they develop any general infectious symptoms following an invasive procedure, whether they have undergone antibiotic therapy.

“Among the antibiotics prescribed by dentists, broad-spectrum amoxicillin was the most common, whereas the use of narrow-spectrum agents such as penicillin V potassium (VK) decreased. This finding is worrisome because narrow-spectrum agents are less likely to lead to resistant bacteria” (Stein et al., 2018, p.2).

The appropriate utilisation of antibiotics is contingent upon an understanding of the principles governing infection management, the microbiology of infectious agents and host response, and the pharmacology of the agent in question. In the clinical setting, these principles are subject to modulation by a number of factors. It is essential to comprehend these factors in order to guarantee the appropriate prescription of antibiotics. (Oberoi et al., 2015).

The objective of this study is to conduct a systematic review of the literature with the aim of evaluating the effectiveness of antibiotics in the treatment of dental infections in comparison to other therapeutic options. The primary research question guiding this review is: "What is the effectiveness of antibiotics in dental infections compared to other therapeutic options?"

This systematic review aims to explore the motivations behind antibiotic prescriptions in dental care, with the goal of promoting appropriate use of antibiotics to combat antibiotic resistance. Additionally, it seeks to enhance patient education regarding proper adherence to prescribed antibiotic regimens.

To address our research question, this review will cover several key topics: current guidelines for antibiotic use in dental infections, the most prescribed antibiotics, the concept of a loading dose, the education of dental professionals, and patient education and adherence to systemic antibiotic therapy.

2. Methodology

1. Protocol registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. (Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA], 2020). The PRISMA checklist and flow diagram were utilized to ensure comprehensive and transparent reporting of the review process.

2. Information sources and search strategy

The search strategy involved an explicit search from multiple databases, namely, PubMed, Cochrane Library, B-On and Scielo. The filter applied limited the selection of articles from the year 2013 until 2024, selecting scientific articles in English and Portuguese language. The search strategy follows a logical structure that combines the following keywords and Boolean operators: (dentists or dentistry or tooth) AND (antibiotics or anti-bacterial agents) AND (systemic use or systemic antibiotics or systemic antibiotic therapy or therapeutic use) AND (odontogenic infection or dental – infection or bacterial infections or periapical abscesses). Search lines adapted to each database is shown in (Table 1).

Board 1:

Line of search for each data base

Line of search for each data base

Database	Line of search	Filters
PubMed	(((dentists or dentistry or tooth[MeSH Major Topic]) AND (antibiotics or anti-bacterial agents[MeSH Major Topic])) AND (systemic use or systemic antibiotics or systemic antibiotic therapy or therapeutic use)) AND (odontogenic infection or dental infection or bacterial infections or periapical abscesses)	Clinical Trial, Randomized Controlled Trial English, Portuguese From 2013 - 2024
Cochrane	(dentists or dentistry or tooth):ti,ab,kw AND (antibiotics or anti-bacterial agents):ti,ab,kw AND (systemic use or systemic antibiotics or systemic antibiotic therapy or therapeutic use):ti,ab,kw AND (odontogenic infection or dental infection or bacterial infections or periapical abscesses):ti,ab,kw	English, Portuguese From 2013 – 2024
B-On	TI (dentistry or dentists or tooth) AND TI (antibiotics or anti-bacterial agents) AND (systemic use or systemic antibiotics or systemic antibiotic therapy or therapeutic use) AND SU (odontogenic infection or dental infection or bacterial infections or periapical abscesses)	English, Portuguese From 2013 – 2024
Scielo	(ti:(*dentists or *dentistry or *tooth)) AND (ti:(*antibiotics or *anti-bacterial agents)) AND (*systemic use or *systemic antibiotics or *systemic antibiotic therapy or *therapeutic use) AND (*odontogenic infection or *dental infection or *bacterial infections or *periapical abscesses)	English, Portuguese From 2013 – 2024

3. Inclusion criteria

The eligibility criteria for the elaboration of the systematic review followed the PICO strategy: Population - patients with dental infection, Intervention - systemic antibiotic therapy, Comparison - other therapeutic option Outcome - improving adequate antibiotic prescription / improving correct use of antibiotics. Leading to our PICO question: What is the effectiveness of antibiotics in the treatment of dental infections? The inclusion criteria are summarized in (Table 2). The studies included were all observational studies, namely cross-sectional studies, a prospective study, a retrospective study and other surveys.

Board 2:

Inclusion criteria

Inclusion criteria (as per PICO analysis)			
Population	**Intervention**	**Comparison**	**Outcome**
Patients with dental infection	Systemic antibiotic therapy	Other therapeutic options	Improving adequate antibiotic prescription / improving correct use of antibiotics

4. Exclusion criteria

The exclusion criteria were, studies not specific to dental profession, studies dealing with paediatric population, that is under eighteen years of age, studies with their focus on prophylactic and/or topic use of antibiotics and studies related to periodontal diseases only.

The focus is on infections that originate from the teeth themselves, i.e. endodontic infections, or combined periodontal/endodontic infections, i.e. periodontal infections of dental origin.

5. Study selection

The search was runed on the different data bases on 18th June 2024.

For all articles found, the titles and abstracts were read. For initially selected articles, the full texts were read, and they were submitted to the application of our inclusion and exclusion criteria for final inclusion.

Based on the article selection conducted, a PRISMA flow diagram was developed, and the systematic review was elaborated. (PRISMA, 2021) (Figure 1)

6. Quality assessment

To assess the risk of bias in the included studies, we used the Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool (Cochrane Methods Bias, 2016). This tool is specifically designed for evaluating the quality of non-randomized studies and allows for a comprehensive assessment across multiple domains. The following steps outline our approach:

The domains assessed were the following ones, the ROBINS-I tool evaluates risk of bias across seven domains: bias due to confounding, bias in selection of participants, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes, bias in selection of the reported result.

Each included study was independently assessed. The assessments were documented and categorized as follows: low risk of bias, moderate risk of bias, serious risk of bias, critical risk of bias, no information.

The quality assessments were synthesized and presented in a traffic light plot (Figure 2). This traffic light plot provides an overview of the risk of bias across the included studies, facilitating the interpretation of the review’s findings.

By employing the ROBINS-I tool, we aimed to systematically evaluate and transparently report the potential sources of bias in the included non-randomized studies, thus enhancing the robustness and reliability of our systematic review.

3. Results

1. Study selection

Based on the article selection conducted, a PRISMA flow diagram was developed, and the systematic review was elaborated. (Figure 1)

According to the selected search criteria, an identification of a total of 384 records were selected from the noted databases. The databases searched included PubMed (170 records), Cochrane Library (193 records), and B-On (21 records). No records were retrieved from Scielo or any registers.

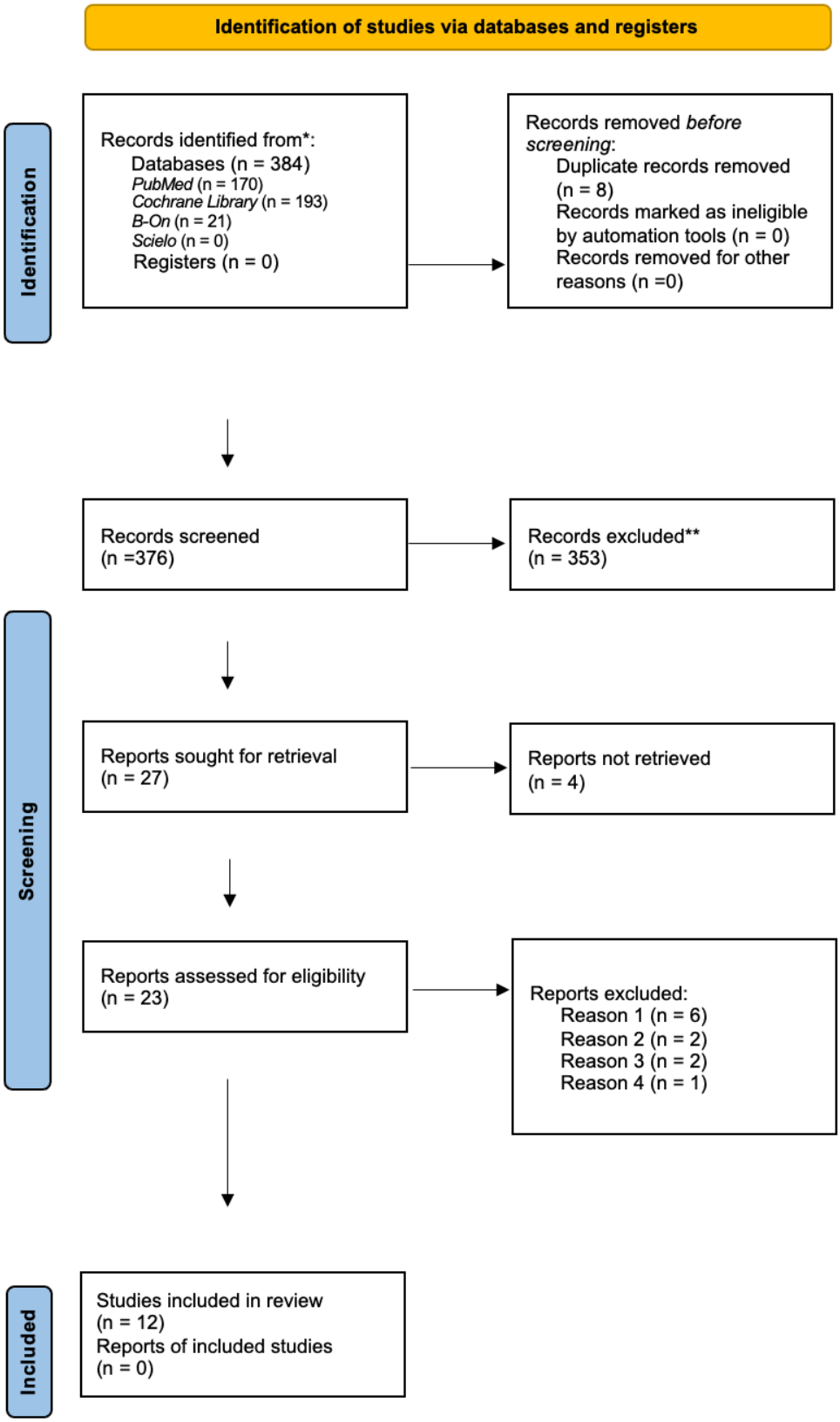
After removing 8 duplicate records, 376 records were screened based on titles and abstracts. From these, 353 records were excluded as they did not meet the inclusion criteria.

Twenty-seven reports were sought for retrieval, but 4 reports could not be retrieved. Subsequently, 23 reports were assessed for eligibility. Of these, 11 reports were excluded for the following reasons: six studies focused on the use of antibiotics and/or intracanal medication, two studies dealt with a paediatric population under 18 years of age, two studies were literature reviews or less relevant studies, one study had its main focus on the periodontium.

Finally, 12 studies were included in the systematic review. We try to pay attention to select studies from different continents around the world to have a more global overview. (Board 3) From the twelve studies included four of them are European studies, four are studies from the Middle East, two are from South Asia, one is from South America, and one is from the United States.

Figure 1:

Prisma 2020 flow diagram



Reason 1 – Studies with their focus on topic use of antibiotics and/or intracanal medication

Reason 2 – Studies dealing with pediatric population, that is under 18 years of age

Reason 3 – Literature reviews, other less relevant studies

Reason 4 – Studies with focus on the periodontium

**Excluded for not meeting inclusion criteria.

Board 3:

Included studies with region or continent

	Author and year	**Region or continent**
Study 1	(Germack et al., 2017)	America
Study 2	(Preus et al., 2017)	Europe
Study 3	(Koyuncuoglu et al., 2017)	Europe
Study 4	(Licata et al., 2021)	Europe
Study 5	(D'ambrosio et al., 2022)	Europe
Study 6	(Asmar et al., 2016)	Middle East
Study 7	(Baskaradoss et al., 2018)	Middle East
Study 8	(Maslamani & Sedeqi, 2018)	Middle East
Study 9	(Abraham et al., 2020)	Middle East
Study 10	(Dias et al., 2022)	South America
Study 11	(Saadat et al., 2013)	South Asia
Study 12	(Ismail et al., 2018)	South Asia

2. Study characteristics

The characteristics of all included studies in final review can be found in (Table 4).

Table 1:

Characteristics table

Author, year and study design	Aim of study	Region or nation assessed for prescription trends	Outcome evaluation method	Population evaluated	Response rate	Antibiotic used commonly	Discussion
Study 1 (Germack et al., 2017) Survey	The aim of this study was to obtain current information on the antibiotic prescribing practices of endodontists in the United States and compare it with previous reports (1994 and 1999).	United States America	Online questionnaire	Endodontists	686/3000 **22,86%**	Amoxicillin (60,71%) Followed by penicillin V (30.43%) **allergic for penicilin:** Clindamycin (95.4%).	Antibiotics are still prescribed in clinical situations for which they are typically not indicated. More than one third of respondents reported prescribing antibiotics that are not necessary, most commonly because of patient expectations.
Study 2 (Preus et al., 2017) Survey	To review antibiotic prescription habits among Norwegian dentists in 2015 and compare them with the previous surveys from 1990 and 2004 as well as with the Norwegian National Prescription Register (2005–2015).	Norway Europe	Online questionnaire	Dentists and specialist dentists	1155/4254 **27.2%**	Phenoxymethylpenicillin was the preferred antibiotic (more than 50% of the prescriptions) Preferred antibiotic for treatment of abscess with general symptoms: Phenoxymethylpenicillin (80.4%)	The present study found an increase (not statistically tested) in prescriptions from 1990 to 2004 and a statistically significant reduction from 2004 to 2015. A more systematic Pan-European and globally coordinated education on antibiotics and their use in dental clinics is needed.

Author, year and study design	Aim of study	Region or nation assessed for prescription trends	Outcome evaluation method	Population evaluated	Response rate	Antibiotic used commonly	Discussion
Study 3 (Koyuncuoglu et al., 2017) Retrospective study	Examine dentists antibiotic prescriptions in a diagnosis-based manner.	Turkey Europe	Based on the national health prescription data of the dentists	Dentists and specialist dentists	-	Amoxicillin + enzyme inhibitor (58.6%)	Dentists usually prescribe antibiotics in an unnecessary manner that is mostly far away from evidence-based medicine.
Study 4 (Licata et al., 2021) Survey, Cross sectional	Evaluate pattern of antibiotic prescription for endodontic infections and adherence to evidence-based recommendations and to explore the role of potential predictors of antibiotic over prescription.	Italy Europe	Online questionnaire	Dentists	563/1250 52.6%	Amoxicillin plus clavulanate allergic to penicillin: clindamycin	Results demonstrated that the Italian dental practitioners overprescribed antibiotics in the management of endodontic infections, for both therapeutic and prophylactic purposes. The development of practical antibiotic prescribing guidelines with a clear description of indications and regimen ease of use is strongly needed.

Author, year and study design	Aim of study	Region or nation assessed for prescription trends	Outcome evaluation method	Population evaluated	Response rate	Antibiotic used commonly	Discussion
Study 5 (D'ambrosio et al., 2022) Survey, Cross sectional	1/ investigate the current antibiotic prescribing habits therapeutic purposes according to dental diagnoses, in relation to dentists' working experience, usual setting, and main practice 2/ assess the sources and frequency of the consultation of the relevant guidelines, awareness and knowledge about antimicrobial resistance, and related antibiotic prescribing behaviors among Italian dentists	Italy Europe	Online questionnaire	Dentists	382/655 **58,32%**	Amoxicillin and phenoxymethylpenicillin: recommended as the first choice therapeutic antibiotics in patients without a penicillin allergy **allergic to penicillin:** macrolides	This study demonstrates that the same trend exists in Italy as in other countries in terms of the high prevalence of misuse and overuse of antibiotics, and that Italian dentists utilize a range of antibiotic management strategies.

Author, year and study design	Aim of study	Region or nation assessed for prescription trends	Outcome evaluation method	Population evaluated	Response rate	Antibiotic used commonly	Discussion
Study 6 (Asmar et al., 2016) Prospective, multicenter study	Investigate patterns of therapeutic prescription of antibiotics followed by Lebanese dentists in the management of patients with dentoalveolar infections.	Liban Middle East	-	Dentists	-	Amoxicillin + clavulanic (prescribed to 88,2% of the patients in this study) **allergic to penicillin:** Clindamycin	The rate of inadequate prophylactic and curative antibiotic prescriptions decreased. Obviously, the need for internationally approved guidelines is of utmost importance. The dentists either ignored or were not familiar with the current antibiotic prescription regimens.
Study 7 (Baskaradoss et al., 2018) Survey, Cross sectional	Investigate pattern of antibiotic prescription and dentists awareness about recent guidelines of antibiotic prescription.	Riyadh, Saudi Arabia Middle East	Questionnaire	Dentists and specialist dentists	282/355 **79.3%**	Amoxicillin **allergic to penicillin:** Clindamycin	High proportion of dentists prescribing antibiotics inappropriately.

Author, year and study design	Aim of study	Region or nation assessed for prescription trends	Outcome evaluation method	Population evaluated	Response rate	Antibiotic used commonly	Discussion
Study 8 (Maslamani & Sedeqi, 2018) Survey, Cross sectional	Determine attitude and knowledge of general dentists and specialists regarding antibiotic and analgesic prescriptions for medically healthy patients during endodontic management.	Kuwait Middle East	Questionnaire	Dentists and specialist dentists	227/300 **75.6%**	Amoxicillin 500 mg (51.5%)	Most dentists in Kuwait prescribe antibiotics and analgesics when appropriate.
Study 9 (Abraham et al., 2020) Prospective survey, Cross sectional	Investigate antibiotic prescribing practices of dentists focusing on the management of endodontic infections in UAE.	United Arab Emirates (UAE) Middle East	Online, questionnaire	Dentists and specialist dentists	174/250 **70%**	Amoxicillin 500mg thrice daily (43.7%) Amoxicillin+ clavulanic acid combination with a wider spectrum, was also prescribed by a smaller proportion of respondents as the drug of first choice in endodontic infections. **allergic to penicillin:** Erythromycin 500mg thrice daily (21.3%)	In general, the antibiotic prescribing practices of UAE cohort of dentists responding to our questionnaire appear to be congruent with the international norms, despite the fact that a surprising number did not follow specific antibiotic guidelines. There were, however, instances of inappropriate antibiotic use for specific endodontic pathologies.

Author, year and study design	Aim of study	Region or nation assessed for prescription trends	Outcome evaluation method	Population evaluated	Response rate	Antibiotic used commonly	Discussion
Study 10 (Dias et al., 2022) Survey, Cross-sectional	Investigate how professionals with different levels of academic education, who provide endodontic treatment in Colombia, prescribed antibiotic.	Colombia, South America	Online questionnaire	Dentists and specialist dentists	320/ 559 **57,2%**	Amoxicillin Amoxicillin + clavulanic acid was the most often cited for acute peri radicular abscess with systemic involvement (only in this situation) ; as has been recommended **allergic to penicillin:** Clindamycin	As verified in the present study, many professionals lack knowledge about the proper use of antibiotics in endodontics. There is a clear need to improve Antibiotic recommendations as well as knowledge of pulpal and periradicular diseases, which are a problem not only locally, but also globally.
Study 11 (Saadat et al., 2013) Study, Cross sectional	Assess antibiotic prescription practice of dentists employed in a public sector teaching institute of Karachi.	Karachi, Pakistan South Asia	Questionnaire	Dentists and specialist dentists	89/110 **81%**	treatment of acute dental infections in patients without any known allergy: Amoxicillin (43.3%) **dosage** 500mg, 3 times daily for 3 days Amoxicillin Clavulanate (34%)	Results of this study demonstrate that majority of the surveyed dentists prescribe antibiotics for many oral conditions where local management would be sufficient and antibiotics are not needed. There is a need of developing guidelines regarding antibiotic

						allergic to penicillin: Clindamycin (30.30%) **dosage** 450mg, twice or thrice a day for 5 days	prescription by the regulatory bodies based on available literature to prevent resistance development and regulating appropriate use of antibiotics.
Study 12 (Ismail et al., 2018) Cross sectional, descriptive, quantitative study	Document the antibiotics prescriptions habits of dentists working in two Lahore Dental Colleges and their knowledge regarding use of antibiotics for odontogenic infections.	Lahore, Pakistan South Asia	Questionnaire	Dentists and specialist dentists	101/not known	Amoxicillin most frequently chosen first line antibiotic for odontogenic infections (61.4%) **allergic to penicillin:** Clindamycin (60.2%)	Consistent international guidelines for antibiotic use in dentistry need to be formalized and kept up-to-date. There was over prescription of antibiotics for pulpitis, sinus tract infections and severe gingivitis, which may be treated by clinical therapy alone.

3. Risk of bias in studies

The results of the risk of bias assessment are visually represented in a traffic light plot (Figure 2), which provides a clear and intuitive summary of the risk of bias for each study included in our systematic review. Each domain for each study is color-coded: green indicates low risk of bias, yellow signifies moderate risk, and red denotes high risk. This visual representation allows for an immediate understanding of the overall quality of the evidence and highlights areas where potential biases may influence the study outcomes.

Of the twelve studies assessed using the ROBINS-I tool, two studies were judged as having a low risk of bias (Study 4 and Study 11) and 10 studies were judged as having a moderate risk of bias. (Study 1, 2, 3, 5, 6, 7, 8, 9, 10 and 12).

Risk of bias domains one and five, bias due to confounding and bias due to missing data, respectively, where the domains with the most 'moderate' signs.

Figure 2:

ROBINS-I traffic light plot

4. Discussion

The objective of the study was to conduct a systematic review of the literature on the efficacy of antibiotics in the treatment of dental infections. Most of the evidence on the use of antibiotics in dental infections is derived from cross-sectional surveys and studies conducted at the national or regional level. These studies typically evaluate prescribing practices through questionnaires, often administered online, targeting practising dentists. The surveys generally include personal information, and a combination of open-ended and closed-ended questions based on case scenarios to assess trends in antibiotic prescriptions.

1. What do we know? Guidelines for antibiotic use in dentistry

Endodontic infection is defined as an infection occurring within the root canal system of a tooth. This system encompasses the dental pulp, which represents the innermost part of the tooth and contains nerves, blood vessels, and connective tissue. When the dental pulp becomes infected, which is typically due to bacterial invasion from dental caries, cracks, or trauma to the tooth, it can result in inflammation and infection of the pulp tissue. “When odontogenic infections are not treated promptly and appropriately, the infection can spread into the fascial spaces, sublingual, submental, submandibular, buccal, and canine spaces.” (Wise et al., 1998) Furthermore, dental infections have the potential to spread rapidly and cause systemic symptoms such as fever, severe swelling, restricted mouth opening, bacteremia and airway obstruction, which can be life-threatening (Baskaradoss et al., 2018). A serious approach is essential.

American Association of Endodontists

In order to circumvent the deleterious effects of unnecessary antibiotics on patients and the environment, it is of the utmost importance to initially ascertain whether the use of antibiotics is indeed necessary. This decision should take precedence over the selection of an appropriate antibiotic. It is estimated that around 60% of human infections can be resolved by the body's own immune system, once the underlying cause of the infection is addressed, without the need for antibiotic treatment. (*Colleagues for Excellence Colleagues for Excellence ENDODONTICS*, 2012)

Most endodontic infections do not require systemic antibiotics if the underlying cause is effectively addressed, including thorough debridement of the pulp space and proper obturation and sealing from the oral environment. (*Colleagues for Excellence Colleagues for Excellence ENDODONTICS*, 2012)

The AAE guidelines clarify the situations in which antibiotics should or should not be prescribed. In summary, asymptomatic apical periodontitis of pulpal origin, chronic apical abscesses of endodontic origin, intraoral and localized acute apical abscesses do not require systemic antibiotic therapy.

Acute apical abscess or infection with systemic involvement (fever or malaise) causing diffuse facial swelling (cellulitis) requires an appropriate regimen of systemic antibiotics and local intervention.

These guidelines do not provide any statement on whether to prescribe antibiotics for pulpitis. In fact, pulpitis is an inflammation of the dental pulp that may be reversible or irreversible. There is obviously no reason to prescribe antibiotics in this case.

It is essential to consider each patient and situation as unique, and as professionals, we must adapt our knowledge in an ethical manner.

European Society of Endodontology (Segura-Egea et al., 2018)

The European Society of Endodontology contraindicates systemic antibiotics in the following situations: symptomatic irreversible pulpitis, pulp necrosis, symptomatic apical periodontitis, chronic apical abscess and acute apical abscess without systemic involvement.

In these situations, the European Society of Endodontology recommends adjunctive systemic antibiotic treatment in conjunction with endodontic therapy; acute apical abscess in medically compromised patients, acute apical abscess with systemic involvement (localized fluctuant swellings, elevated body temperature >38 ° C, malaise, lymphadenopathy, trismus) and progressive infections (rapid onset of severe infection within 24h, cellulitis, or a spreading infection and osteomyelitis).

We can state that the European Society of Endodontology is in line with the American Association of Endodontists.

According to the Columbian study, which is the most recent study included in our systematic review,

"The American Association of Endodontics (AAE) and the European Society of Endodontology (ESE) frequently revise the guidelines for endodontists regarding proper antibiotic prescription. There is consensus that in most clinical endodontic situations, it suffices to provide local treatment with removal or reduction of the infection source, without using systemic antibiotics" (Dias et al., 2022, p.2).

However, the authors also state that various studies worldwide have shown that dentists continue to prescribe antibiotics unnecessarily in endodontics. (Dias et al., 2022)

2. Prescribing trends of antibiotics in dental infections

The (Table 5) shows the percentage of dentists prescribing antibiotics for each condition in the studies. Specific data for each condition were not available in all studies. The averages are shown in the last row of the table. Percentages were excluded from the average calculation when no distinction was made between conditions, such as chronic versus acute abscess, or acute abscess without versus with aggravating symptoms.

Table 2:

Percentage of dentists prescribing antibiotics for each respective condition across the studies

Study	Pulpitis (acute or chronic)	Necrotic pulp	Necrotic pulp with symptomatic apical periodontitis	Chronic abscess (with or without symptoms)	Acute abscess (without aggrieving symptoms)	Acute abscess (with aggrieving symptoms), cellulitis
Study 1 (Germack et al., 2017)	8,16%	_	43.59%	40,24%	95.92%	
Study 2 (Preus et al., 2017)	_	_	_	56%	_	
Study 3 (Koyuncuoglu et al., 2017)	_	_	_	28,1%	_	
Study 4 (Licata et al., 2021)	13%	27%	_	21,5%	62%	78,3%
Study 5 (D'ambrosio et al., 2022)	35,6%	_	_	_	92,1%	
Study 6 (Asmar et al., 2016)	_	_	_	38,1%	51,7%	22,3%
Study 7 (Baskaradoss et al., 2018)	24,5%	_	_	47,2%	_	85,5%
Study 8 (Maslamani & Sedeqi, 2018)	15,2%	24,45%	45,8%	49,8%	88,1%	
Study 9 (Abraham et al., 2020)	12%	20%	_	21%	_	89%
Study 10 (Dias et al., 2022)	32,45%	36,5%	57.2%	65,6%	90,4%	96,2 %
Study 11 (Saadat et al., 2013)	53,90%	_	_	50%	_	85.39%
Study 12 (Ismail et al., 2018)	35%	_	_	76%	87%	
Average	**25,5%**	**27%**	**48,7%**	**43,7%**	**68%**	**76,1%**

It is concerning to see that, on average across our twelve studies, a quarter of dentists prescribe systemic antibiotic treatment for pulpitis. The numbers are particularly high in the cross-sectional study from Karachi, Pakistan, where antibiotics were prescribed for acute pulpitis at a rate of 53.90%. The rates are also high in the two Italian studies, 35.6% and 32.45% respectively. "Antibiotics are not indicated in the case of pulpitis because the pulp is still vital and there is no infection or signs of systemic involvement" (Longman et al., 2000). In a Italian study, the authors explain that pulpitis is typically treated with pulpectomy, and they confirm that antimicrobial administration should only be employed in cases of systemic complications, as outlined in the relevant clinical guidelines. (D'ambrosio et al., 2022)

In a study from the United States, it is noteworthy that the prescription trend for pulpitis is the lowest,

"Respondents reported prescribing antibiotics for irreversible pulpitis with mild symptoms (1.75%), irreversible pulpitis with moderate symptoms (6.41%), necrotic pulp with symptomatic apical periodontitis (43.59%), chronic apical abscess without (10.50%) or with symptoms 29.74%, acute apical abscess (95.92%) …" (Germack et al., 2017, p.1). However, almost half of the endodontists surveyed prescribe in situations such as necrotic pulp with symptomatic apical periodontitis 43.59% and chronic abscess with or without symptoms 40.24%, although these are two situations in which it is not recommended to prescribe systemic antibiotic therapy. This may seem surprising as the practitioners surveyed in this study were only endodontists, i.e., practitioners specialising in odontogenic infections. A lower rate of inappropriate prescribing would have been more reassuring.

In a Norwegian study,

"A diagnosis of abscess without general symptoms caused 56% of the dentists to respond that they would prescribe antibiotics 'sometimes or more frequently', which was significantly less than seen in 2004 ($P < 0.001$). Thirty-five percent reported never to prescribe antibiotics for these conditions when presenting as a single symptom" (Preus et al., 2017, p.4).

It was not specified whether it was an acute abscess without general symptoms or a chronic abscess without general symptoms. In both cases, however, systemic antibiotic

therapy is not recommended because of the absence of general symptoms. Despite this, more than half of dentist still prescribe antibiotics, which is still a concerning high number.

“Regarding antibiotic prescriptions for conditions such as gingivitis, stomatitis, and dental pain or abscess without general symptoms, the present study found an increase (not statistically tested) in prescriptions from 1990 to 2004 and a statistically significant reduction from 2004 to 2015” (Preus et al., 2017, p.7).

In Norway, in the last years a decrease has been noticed, which is positive, but there is still a long way to go. The condition of acute alveolar abscess without aggrieving symptoms and without systemic spread is highlighting a common scenario where antibiotics are used more than necessary to treat dental infections, done with an average of 68% (Table 5).

In a Turkish study, the authors reported that only 3.4% of antibiotics were prescribed for the specific and appropriate diagnosis of "cellulitis and abscess of mouth." The remaining 96.6% were prescribed for reasons that were either irrational or uncertain. (Koyuncuoglu et al., 2017., p.1). These numbers from a Turkish study included in our systematic review are alarming.

“Antibiotics may be prescribed in situations where dentists fail to give sufficient time to patient evaluation. Dentists also prescribe antibiotics based on anecdotal experiences, hearsay or just-in-case, and not on scientific evidence” (Ismail et al., 2018, p.1).

When we look at the results of our twelve studies, it is obvious and clear that there is a global over-prescription of antibiotics around the world. In nine of the twelve studies, one of the findings is that dentists are prescribing antibiotics for oral conditions that should only be treated locally, and in six of the twelve studies, one of the findings is that there is a need for improved recommendations and clear guidelines.

It is remarkable that a number of studies talk about this need for clear guidelines, because there are some guidelines that exist, from the AAE and the ESE. What is alarming is that, knowing that these guidelines exist, we still note alarming results of over-prescribing in situations where it is clear that no prescription is recommended. The problem is that dentists do not seem to consult the guidelines. Dentists should educate themselves,

consult the guidelines and become aware of the huge and serious problem of overprescribing and its consequences.

Regarding guidelines, some confusion exists because of different sources of information, as shown in a study carried out in the United Arab Emirates, "When questioned on guidelines followed by dentists for antibiotic prescription, 58% (n = 101) followed local guidelines, and 42% (n = 73) did not follow any specific guideline perse. Of the 101 dentists who followed guidelines, 52% (n = 53) followed the antibiotic prescribing guidelines promulgated by the Ministry of Health, UAE, while 22% (n = 23) followed the American Association of Endodontists guidelines. Another 22% (n = 23) followed their own institutional guidelines. The remaining 4% (n = 4) followed the guidelines set by the ESE (European Society for Endodontology) and ASE (Australian Society of Endodontology), respectively (Abraham et al., 2020, p.6)".

As an outcome of all our studies, there is a great need for global consensus on guidelines.

Typically, in a Pakistan study conducted in Lahore, it was found that while swelling and fever can be signs of infection, they may also result from trauma or surgical procedures, in which case antibiotics might not be necessary. The authors expressed concern over the high rates of antibiotic prescriptions in cases of fever (57%) and significant facial swelling (71%), suggesting a lack of proper knowledge and application of appropriate prescribing practices. (Ismail et al., 2018) This highlights a significant knowledge gap among practitioners.

Furthermore, in a study conducted in Riyadh, Saudi Arabia the authors observed that most of the dentists who participated had not attended any lectures or workshops on antibiotic prescribing practices over the past year. (Baskaradoss et al., 2018).

Similarly, an Italian study reported that "more than half (55.4%) of the participants claimed to be knowledgeable about guidelines on the use of systemic antibiotics in endodontics, and 79.2% declared that they needed further information on the topic" (Licata et al., 2021, p.2).

These different results show a lack of interest and knowledge among dentists.

"As expected, dentists who had attended a continuing education course on antibiotic prescriptions were less likely to overprescribe than those who had used other sources of

information" (Licata et al., 2021, p.7). In addition, another Italian study, affirms that "The majority of dentists (378/382, 98.9%) reported being aware of the antibiotic resistance phenomenon, but only 28 (7.4%) of them consulted the guidelines for prescribing antibiotics." (D'Ambrosio et al., 2022, p.5) This supports the fact that dentists do not consult guidelines.

Dentists need to understand that most endodontic infections can be effectively treated with operative interventions alone, without the need for antibiotics. Our extracted data highlight the need for strategies aimed at reducing antibiotic prescribing for endodontic infections. These include the implementation of continuing education courses for dentists and the promotion of interest in and adherence to regional guidelines. These measures are essential to promote good antibiotic prescribing practices among dentists worldwide and ultimately help to curb the rise of antibiotic-resistant organisms. Educational programmes should emphasise the importance of consulting the latest guidelines to effectively address this issue.

3. Antibiotics used

According to the AAE guidelines, penicillin V (phenoxymethylpenicillin) is the antibiotic of choice for endodontic infections because of its efficacy against polymicrobial infections, its relatively narrow spectrum of activity against bacteria commonly found in endodontic infections, its low toxicity, and its low cost. The authors state that although amoxicillin and Augmentin (amoxicillin plus clavulanate) showed greater antibacterial efficacy than penicillin V, they should be reserved for unresolved infections and immunocompromised patients because of their broader antibacterial spectrum and the higher cost of Augmentin. "In medicine, antibiotic resistance has been attributed to long-term and repetitive use of broad-spectrum antibiotics." (Jernberg et al., 2010) Metronidazole showed the highest level of bacterial resistance and is only effective against anaerobes, so it should not be used alone to treat endodontic infections. For patients with penicillin allergy, clindamycin is the molecule recommended in these guidelines.

According to the ESE guidelines, penicillin V and amoxicillin are recommended for the treatment of endodontic infections.

Table 3:

Prescribing trends of antibiotics

Study	1st choice	2nd choice	1st choide for Allergic to penicilin patients
Study 1 (Germack et al., 2017)	Amoxicillin (60,71%)	Followed by penicillin V (30.43%)	Clindamycin (95.4%)
Study 2 (Preus et al., 2017)	Phenoxymethylpenicillin (+50%)	Metronidazole + Amoxicillin (29%)	_
Study 3 (Koyuncuoglu et al., 2017)	Amoxicillin + enzyme inhibitor (58.6%)	Spiramycin (9.8%)	_
Study 4 (Licata et al., 2021)	Amoxicillin plus clavulanate	_	Clindamycin
Study 5 (D'ambrosio et al., 2022)	Amoxicillin and phenoxymethylpenicillin	_	Macrolides
Study 6 (Asmar et al., 2016)	Amoxicillin + clavulanic (88,2%)	Spiramycin and metronidazole	Clindamycin
Study 7 (Baskaradoss et al., 2018)	Amoxicillin	Amoxicillin with clavulanic acid	Clindamycin
Study 8 (Maslamani & Sedeqi, 2018)	Amoxicillin 500 mg (51.5%)	_	_
Study 9 (Abraham et al., 2020)	Amoxicillin 500mg thrice daily (43.7%)	_	Erythromycin (21.3%) Clindamycin is (14.4%)
Study 10 (Dias et al., 2022)	Amoxicillin	_	Clindamycin
Study 11 (Saadat et al., 2013)	Amoxicillin (43.3%)	Amoxicillin Clavulanate (34%)	Clindamycin (30.30%)
Study 12 (Ismail et al., 2018)	Amoxicillin (61.4%)	Amoxicillin/Clavulanate (Augmentin) (35.6%)	Clindamycin (60.2%)
Most common	Amoxicillin		Clindamycin

In eight of our twelve studies, amoxicillin was the most chosen first-line antibiotic for odontogenic infections, followed by amoxicillin plus clavulanate in two studies. In a Norwegian study, phenoxymethylpenicillin was the preferred antibiotic representing more than 50% of the prescriptions (Preus et al., 2017). In an Italian study,

phenoxymethylpenicillin has a shared place of first chosen antibiotic with amoxicillin. (D'ambrosio et al., 2022)

The authors of a Lebanese study state that "Amoxicillin is the antibiotic of choice. However, it was alarming to observe that Amoxicillin combined with clavulanic acid was prescribed to 88.20% of the patients in this study" (Asmar et al., 2016, p.6). This rate of first-line prescription of amoxicillin in combination with clavulanic acid is very high in Lebanon. The same findings are exposed in a European study from Italy, "In the present study, the combination of amoxicillin plus clavulanate was the most frequently prescribed antibiotic, although amoxicillin and penicillin V should be the first-line therapeutic antibiotics in patients without a penicillin allergy" (Licata et al., 2021, p.7). These results are worrying because amoxicillin plus clavulanate is a broad-spectrum antibiotic that should be prescribed only in a small number of cases, mostly for unresolved infections and immunocompromised patients Amoxicillin plus clavulanate has a high implication in the development of antimicrobial resistance.

In accordance with guidelines, clindamycin was the first-choice antibiotic for patients with penicillin allergy in more than 50% of the studies included in our systematic review. Except in one study from the UAE, where erythromycin was the first choice 21.3%, followed by clindamycin 14.4%.

In most cases, amoxicillin remains the antibiotic of choice. Phenoxymethylpenicillin is a highly recommended molecule, but curiously, unlike amoxicillin, dentists are less likely to prescribe it.

"When indicated, penicillin and its derivatives are first line antibiotics for odontogenic infections" (Ismail et al., 2018, p.2). "Amoxicillin is a moderate-spectrum, bacteriolytic, beta-lactam antibiotic" (Abraham et al., 2020, p.8). Amoxicillin, like penicillin, is a member of the beta-lactam family. Beta-lactams are cell wall inhibitors and all cell wall inhibiting antibiotics are bactericidal. Beta-lactam antibiotics target the bacterial cell wall, inhibiting its synthesis and causing the bacterial cell to die. This class of antibiotics is called bactericidal because they kill bacteria rather than just inhibiting their growth.

Optimal antibiotic therapy is based on the identification of the micro-organism and its susceptibility to antibiotics. However, the use of antibiotics in clinical practice is more complex for several reasons. In some situations, therapy cannot be delayed and must be

started empirically, which means that the pathogen cannot be identified. The use of bacteriological tests and blood cultures may be justified in more serious infections and in the absence of response to antibiotic therapy. Not performed routinely as it is not justified in current practice.

As endodontic infections are usually polymicrobial, involving a combination of gram-positive and gram-negative facultative and/or strict anaerobic bacteria, broad-spectrum antibiotics are typically prescribed. Amoxicillin is the most frequently prescribed antibiotic during endodontic treatment. (Keiser & Hargreaves, 2002)

A comprehensive understanding of the adversary is a crucial element in the successful resolution of any conflict. The rational use of antimicrobial agents commences with an understanding of the microorganisms most likely to be responsible for common dental infections of pulpal origin. The bacterial flora identified in endodontic infections is indigenous, comprising both Gram-positive and Gram-negative bacteria, and is predominantly anaerobic. A number of species have been identified as being associated with the development of acute apical abscesses. These species include dark-pigmented bacteria (*Prevotella* and *Porphyromonas*), eubacteria, fusobacteria and *Actinomyces*. (Colleagues for Excellence Colleagues for Excellence ENDODONTICS, 2012, p.4).

Among the major antibiotic-resistant bacteria, certain species, like Methicillin-Resistant Staphylococcus Aureus (MRSA), exhibit resistance to nearly all available antibiotics, making MRSA a prime example of extensive resistance. (Saadat et al., 2013)

“Bacteria showing resistance to common antibiotics have been isolated from deep neck infections of odontogenic origin as well as primary and persistent endodontic infections” (Germack et al., 2017, p.1).

Furthermore, molecular methods have identified a wide range of bacterial resistance genes in samples taken directly from infected root canals. (Dias et al., 2022)

The presence of a resistance gene in a sample does not necessarily indicate phenotypic resistance. However, proteomics studies have identified the expression of resistance factors, including TetR and beta-lactamase, in endodontic infections. The indiscriminate use of antibiotics can contribute to the selection of resistant microorganisms, and thus antibiotics should be prescribed with great caution. (Dias et al., 2022)

“Endodontic infections typically have a rapid onset and short duration, of to 7 days or less, particularly if the infective cause is eliminated” (Abraham et al., 2020, p.9).

“It is recommended that antimicrobial agents be used on an intensive basis with vigorous dosage for as short a period as the clinical situation permits. Treatment duration of 3–7 days is often sufficient to control the infection, but patients should be seen after 2 or 3 days to determine whether treatment should be stopped or continued” (Maslamani & Sedeqi, 2018, p.6).

The same idea was pointed out in a study from the United States where the authors say “Ideally, patients placed on antibiotics for an orofacial infection should be evaluated daily and the antibiotic therapy terminated once there is sufficient evidence that the patient’s infection is resolving or resolved. (Germack et al., 2017, p.6). In the same study, the authors state that patients with orofacial odontogenic infections who were treated with beta-lactam antibiotics for three days or more developed beta-lactamase-producing bacteria in at least 50% of cases (Germack et al., 2017).

This is the problem... In fact, beta-lactam antibiotics are effective against bacteria that do not produce beta-lactamase. And as cited before, if there is an acquisition of beta-lactamase producing bacteria, that means the antibiotic is no longer effective, resistance is acquired. This plays in favour of the use of clavulanic acid as it goes against enzyme resistance.

According to the Columbian study, which is the most recent study included in our systematic review, 80.3% prescribe antibiotics for 7 days, and only 1.9% suspend the prescription after the symptoms disappear. (Dias et al., 2022), this is not the way to reduce the problem of antimicrobial resistance. There is a commonly held assumption in medical practice that when antibiotics are prescribed patients should complete the entire course of treatment, this assumption is based on several reasons. Recent evidence is rethinking unnecessarily long courses of antibiotics in the light of concerns about antibiotic resistance. In the AAE guidelines the following principle is advanced, adapted from Dr. Thomas J. Pallasch “The shorter the duration of therapy the lower the risk to the patient for the development of … and a reduced risk of developing resistant microorganisms.” (Colleagues for Excellence Colleagues for Excellence ENDODONTICS, 2012, p.5)

In accordance with a Norwegian study, “Different universities teach different clinical conduct, often coloured by single individual teachers and their opinions, and sometimes there is an inexplicable ‘culture’ of using antibiotics in certain countries and work environments. A more systematic Pan-European and globally coordinated education on antibiotics and their use in dental clinics is needed. However, the question about too frequent and inappropriate antibiotic use versus development of resistance is first and foremost a population problem and should consequently be addressed using political means as carried out by the Norwegian National Assembly” (Preus et al., 2017, p.7).

4. Adequate prescribing and loading dose

“Due to the short half-life of antibiotics, a minimum serum inhibitory concentration is essential for the success of antibiotic therapy. Therefore, a higher initial dose (attack dose) is usually recommended to ensure antibiotic penetration into bone tissue in a concentration high enough to eliminate the microorganisms in the infection site.” (Dias et al., 2022, p.5).

Most antibiotics take 24-48 hours to take effect. This means that patients may not notice an immediate improvement in their symptoms. It may take a day or two for the medication to start reducing the infection and its symptoms. Therefore, healthcare providers need to monitor patients closely during this initial period to ensure that they are responding to treatment as expected and that there are no complications or adverse reactions. By monitoring the patient's condition during the first few days, healthcare providers can make any necessary adjustments to the treatment.

“Amoxicillin has a half-life of 1–1.5 h. A steady-state blood level would then be achieved in 3–7.5 h, thereby leading to a substantial delay in achieving therapeutic blood levels.” (Maslamani & Sedeqi, 2018, p.6) This means that the concentration of amoxicillin in the blood takes 3 to 7.5 hours to reach a consistent level at which the rate of absorption equals the rate of elimination. There is therefore a critical delay before the drug starts to work effectively, making a loading dose necessary in the treatment of acute odontogenic infections. A loading dose, also referred to in the literature as an ‘attack dose’, is an initial higher dose given at the start of treatment to rapidly achieve a therapeutic concentration in the bloodstream. Once the desired concentration has been achieved, the patient continues with a maintenance dose to maintain the drug level.

In only four out of the twelve studies reviewed, the authors mentioned information about a 'loading dose'. "A loading dose of double the maintenance dose is recommended for acute orofacial infections, achieving the goal of rapid, high blood levels rather than initiating therapy with the maintenance dose" (Maslamani & Sedeqi, 2018, p.6).

From data extracted in a Colombian study there was found that "243 professionals (75.9%) responded that they do not prescribe an attack dose" (Dias et al., 2022, p.4). Similarly, a study from the UAE reported that a "loading dose, in cases of infection, was prescribed by a fifth (21.3%; n = 37), with the majority appearing not to prescribe a loading dose" (Abraham et al., 2020, p.6).

"Literature shows that an antibiotic loading dose should be used whenever the half-life of the antibiotic is longer than 3 hours or whenever a delay of 12 hours or more is unacceptable to achieve therapeutic blood levels" (Abraham et al., 2020, p.9).

"Most antibiotics used for orofacial infections have half-lives of less than 3 hours, but the acute nature of these infections requires high therapeutic blood levels. Therefore, a loading dose may ensure rapid elevation of therapeutic blood levels of the antibiotic to help combat the infection efficiently" (Abraham et al., 2020, p.9).

A loading dose is intended to increase the effectiveness of antibiotics in acute dental infections. It is noteworthy that either our studies lack information on this practice or, where data are available, most dentists do not prescribe a loading dose.

In the ESE guidelines for penicillin V and amoxicillin indicate a loading dose of 1000mg, in the AAE guidelines no information about dosage is available. The AAE states that "The goal of antibiotic dosing is to achieve drug levels in the infected tissue equal to or exceeding the minimal inhibitory concentration of the target organism" (Colleagues for Excellence Colleagues for Excellence ENDODONTICS, 2012, p.6).

5. Patient influence on antibiotic prescription

The effectiveness of antibiotic prescriptions is highly dependent on patient adherence to the prescribed regimen, including correct use, dosage, duration of treatment and intervals between doses. Prescribing antibiotic therapy is the responsibility of the dentist, who is also responsible for providing clear instructions and educating patients about the importance of following the indications. Proper education includes being vigilant about

possible side effects and the need to consult the dentist if they occur. A follow-up consultation after two days is recommended to assess the status and effectiveness of the treatment, allowing the dentist to decide whether to continue or discontinue antibiotic therapy.

"The only guide for determining the effectiveness of antibiotic therapy, and, hence, the duration of treatment, is the clinical improvement of the patient. Patients on antibiotic therapy for orofacial infections should be clinically evaluated daily. When there is sufficient clinical evidence that the patient's host defences have regained control of the infection and that the infection is resolving or resolved, the antibiotic therapy should be terminated" (Maslamani & Sedeqi, 2018, p.6).

However, studies show that the decision-making process of dentists can be influenced by various factors, including patient pressure due to pain. Pain should be managed with analgesics, not antibiotics, as antibiotics are not indicated for conditions like pulpitis or apical periodontitis of pulpal origin according to current guidelines. Intense pain does not necessarily mean an infection, always think of inflammation.

According to a Pakistani "About 1/3rd of our sample considered prescribing antibiotics to be on the safe side, on the patient's insistence, or based on anecdotal experience, which is not recommended" (Ismail et al., 2018, p.4). According to a Columbian study "Dentists prescribe antibiotics to reduce the patient's pain, though there is no evidence in the literature justifying it" (Dias et al., 2022, p.5).

Patients have a responsibility as citizens to be aware of issues such as antimicrobial resistance. If patients were better educated and more aware of the risks involved, there would be a significant reduction in over-prescribing, particularly in relation to conflictual situations during consultations where patients put pressure on the professional to obtain a prescription for antibiotic therapy. This cause of over prescription should be eliminated.

"Antimicrobial stewardship should be deeply integrated in dental practice and oral health care. Moreover, through education and training, practitioners' antibiotic administration should be improved to reduce the number of unnecessary prescriptions, and patients' adherence to antimicrobial treatment should be enhanced to limit non-medical prescriptions." (D'ambrosio et al., 2022, p.9)

6. Limitations

The systematic review is subject to several limitations due to the risks of bias identified in the included studies. Sources of bias in this systematic review include publication bias since only articles in English and Portuguese were analysed.

All the included studies are observational studies. Two thirds of the included studies are cross sectional, one is a prospective study, one is a retrospective study, and the two remaining ones are surveys. Cross-sectional studies are limited in their ability to establish causality due to their single-time-point nature and are vulnerable to various biases.

Bias due to confounding and bias due to missing data, where the areas with the most 'moderate' signs are shown. (Figure 2 - ROBINS-I traffic light plot)

Moderate confounding bias in a study means that confounding variables affect the results, but not so much as to invalidate the results. It indicates that the relationship between exposure and outcome is somewhat biased, but the effect is moderate and should be carefully considered and adjusted for. A moderate bias due to missing data in a study means that the missing information affects the results noticeably, but not severely enough to invalidate the results. This bias affects the validity and reliability of the study but doesn't completely undermine the conclusions.

The inclusion of predominantly observational studies and significant heterogeneity among studies further complicate the interpretation and generalizability of the results.

Furthermore, as most studies have used questionnaires to assess prescribers' self-reported knowledge and practice, they are susceptible to social desirability bias, as respondents may give answers that they consider correct or acceptable, thus masking the true extent of inappropriate antibiotic prescribing practices.

These limitations should be considered when interpreting the findings and making recommendations based on this systematic review.

7. Future research

The correct preliminary diagnosis is important for the success of an effective antibiotic therapy. When feasible, a correct preliminary diagnosis supported by microbiological assessments to identify the species and strains involved, can be helpful on the success of an effective antibiotic therapy. Targeted antibiotic therapy can help mitigate the emergence of antibiotic-resistant strains by avoiding the unnecessary use of broad-spectrum antibiotics. Finally, the judicious use of the appropriate dosage for the shortest time should be done.

It is a challenge to use biological samples in clinical practice. However, further studies should be conducted to explore the importance of identifying specific bacteria, and more specific indications for this should be included in guidelines. Improved education, updated guidelines, and better access to diagnostic tools could enhance the precision of antibiotic use in dentistry. The established guidelines are rigorously developed and include studies based on antibiograms. Given the challenges associated with using biological samples in clinical practice, it is preferable to consult the guidelines rather than prescribe antibiotics empirically.

There is confusion regarding the optimal duration of antibiotic prescriptions and the necessity of modifying the antibiotic if the treatment is not effective. It is imperative that questions such as whether to extend the duration of antibiotic therapy or to switch antibiotics during treatment are clarified and included in guidelines. As a result of this lack of clarity, dentists frequently make their own decisions. For example, a study conducted in the UAE revealed that 22.4% of dentists opted to extend the duration of antibiotic therapy in cases where it was not effective. In a Colombian study, 52.5% of dentists altered the antibiotic regimen when the initial treatment was unsuccessful.

Future research should focus on the problems that have been encountered.

5. Conclusion

There is clear evidence indicating that antibiotics are often prescribed for conditions where their effectiveness is no greater than other therapeutic options.

The complexity of antibiotic resistance in the context of endodontic infections represents a significant challenge. This complexity arises from the capacity of bacteria to exchange genetic material, including genes that confer antibiotic resistance, with other bacteria in root canals. Infected root canals can host a variety of bacterial species, and the proximity of these organisms facilitates the exchange of resistance genes. Some bacteria not only develop antibiotic resistance but also gain the capacity to produce biofilms, which are dense protective layers that make them much more difficult to eliminate with antibiotics. Consequently, endodontic infections can become reservoirs for antibiotic resistance through gene transfer and biofilm formation, emphasizing the critical role of dentists in the emergence and propagation of antibiotic resistance.

To address these challenges, it is imperative that more explicit directives are established to ensure a comprehensive understanding of antibiotic prescriptions. It is imperative that a comprehensive diagnostic assessment is conducted to avoid misdiagnosis and inappropriate antibiotic treatment for viral infections and other non-bacterial diseases. Misdiagnosis can result in ineffective treatment, incorrect prescriptions, and the development of antimicrobial resistance. Guidelines do not represent absolute perfection as they are not tailored to every individual clinical case. However, the guidelines should be consulted, as they exist precisely for that purpose.

In order to improve the efficacy of antibiotic utilisation, it is imperative to improve the knowledge and awareness of both dentists and patients regarding the risks associated with antimicrobial resistance.

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