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Review

Resistance profiles to antimicrobial agents in bacteria isolated from acute endodontic infections: systematic review and meta-analysis

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ABSTRACT

Infected root canal or acute apical abscess exudates can harbour several species, including *Fusobacterium*, *Porphyromonas*, *Prevotella*, *Parvimonas*, *Streptococcus*, *Treponema*, *Olsenella* and not-yet cultivable species. A systematic review and meta-analysis was performed to assess resistance rates to antimicrobial agents in clinical studies that isolated bacteria from acute endodontic infections. Electronic databases and the grey literature were searched up to May 2015. Clinical studies in humans evaluating the antimicrobial resistance of primary acute endodontic infection isolates were included. PRISMA guidelines were followed. A random-effect meta-analysis was employed. The outcome was described as the pooled resistance rates for each antimicrobial agent. Heterogeneity and sensitivity analyses were performed. Subgroup analyses were conducted based upon report or not of the use of antibiotics prior to sampling as an exclusion factor (subgroups A and B, respectively). Data from seven studies were extracted. Resistance rates for 15 different antimicrobial agents were evaluated (range, 3.5–40.0%). Lower resistance rates were observed for amoxicillin/clavulanic acid and amoxicillin; higher resistance rates were detected for tetracycline. Resistance rates varied according to previous use of an antimicrobial agent as demonstrated by the subgroup analyses. Heterogeneity was observed for the resistance profiles of penicillin G in subgroup A and for amoxicillin, clindamycin, metronidazole and tetracycline in subgroup B. Sensitivity analyses demonstrated that resistance rates changed for metronidazole, clindamycin, tetracycline and amoxicillin. These findings suggest that clinical isolates had low resistance to β-lactams. Further well-designed studies are needed to clarify whether the differences in susceptibility among the antimicrobial agents may influence clinical responses to treatment.

1. Introduction

Endodontic infections occur due to caries or dental trauma when opportunistic bacterial pathogens gain access to the necrotic dental pulp or periapical tissues [1,2]. The infected root canal or acute apical abscess can harbour several species, including species belonging to the genera *Fusobacterium*, *Porphyromonas*, *Prevotella*, *Parvimonas*, *Streptococcus*, *Treponema* and *Olsenella* spp. as well as not-yet cultivable species [3,4]. Despite the broad range of species that have been isolated in acute endodontic infections, the microbial profiles in these communities show few shared species and a great diversity among subjects [5]. Only the strict anaerobes *Olsenella profusa* and the taxon *Dialister* E1 were detected in all of the samples analysed by Jacinto et al [6] and Munson et al [7], respectively. However, *Tannerella forsythia*, *Shuttleworthia satelles* and *Filifactor alocis* were only detected in one sample [6]. Interactions among biofilm community members are responsible for the presence of painful symptomatology [8,9]. Clinical signs and symptoms have been associated with specific bacterial species: pain with *Peptostreptococcus micros*, *Prevotella intermedia/nigrescens* and *Eubacterium* spp.; tenderness to percussion with *Porphyromonas*, *Peptostreptococcus* and *Fusobacterium* spp.; and swelling with *Peptostreptococcus*, *Porphyromonas* and *Fusobacterium* spp [3].

Clinical management of an acute endodontic infection involves root canal debridement and local drainage, whenever possible. In specific situations, antibiotics may be prescribed as a complementary

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measure, especially for: abscesses that are associated with systemic involvement, including fever, malaise and lymphadenopathy; disseminating infections resulting in cellulitis, progressive diffuse swelling and/or trismus; and abscesses in systemically compromised patients who are at an increased risk of a secondary infection following bacteraemia [2]. The choice of antibiotic is usually based upon previously published susceptibility, testing and clinical trials [1]. The β-lactam antibiotics, especially penicillin, have been recommended as being the first-line antibiotics because they work well against most causative bacteria and because penicillin has a low incidence of side effects [10,11]. Clindamycin has often been recommended in cases of allergy to penicillin or when penicillin has not been effective [10–12]. In the latter clinical situation, β-lactamase inhibitors such as clavulanic acid in a combination with amoxicillin have also been indicated to extend the spectrum of coverage [10,11].

The emergence of antibiotic-resistant bacterial strains has increased, especially due to excessive and incorrect use of these particular agents [13]. Gomes et al reported an increase in resistance among anaerobic bacteria isolated from primary endodontic infections over a 9-year period in a Brazilian population [14]. Rational prescription of antimicrobial agents must be based on the resistance patterns of the micro-organisms, the characteristics of the patient (immunosuppression, previously reported allergy) and the drug's characteristics (cost, effectiveness, adverse effects). From a microbiological viewpoint, it requires a comprehensive analysis of the resistance profiles among microbial isolates from endodontic infections. Recently, Moraes et al performed a systematic review to describe the presence of resistance genes to antimicrobial agents in oral environments such as saliva, dental biofilm and endodontic infections [15]. However, there is a lack of information regarding whether the microbial isolates from endodontic infections expressing these virulence factors are conveyed as resistance to antimicrobial agents.

Therefore, the aim of this systematic review and meta-analysis was to depict the antimicrobial resistance profiles of bacterial isolates from primary acute endodontic infections as reported in the current literature.

2. Materials and methods

2.1. Focused patient, intervention, comparison and outcome (PICO) question

A systematic review was performed using the checklist items reported by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [16]. The following focused question was developed in accordance with the recognised PICO format: 'What are the resistance rates to antimicrobial agents in studies that have isolated bacteria from those patients with acute endodontic infections?'

2.2. Eligibility criteria

Clinical studies evaluating the antimicrobial resistance of bacterial isolates in primary acute endodontic infections in humans by disk diffusion or Etest (bioMérieux, Marcy-l'Étoile, France) methods were included in the survey.

2.3. Search strategy and information sources

Electronic searches were performed in PubMed, the Cochrane Library (all results), ISI Web of Knowledge, Scopus, LILACS, OpenGrey, SciELO, the CAPES database, the Grey Literature Report, Curtin University, GreyNet International and the Grey Literature Dentistry Database. Hand-searching was independently and extensively performed by two authors (PML and FM) of the reference sections of the selected studies and the available systematic reviews. No language restriction was applied to the search, except for ISI Web of Knowledge. The search comprised those articles published from the inception of the database up to May 2015. Fig. 1 describes the search strategies that were adopted in the study for the PubMed database. This strategy was also employed and adapted for the other databases.

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((("dental pulp cavity"[MeSH Terms] OR ("dental"[All Fields] AND "pulp"[All Fields] AND "cavity"[All Fields]) OR "dental pulp cavity"[All Fields] OR ("root"[All Fields] AND "canal"[All Fields]) OR "root canal"[All Fields]) OR ("periapical abscess"[MeSH Terms] OR ("periapical"[All Fields] AND "abscess"[All Fields]) OR "periapical abscess"[All Fields])) AND ("microbial sensitivity tests"[MeSH Terms] OR ("microbial"[All Fields] AND "sensitivity"[All Fields] AND "tests"[All Fields]) OR "microbial sensitivity tests"[All Fields] OR ("microbial"[All Fields] AND "sensitivity"[All Fields] AND "test"[All Fields]) OR "microbial sensitivity test"[All Fields]) AND "humans"[MeSH Terms]
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Fig. 1. Search strategy adopted for the study, presenting the MeSH keywords and search terms for antimicrobial activity and the resistance of bacterial isolates from acute endodontic infections, as performed in the PubMed database and adapted for other databases.

The following limits were used for the ISI Web of Knowledge database: Database (Web of Science™ Core Collection, Biological Abstracts® and the SciELO Citation Index); Areas of Research (Dentistry and Oral Surgery Medicine, Infectious Diseases, Pharmacology Pharmacy, Microbiology); Document Type (article); and Language (English, Portuguese and Spanish).

2.4. Study selection and data collection processes

Following title review and abstract selection, full-text articles were revised based upon the following inclusion criteria: clinical studies in humans that evaluated the antimicrobial resistance of bacterial isolates in primary acute endodontic infections by disk diffusion or Etest methods. Exclusion criteria comprised: (i) studies that did not specify the cause of the odontogenic abscess or the odontogenic infection (whether endodontic or not) or that did not specify the microbial susceptibility results for each source of infection; (ii) studies that did not specify whether the endodontic infection was acute or chronic; and (iii) studies that did not report the method used to evaluate antimicrobial resistance or if another method was used. After reading the included articles, an independent manual search was performed by two of the authors (PML and FM) in the reference section and for the authors of the selected articles.

Data regarding the research group, number of subjects included in the study, description of the recruitment, antibiotic exposure as an exclusion criteria, sample size, methods for sample size determination, conflicts of interest, microbial source/sampling, methods used to measure outcomes, antimicrobial agents tested, statistical analysis, number of bacterial strains and number of resistant strains were collected from all of the studies.

The overall percentage resistance to a specific antimicrobial agent was calculated for each study, regardless of the bacterial species tested. The overall percentage resistance for each tested antimicrobial agent was the average between the total number of resistant strains and the total number of tested strains. Strains that had an intermediate profile were considered susceptible to the antimicrobial agent. According to the National Committee for Clinical Laboratory Standards (NCCLS) [17], the 'intermediate' category included isolates with minimum inhibitory concentrations (MICs) of an antimicrobial agent that approach usually attainable blood and tissue levels and for which response rates may be lower than that