Distribution of Genes Related to Antimicrobial Resistance in Different Oral Environments: A Systematic Review

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Abstract

Introduction: The oral cavity is the main source of microorganisms for odontogenic infections. It is important to perform an extensive analysis regarding the reports on the presence of bacteria that carry resistance genes to antimicrobial agents. The aim of the study was to verify the reports on the distribution of genes associated with resistance to antibiotics prescribed in dentistry in different human oral sites. **Methods:** A systematic review was conducted in electronic databases and gray literature to analyze clinical studies that detected genes of bacterial resistance to antibiotics in saliva, supragingival biofilm, and endodontic infections. Data regarding the research group, geographic location, sample source, number of subjects, methods for sample analysis, the targeted gene groups, and the detection rates were collected. Descriptive data analysis was performed. **Results:** Preliminary analysis was performed in 152 titles; 50 abstracts were reviewed, and 29 full texts were obtained. Nine articles matched the inclusion criteria (saliva = 2, supragingival biofilm = 1, and endodontic infections = 6). The presence of 33 different targeted genes was evaluated. The most frequently investigated groups of genes were tetracycline and lactamics (*tetM*, *tetQ*, *tetW*, and *cfx*A). There was a wide range for the detection rates of each resistance gene among studies and for each specific gene group. **Conclusions:** This systematic review highlights the presence of resistance genes to antimicrobial agents in saliva, dental biofilm, and endodontic infections, especially for tetracycline and lactamics. There is a lack of reports on the presence of genes and resulting outcomes obtained through the therapeutic approaches for infection control. *(J Endod 2015;41:434–441)*

Key Words

Dental plaque, dental pulp cavity, drug resistance, saliva

The human mouth harbors a wide number of microorganisms, comprising the commensal microbiota. It has an important role in maintaining oral and systemic health. The microbiota of the mouth is the source for microorganisms associated with dental caries, endodontic diseases, and periodontal diseases (1). Oral bacteria start colonizing the root canal system after pulp necrosis, remaining suspended in the root canal (planktonic state) or attached to its walls (biofilms) (2). They can reach the apical tissues causing extraradicular infections and constitute complex microbial communities associated with acute apical abscesses (3), extraradicular biofilms (4), and persistent infections (5). The composition of microbial communities associated with endodontic infections is heterogeneous and can be modulated by several factors such as the geographic location (6), the presence or absence of symptoms (7), and the clinical condition (8). Some studies also report distinct microbial profiles in paired samples from root canals and abscesses collected from the same patient (3). Few representatives of the domains Eukarya and Archea have been described; the domain Bacteria is the most predominant and diverse in endodontic infections (2). After a comprehensive review on the microbial communities associated with endodontic infections, Siqueira and Rôças (2) emphasized the need for determining microbial functional roles in the community and the susceptibility to antimicrobial treatment procedures.

Oral or parenteral antibiotics are generally considered adjunctive therapy for urgency endodontic treatment. Their value should not be underestimated, especially when drainage cannot be achieved or the infection shows signs of local extension or systemic involvement (9). Beta-lactam, tetracycline, and macrolide antibiotics have been prescribed in endodontics, especially for the treatment of acute apical abscesses associated with systemic involvement, spreading infections, abscesses in medically compromised patients who are at increased risk of a nonoral secondary infection after bacteremia, prophylaxis for medically compromised patients during routine endodontic therapy, and replantation of avulsed teeth (10). Local application of antimicrobial agents has been considered a possibility to improve root canal disinfection during the chemomechanical preparation (11, 12) or as an intracanal medicament (13). However, it should be emphasized that the use of antibiotics instead of biocides such as hypochlorite or chlorhexidine appears unwarranted, mainly because of the narrower spectrum of activity and resistance (14).

Antibiotic resistance is a phenomenon of crucial importance in the treatment of diseases caused by pathogenic microorganisms (15). Bacterial resistance to antibiotics is multifactorial. Antibiotic resistance occurs by both intrinsic defenses (16) and genetic mutation in bacteria. Some mechanisms of bacterial resistance to antibiotics have been attributed to the resistance genes. Diverse resistance genes have been found

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and characterized in human microflora, which can operate as a reservoir for antibiotic-resistant bacteria (17).

The objective of this systematic review was to evaluate the distribution of genes of bacterial resistance to antibiotics in different sites of the oral cavity. A search strategy was formulated to answer a question in the PICO (Population, Intervention, Comparison, Outcome) format, defining inclusion and exclusion criteria. The question was framed as follows: In the oral sites saliva, supragingival biofilm, and endodontic infections, how are distributed genes associated with bacterial resistance to antibiotics frequently prescribed in dentistry?

Materials and Methods

A systematic review was performed to check all clinical studies that detected genes of bacterial resistance to antibiotics in 3 sites of oral cavity: saliva, supragingival biofilm, and endodontic infections. The terms were used in various combinations in the electronic databases as follows: Medline (PubMed), Embase, Web of Science, Scopus, and OpenGrey. No language restriction was applied to the search. Figure 1 describes the search strategy adopted in the study. The search comprised articles published until January 14, 2014. The references reported on the selected articles were also reviewed.

After title screening and abstract analysis, the full text of each study was obtained. The relevance of each study to the question of interest was determined through inclusion and exclusion criteria. The full texts of the articles were revised by 2 reviewers (F.M. and L.C.M) based on the following inclusion criteria:

1. Clinical studies in healthy patients or in patients with oral disease (cross-sectional or longitudinal studies)
2. Studies that detected bacterial resistance genes of antibiotics by molecular techniques
3. Studies with samples collected from oral cavity (saliva, supragingival biofilm, or root canal with primary endodontic infection)

Exclusion criteria comprised the following:

1. Literature reviews
2. *In vitro* studies
3. Studies that analyzed mixed samples from different environments
4. Studies that detected genes in other environments besides those cited in the inclusion criteria
5. Studies that did not use molecular methods for detection of the presence of the resistance genes
6. Studies in which the objective was not the detection of resistance genes
7. Lack of data

Terms: ("mouth"[MeSH Terms] OR "mouth"[All Fields] OR ("oral"[All Fields] AND "cavity"[All Fields]) OR "oral cavity"[All Fields]) AND ("drug resistance, microbial"[MeSH Terms] OR ("drug"[All Fields] AND "resistance"[All Fields] AND "microbial"[All Fields]) OR "microbial drug resistance"[All Fields] OR ("antibiotic"[All Fields] AND "resistance"[All Fields]) OR "antibiotic resistance"[All Fields]) AND ("genes"[MeSH Terms] OR "genes"[All Fields] OR "gene"[All Fields])

Figure 1. The search strategy adopted for the study, presenting the MeSH keywords and search terms for the presence of resistance genes to antimicrobial agents in the oral environment.

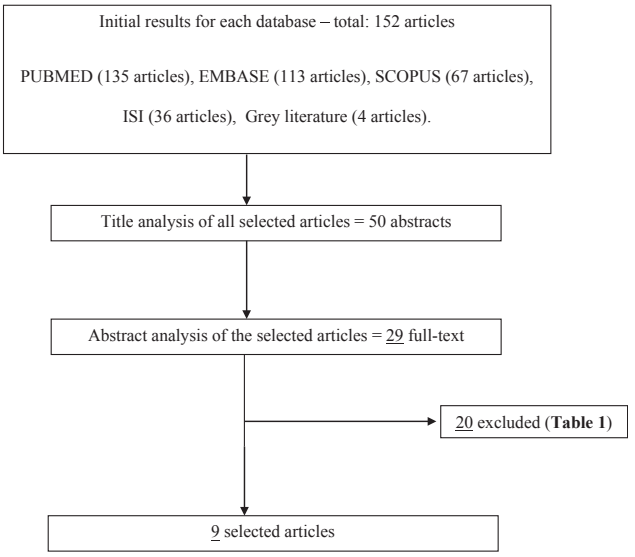

Figure 2. Results after the search strategy developed to find studies related to the presence of resistance genes to antimicrobial agents in different oral environments.

Data regarding research group, geographic location, sample source, number of subjects included in the study, methods for sample size determination, statistical analysis, the targeted genes, and their detection rates were collected from the studies. Because of the methodologic differences among the studies, it was not possible to perform a meta-analysis. Descriptive data analysis was performed.

Results

Considering all the databases, a total of 152 titles were identified after subtraction of duplicates for preliminary analysis. After title screening, 50 abstracts were revised, and full texts of 29 studies were obtained (Fig. 2). The 20 excluded articles are listed in Table 1, and the reasons for their exclusion are also shown.

Nine articles matched the inclusion criteria regardless of the oral environment. There were 2 articles for saliva samples, 1 for supragingival biofilm, and 6 studies on primary endodontic infections. There was no age limit in the search, and only 1 of the selected articles reported data for children. Tables 2, 3, and 4 provide information about the selected studies. They were performed in different periods of time (from 2003–2014), and the samples were collected in Japan, the United States, Brazil, and European countries. The great majority of the authors reported ethics statements and/or conflicts of interest, except in 1 study (38). There was no description for the sample size determination methods adopted. The most frequently adopted exclusion criteria were previous exposure to antimicrobial agents, ranging from 1 to 6 months. The presence of resistance genes was assessed in clinical isolates (38–40, 43, 44, 46) and in samples from each environment (41, 42, 45). The presence of resistance genes in saliva samples was determined only from healthy subjects (38, 41). The only study that tested resistance genes in supragingival biofilm was conducted in children (39). Endodontic samples were collected from root canals (symptomatic and asymptomatic cases) and apical swelling. Descriptive statistics were reported in all studies. Inferential statistics were used to compare the prevalence of specific genes in the groups (primary vs persistent infections, preoperative vs preobturation samples, before vs after root canal preparation, and abscess vs asymptomatic apical periodontitis).