Prevalence of *Treponema* Species Detected in Endodontic Infections: Systematic Review and Meta-regression Analysis

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Abstract

Introduction: This systematic review and meta-regression analysis aimed to calculate a combined prevalence estimate and evaluate the prevalence of different *Treponema* species in primary and secondary endodontic infections, including symptomatic and asymptomatic cases. **Methods:** The MEDLINE/PubMed, Embase, Scielo, Web of Knowledge, and Scopus databases were searched without starting date restriction up to and including March 2014. Only reports in English were included. The selected literature was reviewed by 2 authors and classified as suitable or not to be included in this review. Lists were compared, and, in case of disagreements, decisions were made after a discussion based on inclusion and exclusion criteria. A pooled prevalence of *Treponema* species in endodontic infections was estimated. Additionally, a meta-regression analysis was performed. **Results:** Among the 265 articles identified in the initial search, only 51 were included in the final analysis. The studies were classified into 2 different groups according to the type of endodontic infection and whether it was an exclusively primary/secondary study (n = 36) or a primary/secondary comparison (n = 15). The pooled prevalence of *Treponema* species was 41.5% (95% confidence interval, 35.9–47.0). In the multivariate model of meta-regression analysis, primary endodontic infections (P < .001), acute apical abscess, symptomatic apical periodontitis (P < .001), and concomitant presence of 2 or more species (P = .028) explained the heterogeneity regarding the prevalence rates of *Treponema* species. **Conclusions:** Our findings suggest that *Treponema* species are important pathogens involved in endodontic infections, particularly in cases of primary and acute infections. *(J Endod 2015;41:579–587)*

Key Words

Endodontic infection, meta-regression analysis, systematic review, *Treponema*

Endodontic infection is polymicrobial and causes disruption of host homeostasis. The increase in infection intensity is intimately linked with the complexity and physiology of bacteria biofilm, host genetic heritage, and systemic disorders (1). Symptoms emerge by the enhancement of biofilm pathogenicity/complexity (2). Actually, near 700 bacterial species were described in the oral cavity, and more than half are uncultivable, being detected only by molecular systems (3).

Biofilm organization changes as the endodontic infection advances, with an increase of some bacterial species such as *Porphyromonas spp.*, *Tannerella spp.*, and *Treponema spp.*, which are correlated with endodontic infection, periodontitis, and necrotizing types of gingivitis. In addition, these species have been associated with an increased risk of developing cardiovascular diseases, low birth weight, and diabetes mellitus (4, 5).

Spirochetes present a spiral-shaped or flat waveform, and their phylum can be divided into 3 families (*Spirochaetaceae*, *Brachyspiraceae*, and *Leptospiraceae*) with *Treponema, Borrelia*, and *Leptospira* representing a concern to human health. In a seminal study of endodontic infections published in 1894, Willoughby Dayton Miller suggested that spirochetes could play a role in the etiology of abscesses (6). They were firstly observed in humans by Antonie van Leeuwenhoek at the end of the 17th century (7) and then initially cultured by Noguchi in 1912 (8). Microscopic studies have revealed the presence of spirochetes in infections of endodontic origin, including abscessed teeth (6, 9, 10).

Oral spirochetes fall within the genus *Treponema* and have been linked to several oral diseases. The percentage of *Treponema* species in oral biofilm from endodontic infection and periodontal pockets is increased (11–13). These obligatory anaerobic bacteria may represent 50%–89% of the total amount of bacteria in an endodontic infection, and a large body of evidence supports their relationship with clinical signs of inflammation, connective tissue destruction, and so on (14, 15). Spirochetes range from 5–20 μm in length and 0.1–0.5 μm in diameter, presenting inner and outer membranes and most lacking lipopolysaccharides, which is replaced by lipoproteins and glycolipids (4).

Different molecular methods have been used to detect *Treponema* species from root canal infections. The presence of *Treponema* members can be underestimated by

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the sensitivity of the technique because their low prevalence could not trigger the minimum detection threshold of the technique. Among the most cited and detected oral *Treponema* species, *Treponema denticola* and *Treponema medium* are asaccharolytic, whereas *Treponema socranskii* and *Treponema maltophilum* are saccharolytic (2, 16). Around 6% of *T. denticola* genomes encode motility and chemotaxis genes, implying its ability to be probably chemoattracted by serum, albumin, or glucose although this remains unclear (17, 18). Jacinto et al (19) detected no *Treponema* species in endodontic infection when the bacterial 16 ribonucleic RNA gene was amplified and cloned. In contrast, Siqueira and Rôças (20), Montagner et al (21), and Baumgartner et al (16) found *T. socranskii* to be frequently recovered from root canal infection (25%, 75%, and 44.9%, respectively).

Based on epidemiologic studies relying on molecular genetic evidence, different spirochetal species have been suggested to be candidate endodontic pathogens (15, 16, 22–24). About 90% of the samples from different types of endodontic infections have been shown to harbor at least 1 species of spirochetes (15, 20, 25).

It is important to highlight that an overall analysis of data from studies performed to evaluate the presence and methods of detection of *Treponema* species in endodontic infections has not been performed yet. The main advantage of a systematic review with a statistical approach, such as meta-regression, is to address sources of bias with the goal of producing the most valid and precise estimate of effect as possible (26). Therefore, the main purpose of this study was to conduct an extensive and systematic review of the literature on the prevalence of different *Treponema* species in endodontic infections in order to calculate a pooled prevalence estimate and determine factors implicated in the variability of estimates by assuming the assumptions of different estimates based on the types of endodontic infection as well as on the symptomatic and asymptomatic cases.

Materials and Methods

Focused Question

Are there differences in *Treponema* species involved in primary and secondary endodontic infections? Is the prevalence of *Treponema* species present in symptomatic and asymptomatic endodontic infections different? Moreover, what are the most common detection methods used?

Search Strategy

The literature was searched in a structured way to identify studies that analyzed the presence of *Treponema* species in endodontic infection. Electronic database searches of MEDLINE/PubMed, Embase, Scielo, Web of Knowledge, and Scopus were performed up to and including March 2014 by using Medical Subject Heading terms and other keywords in the following combinations "Dental Pulp Diseases OR Periapical Diseases OR endodontic infection AND Treponema." A subsequent screening was performed at the title and abstract level before application of the inclusion and exclusion criteria. Studies not presenting clear information were included for complete analysis.

Additional publications were screened by the same 2 authors using a hand search of the reference lists of the studies that were found to be relevant in the previous step. Cases of disagreement between authors were solved after discussion. Predefined data collection work sheets were used for the assessment of each selected publication.

Studies were included based on the following inclusion criteria:

1. Original studies
2. In humans over 18 years old
3. With any type of endodontic infection
4. Prevalence rates of at least 1 *Treponema* species
5. Clear statement of the method used for bacteria detection
6. Publication in English

Studies were eliminated if the inclusion criteria were not met or if they presented any of the following exclusion criteria:

1. It was an *in vitro* or animal study, case report, review article, or opinion article.
2. Prevalence rates or data that allowed their calculation were absent.
3. Study did not evaluate the presence of at least 1 *Treponema* species.
4. A description of the type of endodontic infection was absent.
5. The publication was based on a population that was part of another study.
6. There was a lack of clear definition of the method used for bacteria detection.
7. The study was conducted in any other language than English.

Data Extraction

Prevalence data on all *Treponema* species were collected and calculated if necessary. In cases when more than 1 species was detected when there was no information about the concomitancy between the subjects, only the most prevalent species was considered for meta-analysis. The endodontic clinical diagnosis was determined by information presented by the authors in their respective studies. Cases described as "apical periodontitis" with symptoms or "exacerbated apical periodontitis" were classified as "symptomatic apical periodontitis." Additionally, when different diagnoses were presented in the same article, the prevalence was entered in the analysis considering the evaluated cases and diagnosis (acute apical abscess [AAA], symptomatic apical periodontitis [SAP], or asymptomatic apical periodontitis [AAP]). Data regarding the site of collection (root canal, purulent exudate, or apical cyst), type of infection (primary or secondary), method of bacteria identification (polymerase chain reaction [PCR] assay, nested PCR, real-time PCR, dot blot PCR, checkerboard, or microarray), geographic location (South America, North America, Europe, Asia, or Middle East), presence of more than 1 species (only 1 or 2 or more), and most prevalent species were assessed. Studies whose prevalence data could not be obtained were excluded from the review. When a comparison between different identification methods was performed, only the method with the highest prevalence was considered for statistical analysis.

Statistical Analysis

The estimated global prevalence of *Treponema* species was calculated by using both fixed- and random-effects models. When heterogeneity was statistically significant ($P < .05$), the random-effects model was used. Meta-regression was used to identify possible sources of heterogeneity between studies. This analytic strategy evaluated which variables affected the results. Initially, univariate analysis was performed, and all related variables ($P \leq .20$) in the univariate analysis were included in the final multivariate meta-regression model. Only variables with $P < .05$ in the final model were considered statistically significant. At this stage, the pooled estimates for each diagnosis and type of infection were determined. All analyses were performed by using the software STATA 12.0 (Stata Corp, College Station, TX).

Results

The literature search revealed 265 articles. From this total, 84 studies were duplicated and removed, leaving 181 articles for review consideration. A subsequent screening was performed at the title and abstract level, and then inclusion and exclusion criteria were applied.