Review Article

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Persistence of bacteria and its role in endodontic treatment failure

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ABSTRACT

Bacterial persistence has been reported to play critical roles in endodontic treatment failure, which attribute to deficient root canal filling and inadequate chemomechanical preparation. The persistence of bacteria to the different eradication approaches during endodontic treatment has been an area of interest in the field of dentistry due to the different roles by which these bacteria might impact endodontic treatment and can even lead to treatment failure. The present investigation provides evidence regarding the persistence of bacteria and its role in the failure of endodontic treatment. At first, we provided an overview of the potential role that bacterial infections might play in endodontic treatment and how the outcomes can be potentially impacted. Then, we discussed the virulence factors that help the different organisms to persist against the different eradication approaches, which can finally lead to the development of endodontic treatment failure. Our findings show that *E. faecalis* is the most prevalent bacteria causing endodontic treatment failure. However, many studies have reported that other bacteria and pathogens might also be prevalent and exceed the rate of *E. faecalis*. This indicates the importance of detecting appropriate biofilms to adequately eradicate the underlying pathogens and enhance the treatment and prognostic outcomes.

Keywords: Endodontics, Bacteria, E. faecalis, Pathogenesis, Persistance, Infection, Periodontitis

INTRODUCTION

Endodontics is a widely accepted approach that mainly aims at eradicating any bacterial infections, with estimated success rates of 86-98%. The clinical

manifestations and radiological findings can adequately determine the success and failure of these approaches. Bacterial persistence has been reported to play critical roles in endodontic treatment failure, which attribute to

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deficient root canal filling and inadequate chemomechanical preparation.¹

The impact of bacterial persistence on endodontic treatment failure has been extensively studied in the literature among the different investigations of variable study designs. Endodontic infections and treatment failure are mainly attributable to the presence of several microorganisms, which are usually isolated as biofilms or planktonic cells. These gatherings provide the underlying microorganisms with a suitable environment where they can live and multiply. Furthermore, evidence indicates that such environments provide the bacteria with adequate protection against host immune defense mechanisms, antimicrobial drugs, and virulence of other microbial pathogens, and therefore, the virulence and pathogenicity of the microorganisms within the biofilm increases with time.²

The persistence of bacteria to the different eradication approaches during endodontic treatment has been an area of interest in the field of dentistry as a result of the different roles by which these bacteria might impact endodontic treatment and can even lead to treatment failure.³ In the present literature review, we aim to elaborate on the prevalence of the different bacteria, their persistence, and associated mechanisms, in addition to their roles in the failure of endodontic treatment.

LITERATURE REVIEW

This literature review is based on an extensive literature search in Medline, Cochrane, and EMBASE databases on which was performed 3rd October 2021 using the medical subject headings (MeSH) or a combination of all possible related terms, according to the database. To avoid missing poetential studies, a further manual search for papers was done through Google Scholar, while the reference lists of the initially included papers. Studies discussing bacteria and its role in endodontic treatment failure were screened for useful information, with no limitations posed on date, language, age of participants, or publication type.

DISCUSSION

Overview

It should be noted that evidence shows that it is not always clear whether an endodontic infection has been caused by the impact of this biofilm or not. Accordingly, a previous investigation by Parsek and Singh suggested some criteria that can indicate whether the endodontic infection was primarily caused by a biofilm or not. The bacteria must be associated or attached to a surface, and microcolonies should be discovered on the different tissues where these microorganisms were suspected. The bacterial microcolonies should be surrounded by an extracellular matrix, which usually limits the spread of these microorganisms into a certain area. The elimination of these microcolonies has also been demonstrated to be

extremely difficult by antibiotics. It has been furtherly demonstrated that biofilms can be located extra-or intraradicular. Estimates show that most of the cases are present intra-radicular (77%), while in a small percentage (6%), the location of the biofilm is intra-radicular. Furthermore, evidence demonstrates that peripheral lesions are usually associated with intra-radicular biofilms, unlike what has been expected. Moreover, evidence shows that these lesions are usually present in cysts more than granulomas, and the frequency difference has been statistically significant.^{4,5} Further studies also showed that E. faecalis are able to induce their pathogenesis without the help of other bacteria. Furthermore, the release of different endotoxins. enzymes, and surface adhesions was also reported, gelatinase. including cytolysin, hyaluronidase, extracellular superoxide, and lipoteichoic acid.6 The adhesion substances are found as intermediates between the host cell and the pathogen to facilitate the transmission of the plasmid to the pathogen. Moreover, it has been demonstrated that these mechanisms enhance the binding ability of the pathogens to the surrounding dentin and collagen fibers type I. Therefore, increase their virulence, and making them more resistant to neutrophils. Microorganisms that can produce adhesion molecules can also influence the release of tumor necrosis factor- α from the surrounding macrophages and interferon-γ, and tumor necrosis factor-β from the surrounding T-lymphocytes. These substances are mainly responsible for the process of bone resorption. In another context, interferon molecules are mainly responsible for significant tissue damage that is mediated by the increased release of superoxide anions and hydrogen peroxide.^{6,7}

Pathogenesis

Many previous investigations have reported the prevalence of several bacterial pathogens in relation to endodontic infections, and subsequent treatment failure. Among the different investigations, it has been reported that E. faecalis has the highest prevalence rates among the different microorganisms. E. faecalis is an opportunistic anaerobic gram-positive pathogen that survives during unfavorable environments due to the various mechanisms that the pathogen has to overcome the different circumstances. For instance, previous reports show that the organism can build a biofilm, survive exposure to Ca(OH)₂ solutions, with an estimated pH value of 11.5, suppress the action of the different immune cells, survives at different temperatures (between 10 and 60 °C), live at an alkaline medium, and with and without O₂ supplementation.⁸ Many other mechanisms were also proposed, including adherence to collagen, the ability to use fluids within the periodontal ligament as their nutrients, invasion of the dentinal tubules, surviving high salinity, having a large profile of antimicrobial resistance, including azithromycin and erythromycin, in addition to being able to survive with no nutrients and in the presence of intracranial irrigants and antimicrobials.^{9,10} The relationship between E. faecalis biofilms during

endodontic treatment and surrounding collagen fibers was previously investigated, and it largely depends on the type of the present collagen fibers. It has been demonstrated that free collagen reduces the adhesion ability of the pathogen, and therefore, reduces its virulence. On the other hand, the presence of immobilized type I collagen was reported to increase the adhesive ability of the pathogen to the surrounding dentin, increasing its virulence and pathogenicity. 11,12 A previous investigation by Stuart et al also reported that E. faecalis can alter the immune response of the host, compete with the adjacent cells using fluids as their nutrients, maintain pH hemostasis, and release lytic enzymes.¹³ Accordingly, it has been concluded that the human serum media aids the virulence of the organism and increases its ability to adhere to the adjacent dentin, and increases its ability to form biofilms.¹¹ It has been furtherly demonstrated that these bacteria can form calcified biofilms that help them adhere to the adjacent dentin structures, induce a state of inflammation as a result of the increased formation and release of endotoxins and inflammatory mediators, share and acquire extrachromosomal elements, and survive high NaOCl concentrations for up to 6.5%. Besides, evidence also shows that these microorganisms have reduced sensitivity profiles to alkalinity and acidity, heat, hydrogen peroxide, ethanol, hyperosmolarity, and sodium dodecyl sulfate.6,7

Prevalence and bacterial profile

In a previous investigation by Pinheiro et al the authors estimated that the most prevalent bacteria in their included samples were E. faecalis, Fusobacterium, and Propionibacterium in 45.8%, 6.7%, and 3.3% of the root canals that were previously filled. 10 Similar findings were also reported in previous investigations. 14,15 Sedgley et al reported that the prevalence of E. faecalis was found to be 79.5%, while another investigation by Siquiera and Roças estimated that the prevalence of E. faecalis in their sample was 77%. 14,15 It is worth mentioning that both of these investigations also used polymerase chain reaction (PCR) for adequate detection of the bacteria. It has been furtherly demonstrated that the prevalence of E. faecalis is significantly higher within secondary than primary infections, with estimated rates of 89.6% and 67.5%, respectively.¹⁵ On the other hand, it should be noted that other investigations did not report E. faecalis as the main source of endodontic infection and treatment failure. However, it should be noted that even among these investigations, the prevalence of these bacteria was still reported but in smaller frequencies. Among these investigations, the prevalence rates of the organism ranged between 0.52% and 30%.16-21

Based on the abundant reports indicating the high prevalence rates of *E. faecalis*, many approaches were conducted to identify the pathology and mechanism by which the organism is significantly resistant to the different disinfection approaches that are usually applied during the endodontic treatment. On the other hand, other

investigations indicated that this organism was not the most prevalent pathogen causing endodontic infection and treatment failure. In this context, a previous investigation by Endo et al.20 Parvimonas micra was the most prevalent organism, which was isolated in 24% of the cases. Another investigation by Schirrmeister et al also reported that other bacterial pathogens were the most prevalent organisms causing bacterial persistence after endodontic treatment.¹⁷ The most prevalent isolated bacteria in their investigation included Solbacterium moorei, Fusobacterium nucleatum, and Parvimonas micra. 19 Besides, Fusobacterium nucleatum was the second most prevalent pathogen in another investigation that was conducted in 2012 by Rôças and Siqueira, with an estimated rate of 24%.²² Another investigation by Pereira et al. ¹⁹ also assessed the prevalence of bacteria posttreatment periodontitis and reported Fusobacterium nucleatum was the most prevalent pathogen, with an estimated rate of 71.6%. Siqueira et al. ²³ also estimated a prevalence rate of 15% for Fusobacterium nucleatum.

Other bacterial pathogens were also reported by other investigations. For instance, the study by Henriques et al indicated that Corynebacterium diphtheria was the most prevalent pathogen in their investigation in relation to endodontic treatment failure. 18 Siqueira reported that proteobacteria were the most prevalent in cases of posttreatment root canal infections, as detected in 46% of the cases.¹⁶ Post-treatment apical periodontitis was also mainly caused by Propionibacterium acnes and Efaecalis in 52% of the cases in a previous investigation.²² Another case series also reported that in 2/10 of the included cases, Propionibacterium acnes responsible for endodontic treatment failure. 17 The increased prevalence of this pathogen is probably attributable to the increased virulence in the relevant media as previously explained, and being able to survive within the extra-radicular areas.^{7,24}

Investigations also reported some pathogens that can survive extra-radicular environments. A previous investigation by Noguchi et al reported that Porphyromonas gingivalis is a pioneer pathogen that usually causes infection in the extra-radicular area, with an estimated prevalence rate of 28.17%.25 Other studies also demonstrated that this pathogen is prevalent in this location. Nevertheless, the prevalence rates are variable across the different investigations. 17,26 Endodontic retreatment was also required due to of the persistence of Treponema infections. 27,28 In a previous investigation by Nobrega et al it has been demonstrated that the prevalence of Treponema denticola and Treponema vicentii was 30.8% and 17.9%, respectively.27 The high prevalence rate of the organism was also attributed to the aforementioned mechanisms for the resistance of these organisms to endodontic treatment. Fungal infection is also important and was also frequently reported across the different investigations. For instance, it has been estimated that Candida albicans was isolated in 36.7% of

the cases with apical lesions, which was more frequent than other cases that did not have these lesions, with an estimated rate of 13.3%.²⁹ Among previously sealed root canals, a previous study estimated that Candida albicans was the most prevalent fungal infection.¹⁴ The persistence of Candida infection was also reported in a previous investigation, which indicated that the infection persisted even after the application of both mechanical and chemical disinfectant measures, indicating pathogenicity of Candida and its ability to survive such circumstances.³⁰ Some other pathogens were also reported with variable prevalence rates, including forsythia (48.3%), Pseudoramibacter Tannarella alactolyticus (52%), Dialister pneumosintes (48-58.3%), and Filiphactor alocis (48%). 14,19 Other bacteria and pathogens were also reviewed in previous investigations in the literature but with reduced prevalence rates than the discussed types in the current review. ^{3,31,32} This indicates that this topic is critical among the endodontic settings, and adequate attention should be given to enhance the associated outcomes.

CONCLUSION

E. faecalis is the most prevalent bacteria causing endodontic treatment failure, however, many studies have reported that other bacteria and pathogens might also be prevalent and exceed the rate of *E. faecalis*. This indicates the importance of detecting appropriate biofilms to adequately eradicate the underlying pathogens and enhance the treatment and prognostic outcomes.

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