Dental pathologies of endodontic origin and subsequent bacterial involvement – a literature review

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Abstract

Dental pathologies of endodontic origin are varied in nature, and include infectious and non-infectious causes. Through this review, we aim to provide a deeper understanding of the role of bacterial involvement and in the pathogenesis of endodontic pathologies, by reviewing the relevant literature on the most common bacterial species involved, and their capacity to organize as biofilms. Furthermore, we focus on the most important recent updates in the management of endodontic infections, from a multidisciplinary perspective.

Keywords **Endodontics, endodontic infections, root canal treatment, biofilm, dentistry**

Introduction

Dental pathologies of endodontic origin are varied in nature, and may have infectious and non-infectious causes. Bacteria have been investigated as possible causes for endodontic infections for more than a century,[1] and researchers have tried to identify possible treatments with drug combinations that can complement the primary endodontic treatment.[2,3] Through this narrative review, we aim to provide a deeper understanding of the role of bacterial involvement and bacterial biofilms in the pathogenesis of endodontic pathologies. Furthermore, we focus on the most important recent updates in the management of endodontic infections, from a multidisciplinary perspective.

Review

Pathogenesis of endodontic infections

The pathogenesis of endodontic infections involves a series of events leading to the initiation, progression, and persistence of infection within the root canal system of a tooth. The key steps in the pathogenesis of endodontic infections are as follows:

- Pulpal Injury or Necrosis:

The process often begins with some form of injury or damage to the dental pulp, which can result from dental caries, trauma, cracks, or other causes.[4] Following this primary event that disrupts dentin, the protective barrier of the dental pulp, the next step is the microbial invasion of the oral cavity microbiota.

- Microbial invasion:

Microorganisms, primarily bacteria, gain access to the pulp chamber through the abovementioned lesions that induce openings in the tooth structure.[5] Bacteria from the oral microbiota, including both aerobic and anaerobic species, can invade the pulpal chamber and then the endodontic system.

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- Pulpal inflammation (pulpitis):

The presence of bacteria and their byproducts triggers an inflammatory response within the pulp.[6] This inflammatory process is known as pulpitis, and while in the early stages it is reversible, in the absence of treatment it will become irreversible, leading to the destruction of pulp tissue.[7]

- Root canal infection:

As the infection advances, bacteria within the pulp chamber and root canal system form biofilms on the dentin surfaces.[8] As will be showed further on, biofilms protect bacteria from host defenses and antimicrobial agents, contributing to the persistence of the infection.

- Periapical pathology:

Periapical pathology, including periapical granulomas and radicular cysts, may develop as a consequence of the chronic inflammation and immune response in the periapical tissues. Periapical lesions can also form as a response to bacterial endotoxins, and while some of them can be asymptomatic, others can lead to periapical abscesses,[9] jaw bone osteomyelitis,[10] or even suppurations in the head and neck spaces.[11]

Bacterial involvement in endodontic pathologies

Endodontic disease refers to infections and inflammation that affect the pulp of a tooth. Even though relatively recent studies[12] have identified different microorganisms inside lesions of endodontic origins, including fungi and viruses,[12] bacterial infections remain the primary cause of endodontic diseases.[13] The most common bacteria involved include:

***Streptococcus* species**. Several species of *Streptococcus*,[14] such as *Streptococcus mutans, Streptococcus sanguis* and *Streptococcus sobrinus*, are commonly associated with dental caries and can contribute to endodontic infections. One subset of *S. mutans* is among the pathogens highly associated with dental caries, mostly because of its collagen binding protein – Cnm – which is responsible for its pathogenicity.[15] Even though other bacterial species also present collagen binding proteins, Cnm is specific to *S. mutans*.

***Enterococcus* species**. *Enterococcus faecalis* is a Gram-positive bacterium that is often implicated in persistent and resistant endodontic infections. It is known for its ability to survive in harsh environments, including root canal systems.[16] Just like *S. mutans*, it has the ability to form a biofilm, thereby increasing its resistance.[16] *E. faecalis* appears to be the most frequently isolated bacteria in teeth that failed endodontic treatment.[17]

***Staphylococcus* species**. According to different studies, several species from the *Staphylococcus* genus, such as *Staphylococcus aureus* and *Staphylococcus epidermidis* may be involved in endodontic infections.[18] Even though they are not as often isolated from infected root canals as *E. faecalis* and *S. mutans*, *S. aureus* was often found to be associated with osteomyelitis of the jaw bones.[10]

***Porphyromonas* species**. *Porphyromonas gingivalis* and other species within the *Porphyromonas* genus are frequently found in infected root canals, followed by members of the ***Prevotella* genus** such as *Prevotella loesschii* and *Prevotella intermedia*.[19]

***Fusobacterium* species**. *Fusobacterium nucleatum* is an anaerobic bacterium commonly found in dental infections. However, a recent meta-analysis did not find a statistically significant association between the presence of *Fusobacterium* spp. and the type of infection or the presence of symptoms.[20]

***Actinomyces* species**. *Actinomyces israelii* and other *Actinomyces* species such as *A. naeslundii*, and *A. viscosus* may be involved in endodontic infections, particularly in cases of chronic apical abscesses.[21]

***Eubacterium* species.** Various species of *Eubacterium*, such as *Eubacterium saphenum*, have also been identified in root canal infections.[22]

***Bacteroides* species**. *Bacteroides forsythus* and other *Bacteroides* species (*B. buccae*, *B. intermedius*, *B. denticola*, *B. oris*, *B. oralis*, and *B. gingivalis*) are anaerobic bacteria that can contribute to endodontic diseases.[23]

***Treponema* species.** *Treponema denticola* and other *Treponema* species are spirochetes associated with periodontal disease, but they may also be present in infected root canals. They are mainly responsible of primary and acute infections.[24]

Polymicrobial infections in endodontic diseases

Polymicrobial infections are common in endodontic diseases, with a diverse range of bacteria contributing to the infection.[25] Additionally, it has been demonstrated many years ago that the presence of fungi and other microorganisms may also play a role in certain cases,[26] and particularly in interkingdom biofilm formation. In theory, primary infections are characterized by polymicrobial flora, while endodontic failures exhibited mostly single bacterial strains.[13]

Polymicrobial endodontic infections involve the presence of multiple bacterial species within the root canal system. The complexity of these infections makes it challenging to pinpoint specific associations universally.[27]

Research in this field is ongoing, and advancements in molecular techniques, such as next-generation sequencing, have allowed for a more in-depth understanding of the microbial communities in endodontic infections. As a result, new associations and interactions among bacteria in these infections continue to be discovered. For example, a study published in 2015 showed that in primary infections, the most abundant bacterial species belonged to the Bacteroidetes and Firmicutes phyla, while in persisting endodontic infections predominated bacteria from the *Lactobacillus*, *Streptococcus*, and *Sphingomonas* genera.[28]

Another study employed proteomic technologies to analyze the bacterial proteins involved in endodontic pathologies,[12] with extremely interesting results. It identified the presence of 308 microbial proteins, many of them being involved in microbial virulence and pathogenicity, tissue invasion, but also in adhesion and biofilm formation, stress-response, microbial survival and antimicrobial resistance.[12]

Role of biofilms in endodontic pathology

Biofilms represent the main form of existence for microbial communities in the human flora in general, and the oral flora in particular.[29] They play an important role in endodontic infections, as they can drive pathogenesis and influence the choice of treatment as well as the host's response to conservative treatment.

In order to form biofilms, microorganisms such as bacteria and fungi adhere to each other and to natural or artificial substrates and build complex three-dimensional structures embedding themselves in multiple layers of self-produced extracellular matrix. The extracellular matrix is composed of polymeric substances and includes exopolysaccharides, proteic materials and extracellular DNA; it provides the biofilm with protection from outside factors such as host immune response, or antibiotics. Apart from its structural role, the extracellular matrix also plays a functional role, being involved in molecular signaling, amplification of quorum sensing responses, driving bacterial migration and surface colonization processes, mediating within-biofilm genetic exchanges, chelating and sequestering ions, as well as depositing and transporting nutrients.[30]

In the context of endodontic infections, the formation of biofilms within the root canal system allows bacteria to survive in this nutrient-poor environment. Moreover, the presence of biofilms and their metabolic byproducts can further contribute to the inflammation of periapical tissues. The complexity and resilience of biofilms make it difficult to completely eliminate all bacteria through endodontic treatment, particularly from areas unreachable by root canal instrumentation techniques, such as accessory canals or apical ramifications,[31] leading to failure of conservative treatment in certain instances.[32]

The goal of endodontic treatment is to remove bacteria and their biofilms, as well as pulp tissue, vital or necrotic, through combined mechanical and chemical methods of instrumentation, irrigation, and shaping before sealing the root canal system three-dimensionally.[33] During this process, different types of root canal irrigants can be used, coupled with various sonic, ultrasonic or laser-assisted removal techniques.[34] When assessing the anti-biofilm effect of irrigants, it is important to study their activity on planktonic as well as biofilm-embedded bacteria, and on the biofilm's extracellular matrix per se. Furthermore, their impact on the different elements that define biofilms should be considered, i.e.,: morphology, biofilm thickness, extracellular matrix-to-cell ratio, as well as dominant bacterial morphotypes;[35] these characteristics can differ based on the predominant bacterial or fungal species in the biofilm, the type of tooth, the type of lesions present in the tooth, or the history of previous tooth instrumentation.

Sodium hypochlorite, the most widely used root canal irrigant, possesses important antimicrobial activity, coupled with concentration-dependent tissue dissolution and biofilm disruption action,[8] and is particularly efficient against multi-species biofilms.[36] Its anti-biofilm activity is mediated by proteolysis[8] and by its ability to break glycosidic bonds and dissolve glycoconjugates in the biofilm matrix.[37] Its activity is enhanced by alternative applications of decalcifying agents such as ethylenediaminetetraacetic acid (EDTA), or by increasing the temperature of the irrigation solution in the root canal, through agitation or ultrasonic activation.[8] However, standardization of the optimal concentration of sodium hypochlorite is still needed.

When studied as standalone irrigation solution, EDTA has been reported to be effective in cell-rich biofilms, to induce destabilization of extracellular polymeric substances from the biofilm structure, and to display antibacterial activity on Gram-negative bacteria.[38]

Among other irrigants, chlorhexidine gluconate displays important and wide-spectrum antimicrobial activity, which is further enhanced by the addition of surface modifiers or by mechanical agitation; however, it does not present anti-biofilm action or dissolution activity on the organic matrix.[8] Additionally, not only does chlorhexidine not display antibiofilm activity, but it has been shown to cause a structural rearrangement of the biofilm, with paradoxical increase of extracellular polymeric substances of the top biofilm layer, reason why certain authors recommend against its use as irrigant.[38] Moreover, its use together with sodium hypochlorite poses the risk of precipitation in the root canal system, which can lead to occlusion of dentinal tubules[39,40] and can compromise the sealing of the obturated root canal.[40]

A recent systematic review has reported that citric acid exhibits good activity on smear layer removal, in particular in the coronal and middle thirds of the root canal, but also that it can decrease dentine microhardness and cause decalcifications or erosions when used administered immediately prior to sodium hypochlorite.[41]

Some essential oils are also explored as adjuvants, as they may display a certain degree of antibacterial and antibiofilm activity, but more standardized studies are needed in this regard.[42]

As none of the individual irrigants display optimal antimicrobial and antibiofilm activity, they are generally used in conjunction, in alternating sequences. Future options to be explored and further studied include enzymatic irrigation, functionalized nanoparticles, and different methods for irrigant activation.[8]

Intracanal medications are also considered in selected cases, either as temporary fillings in case of multi-appointment sessions, an approach that is less often used nowadays, or as an intermediate treatment step during a single-appointment session. Among these, calcium hydroxide contributes to elimination of microorganisms as well as inactivation of bacterial byproducts.[43] Furthermore, it decreases the levels of intra-canal matrix metalloproteinases and pro-inflammatory cytokines,[44] the latter being considered one of the potential mechanisms behind its effect of decreasing post-procedural pain.[45] It has limited antibacterial efficacy when used on its own,[46] but it displays synergy when combined with chitosan nanoparticles,[47] chitosan gel,[48] or with other vehicles, increasing its antimicrobial activity on *Enterococcus faecalis*[47] which, as mentioned above, is one of the most important pathogens involved in endodontic pathology, particularly in cases of prior endodontic treatment failure.[49]

All of these represent important considerations, as residual biofilms have been associated with failure of conservative treatment.[32,50,51] Some researchers have gone as far as to propose fluorescent staining solutions for rapid intraprocedural bacterial detection to guide endodontic treatment; these techniques are highly innovative and may ensure better precision of personalized endodontic treatment, but require on-site access to microspectroscopy,[52] which hinders their widespread implementation.

While intra-canal biofilms can be eliminated, to a large extent, by thorough root canal instrumentation, irrigation and sealing, extraradicular biofilms may pose other complex challenges, being associated with persistent periapical lesions,[53] and precluding conservative treatment of the affected tooth.

When exploring causes of endodontic treatment failure in a study from Japan, open apices perforation and root fracture were identified as main risk factors associated with refractory periapical periodontitis. Only in the subgroup of teeth with open apices that required apicoectomy or extraction, extraradicular biofilms were considered to have also been contributing factors,[54] suggesting the importance of appropriate apex sealing of the root canal system after endodontic instrumentation.

The composition of extraradicular biofilms includes abundant amorphous extracellular matrix and is often polymicrobial, with *Actinomyces* spp. and *Propionibacterium* being the predominant species, followed by *Prevotella* spp. *Streptococcus* spp., *Porphyromonas endodontalis*, and *Burkholderia* spp., as identified through polymerase chain reaction from apical samples collected following root-end surgery.[53] High-throughput sequencing of teeth with persistent apical periodontitis identified the presence of 31 different phyla and 557 different microbial genera, and showed that the microorganism sequences found in the root canal are superposable with the sequences from periapical lesions and extraradicular biofilms in percentages ranging from 60.8% to 77.7%, with shared predominance of *Fusobacterium* spp., *Morganella* spp., *Burkholderia* spp., *Porphyromonas* spp., *Streptococcus* spp. and *Bifidobacterium* spp.[55] Furthermore, the formation of sinus tracts from lesions of persistent apical periodontitis was associated with predominance of *Porphyromonas* spp., *Eubacterium* spp., *Treponema* spp., *Phocaeicola* spp., *Tannerella* spp., and *Prevotella* spp., while the absence of sinus tracts was seen in lesions where *Microbacterium* spp. and *Enterococcus* spp. predominated.[55]

The advent of performant microscopy systems and culture-independent microbial identification techniques have allowed a better understanding of the structure and composition of microbial biofilms. However, in order to understand the exact role that various microbial genera or species play in the pathogenesis of endodontic infections, it is important to interpret sequencing results in the general context of the high complexity of the oral flora, to assess the relative abundance of each phyla, genera or species in healthy compared to diseased teeth, and to exert caution when making causal inferences.

Updates in the management of endodontic infections

The treatment of endodontic infections typically involves root canal therapy, which aims to remove the infected pulp, disinfect the root canal system, and seal the canal to prevent reinfection.[56] In some cases, surgical intervention may be necessary, particularly if there is persistent infection or the presence of periapical lesions.[57] The understanding of the pathogenesis of endodontic infections is crucial for developing effective strategies for their diagnosis and management.[56]

Efforts to improve the management of endodontic infections often involve strategies to disrupt or eliminate biofilms.[8,49,58] This may include, as described above, the use of antimicrobial agents, irrigants, and instrumentation techniques aimed at disrupting the biofilm structure and enhancing the penetration of disinfectants into the root canal system.[43,59] Advances in understanding the biofilm biology in endodontic infections continue to inform the development of more effective treatment approaches.

Conclusions

In conclusion, bacteria play an important role in the pathogenesis of endodontic infections, alongside other contributing factors. The management of endodontic infections should take into consideration novel methods of local treatment, addressing the presence of bacterial biofilms alongside planktonic bacteria.

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