Review Article

FUNCTIONAL ROLES OF VIRULENCE GENES IN ADHESION, BIOFILM FORMATION, AND IMMUNE EVASION OF ENTEROCOCCUS FAECALIS

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ABSTRACT

Enterococcus faecalis is an opportunistic pathogen strongly associated with persistent endodontic infections and root canal therapy failure. Its pathogenicity is influenced by multiple virulence determinants that promote adhesion to host tissues, biofilm formation, and evasion of host immune defenses. This scoping review aimed to synthesize current evidence on the functional roles of the virulence genes *gelE, asa1, ace, cylA, hylE,* and *efaA* in the pathogenicity of *E. faecalis*. The review protocol was prospectively registered in the Open Science Framework (OSF) database .The study followed the PRISMA Extension for Scoping Reviews (PRISMA-ScR) guidelines. Electronic databases were systematically searched to identify studies investigating virulence determinants of *E. faecalis*. After duplicate removal and screening, eligible studies were selected for qualitative synthesis and data extraction. The search identified 152 records, of which 69 duplicates were removed, leaving 83 studies for title and abstract screening. Seventeen articles underwent full-text evaluation, and 15 met the inclusion criteria. The most frequently reported virulence genes were gelatinase (*gelE*), aggregation substance (*asa1*), collagen adhesion protein (*ace*), cytolysin (*cylA*), hyaluronidase (*hylE*), and endocarditis antigen (*efaA*). These determinants were consistently associated with adhesion, biofilm formation, tissue colonization, and immune evasion. Current evidence indicates that these virulence genes play significant roles in the pathogenic mechanisms of *E. faecalis*. Understanding their biological functions may support the development of improved therapeutic strategies for managing persistent endodontic infections.

Key words: *Enterococcus faecalis*, Virulence genes, Biofilm formation, Adhesion, Immune evasion, Endodontic infections.

Introduction

Enterococcus faecalis is a Gram-positive facultative anaerobic bacterium that naturally colonizes the gastrointestinal tract of humans and animals. Although commonly regarded as a commensal organism, E. faecalis has increasingly been recognized as an opportunistic pathogen capable of causing a variety of infections, including urinary tract infections, bacteremia, infective endocarditis, and persistent root canal infections. Within the field of dentistry, this microorganism is particularly significant because it is frequently isolated from teeth exhibiting failed endodontic therapy and chronic periapical pathology. Its ability to tolerate unfavorable environmental conditions, such as nutrient scarcity, elevated salinity, alkaline pH levels, and exposure to antimicrobial agents, greatly contributes to its survival within treated root canal systems.

A key factor contributing to the pathogenic success of E. faecalis is its capacity to form complex biofilms. Biofilms represent highly organized microbial communities embedded within a self-produced extracellular polymeric matrix that enables microorganisms to adhere to both biological tissues and abiotic surfaces. The biofilm structure offers protection against host immune defenses and significantly reduces the susceptibility of bacteria to antimicrobial agents. In the context of the root canal system, biofilm formation allows E. faecalis to penetrate dentinal tubules, survive intracanal medicaments, and persist despite host defense mechanisms. Microorganisms within biofilms may demonstrate resistance to antimicrobial agents that is several hundred times greater than that observed in planktonic bacterial cells [1, 2]. Consequently, biofilm persistence is widely considered one of the principal factors responsible for endodontic treatment failure.

The pathogenicity of E. faecalis is mediated by numerous virulence factors that enable the organism to adhere to host tissues, invade biological structures, evade immune responses, and establish biofilm communities. Among these determinants, several genes have been repeatedly identified as important contributors to bacterial adhesion and virulence, including gelatinase (gelE), aggregation substance (asa1), adhesin to collagen (ace), cytolysin (cylA), hyaluronidase (hylE), and endocarditis antigen (efaA). The proteins encoded by these genes interact with host tissues, degrade extracellular matrix components,

promote bacterial aggregation, and enhance bacterial survival within host environments.

Gelatinase, encoded by the gelE gene, is a secreted metalloprotease that plays a significant role in both tissue degradation and biofilm development [1, 3]. This enzyme hydrolyzes substrates such as collagen, gelatin, and other host proteins, facilitating bacterial invasion and nutrient acquisition. The expression of gelatinase is controlled by the Fsr quorum-sensing regulatory system, which coordinates bacterial communication and modulates the production of several virulence factors. As a result, gelatinase activity is closely linked to the regulation of virulence and the maturation of bacterial biofilms.

Aggregation substance, encoded by the asa1 gene, represents another important virulence determinant [4, 5]. This surface protein promotes bacterial aggregation and enables plasmid transfer between bacterial cells. Such interactions enhance the ability of E. faecalis to adhere to host tissues and contribute to the development of dense biofilm communities. The presence of aggregation substance has also been associated with increased pathogenic potential in systemic infections such as infective endocarditis.

The adhesin to collagen protein encoded by the ace gene is responsible for facilitating the attachment of E. faecalis to collagen and other extracellular matrix proteins. This adhesion mechanism plays a critical role in colonization of dentinal tissues and cardiac structures, particularly during endodontic infections and infective endocarditis. The ability to bind collagen-rich tissues significantly enhances bacterial persistence and biofilm formation within host environments.

Cytolysin, encoded by the cylA gene, is a toxin with hemolytic properties that contributes to bacterial virulence by damaging host cells and inhibiting competing microorganisms. The production of cytolysin has been associated with increased disease severity and improved bacterial survival within host tissues. Similarly, hyaluronidase encoded by the hylE gene assists in bacterial dissemination by degrading hyaluronic acid in the extracellular matrix, thereby enabling microorganisms to penetrate host tissues more effectively.

Another significant virulence determinant is the endocarditis antigen efaA, which has been implicated in bacterial adhesion and colonization during infection. The efaA protein contributes to the attachment of E. faecalis to host tissues and has been associated with enhanced pathogenic potential in both oral and systemic infections.

Although numerous investigations have examined individual virulence factors of E. faecalis, the combined roles of these genes in adhesion, biofilm development, and immune evasion remain incompletely understood. In addition, variations in the distribution and interaction of these virulence determinants among clinical isolates continue to represent an important area of research. Understanding the molecular pathways regulating these virulence factors is essential for the development of novel therapeutic strategies aimed at preventing persistent infections, particularly within endodontic environments.

Scoping reviews represent a valuable methodological approach for mapping the breadth of available scientific evidence and identifying knowledge gaps within a research field. In contrast to traditional systematic reviews that focus on narrowly defined clinical questions, scoping reviews provide a broader overview of existing literature and highlight areas requiring further investigation. Given the increasing volume of research examining virulence mechanisms in E. faecalis, a scoping review can provide meaningful insights into the functional roles of major virulence genes involved in bacterial pathogenicity.

Therefore, the purpose of this scoping review was to comprehensively examine the functional roles of selected virulence genes—gelE, asa1, ace, cylA, hylE, and efaA—in adhesion, biofilm formation, and immune evasion in Enterococcus faecalis. By synthesizing findings from experimental and observational studies, this review aims to clarify the molecular mechanisms underlying E. faecalis pathogenicity and to identify potential targets for future therapeutic strategies in both dental and systemic infections.

Materials and Methods

Study design

The present study was designed as a scoping review intended to systematically map and summarize the available evidence concerning the functional roles of specific virulence genes of Enterococcus faecalis in processes such as adhesion, biofilm formation, and immune evasion. The methodological framework followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) guidelines to ensure transparency, reproducibility, and methodological rigor.

To enhance transparency and reduce the potential for reporting bias, the review protocol was prospectively registered in the Open Science Framework (OSF) database (HTTPS://DOI.ORG/ 10.17605/OSF.IO/RJ67F).

Information sources and search strategy

A comprehensive electronic literature search was performed to identify relevant studies investigating the virulence mechanisms of Enterococcus faecalis. The following databases were searched:

PubMed
Scopus
Web of Science

The search strategy incorporated both Medical Subject Headings (MeSH) terms and free-text keywords related to E. faecalis virulence factors and biofilm formation. The following search string was used:

Enterococcus faecalis AND (virulence genes OR gelE OR asa1 OR ace OR cylA OR hylE OR efaA) AND (biofilm formation OR adhesion OR immune evasion)

To focus on contemporary evidence and reflect recent developments in the field, the search was limited to studies published between 2016 and 2026. The reference lists of relevant publications were manually screened to identify additional eligible studies that may not have been retrieved through database searching.

Eligibility criteria
Studies were selected according to predefined inclusion and exclusion criteria.

Inclusion criteria
Studies investigating Enterococcus faecalis virulence genes, including gelE, asa1, ace, cylA, hylE, or efaA
Studies examining mechanisms related to adhesion, biofilm formation, or immune evasion
Experimental, molecular, observational, or clinical studies
Articles published in peer-reviewed journals
Publications written in the English language

Exclusion criteria
Studies that did not investigate the selected virulence genes
Studies focusing on bacterial species other than E. faecalis without a specific analysis of this organism
Review articles, editorials, and conference abstracts.
Studies lacking sufficient methodological or outcome data related to virulence mechanisms

Study selection
All retrieved records were imported into the Rayyan systematic review software to facilitate duplicate removal and screening procedures. The initial database search identified a total of 152 articles. Duplicate detection revealed 118 duplicate records, of which 69 were removed, leaving 83 unique articles for further screening.

Title and abstract screening resulted in the exclusion of 66 studies that did not satisfy the predefined eligibility criteria. Seventeen articles remained for full-text evaluation. After a detailed full-text assessment, two studies were excluded because they did not report outcomes related to virulence gene function.

Consequently, fifteen studies fulfilled the inclusion criteria and were included in the qualitative synthesis. The overall study selection process is illustrated in **Figure 1**.

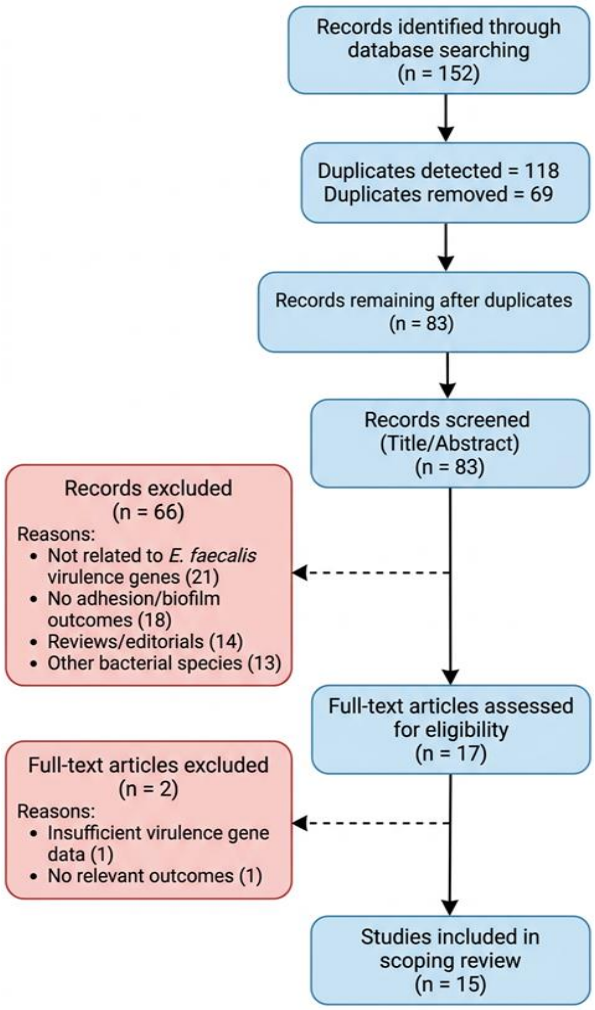

Figure 1. PRISMA flow diagram illustrating the study selection process for the scoping review.

Analysis of the included studies revealed that several virulence genes were consistently reported in association with adhesion, biofilm formation, and immune evasion. Among these determinants, gelatinase (gelE) was the most frequently investigated factor. GelE is a secreted metalloprotease capable of degrading host proteins and facilitating bacterial dissemination. Its activity also contributes to biofilm maturation and increased resistance to antimicrobial agents.

The aggregation substance gene (asa1) plays an important role in mediating bacterial aggregation and cell-to-cell adhesion. This mechanism facilitates plasmid transfer and enhances colonization within host tissues. Similarly, the collagen-binding adhesin encoded by ace enables E. faecalis to adhere to collagen-rich tissues such as dentin, which is particularly relevant in the context of persistent endodontic infections.

Cytolysin encoded by cylA contributes to virulence by damaging host cells and promoting tissue destruction. Meanwhile, hyaluronidase (hylE) facilitates tissue invasion

through degradation of extracellular matrix components. The endocarditis antigen efaA has also been implicated in bacterial adhesion and pathogenicity.

Table 1. Characteristics of Included Studies

Author (Year)	Country	Study Design	Sample Source	Virulence Genes Investigated	Methods Used	Key Findings
Tibúrcio *et al*. (2022) [6]	Not specified	Experimental in-vitro study	Laboratory strains of E. faecalis	gelE, asa1, ace	Biofilm assays, RT-PCR	Exposure to sub-inhibitory antibiotic concentrations enhanced biofilm formation and influenced expression of virulence genes.
Manias *et al*. (2018) [7]	USA	Molecular study	E. faecalis OG1RF strain	ace, ebp locus	RNA sequencing, transcription analysis	ArgR family transcription factors regulate the expression of adhesive pili and Ace, thereby influencing adhesion and biofilm development.
Antypas *et al*. (2026) [8]	Europe	Molecular experimental study	E. faecalis clinical strains	gelE, fsr quorum-sensing system	Gene regulation analysis, biofilm assays	Alterations in the Fsr quorum-sensing system were associated with enhanced biofilm formation and increased pathogenic potential.
Hashem *et al*. (2021) [5]	Egypt	Observational study	Clinical isolates from patients	ace, gelE, cylA, asa1, efaA	PCR analysis, phenotypic assays	Virulence genes were widely distributed among clinical isolates and correlated with increased biofilm formation capacity.
Mubarak *et al*. (2016) [4]	Indonesia	Observational study	Root canal and saliva isolates	gelE, asa1, esp	PCR, biofilm assays	The presence of virulence genes was strongly associated with increased biofilm-forming ability in endodontic isolates.
Kart *et al*. (2019) [3]	Turkey	Observational study	Clinical isolates	gelE	PCR, biofilm growth models	Gelatinase gene expression was significantly associated with biofilm formation and bacterial persistence.
Parga *et al*. (2023) [9]	Italy	Experimental study	E. faecalis laboratory strains	fsrC, cylA, ace, efaA	RT-PCR, biofilm assays	Quorum-sensing signals enhanced the expression of virulence genes and promoted biofilm development.
Seyedolmohadesin *et al*. (2024) [10]	Iran	Observational molecular study	Urinary tract infection isolates	ace, gelE, esp, cylA	PCR, MLST	The ST150 lineage demonstrated strong biofilm formation and a high prevalence of virulence genes.
Nešuta *et al*. (2017) [1]	Czech Republic	Experimental study	Laboratory strains	gelE, sprE	Peptide degradation assays	Gelatinase contributed to the degradation of antimicrobial peptides, supporting bacterial survival within biofilms.

Nešuta *et al*. (2017) [11]	Poland	Experimental study	E. faecalis strains	gelE	Proteolytic activity assays	Proteolytic cleavage mediated by gelatinase influenced antimicrobial peptide stability and bacterial resistance.
Singh *et al*. (2018) [12]	USA	Animal experimental study	Rat endocarditis model	ace	Adhesion assays, in vivo infection model	Anti-Ace monoclonal antibodies reduced bacterial adhesion and decreased infection severity.
Xu *et al*. (2017) [2]	USA	Experimental study	E. faecalis OG1RF strain	gelE, fsrA	Proteomics, gene deletion studies	ClpP protease influenced stress tolerance and regulated virulence-related protein expression and biofilm formation.
Hashem *et al*. (2021) [13]	Egypt	Experimental study	Clinical isolates	fsrB, fsrC, gelE, asa1	RT-PCR, gelatinase assays	Quorum-sensing inhibition significantly reduced gelatinase production and biofilm formation.
Parga *et al*. (2023) [14]	India	In-silico and in-vitro study	Endodontic isolates	ace, esp	Molecular docking, RT-PCR	Natural photosensitizers downregulated adhesion genes and reduced biofilm development.
Xu *et al*. (2017) [15]	China	Experimental study	Root canal biofilms	gelE, ace, efaA	SEM imaging, qPCR	Nanoparticle-based antimicrobial therapy significantly reduced biofilm formation and virulence gene expression.

Results and Discussion

Analysis of the included studies revealed that several virulence genes were consistently reported in association with adhesion, biofilm formation, and immune evasion. The characteristics of the included studies are summarized in **Table 1.** Among these determinants, gelatinase (gelE) was the most frequently investigated factor. GelE is a secreted metalloprotease capable of degrading host proteins and facilitating bacterial dissemination. Its activity also contributes to biofilm maturation and increased resistance to antimicrobial agents. The aggregation substance gene (asa1) plays an important role in mediating bacterial aggregation and cell-to-cell adhesion. This mechanism facilitates plasmid transfer and enhances colonization within host tissues. Similarly, the collagen-binding adhesin encoded by ace enables E. faecalis to adhere to collagen-rich tissues such as dentin, which is particularly relevant in the context of persistent endodontic infections.

Cytolysin encoded by cylA contributes to virulence by damaging host cells and promoting tissue destruction. Meanwhile, hyaluronidase (hylE) facilitates tissue invasion through degradation of extracellular matrix components. The endocarditis antigen efaA has also been implicated in bacterial adhesion and pathogenicity.

The present scoping review synthesized the available evidence regarding the functional roles of six key virulence genes of *Enterococcus faecalis—gelE, asa1, ace, cylA, hylE,* and *efaA*—in bacterial adhesion, biofilm formation, and immune evasion. Analysis of the fifteen included studies revealed that these virulence determinants collectively contribute to the persistence and pathogenic potential of *E. faecalis*, particularly in environments such as the root canal system, where bacteria are exposed to antimicrobial agents and host immune responses.

Among the investigated virulence determinants, gelatinase encoded by the *gelE* gene was the most frequently reported factor associated with biofilm formation and virulence. Several studies demonstrated that gelatinase contributes to the degradation of host extracellular matrix proteins and facilitates biofilm maturation, thereby enhancing bacterial survival within hostile environments [1, 3, 6, 11]. Gelatinase activity has also been linked to the degradation of antimicrobial peptides, which may further contribute to bacterial persistence within biofilm communities [1]. Furthermore, the expression of gelatinase is regulated by the Fsr quorum-sensing system, which coordinates bacterial communication and modulates the expression of multiple virulence-associated genes [8]. Disruption of this regulatory system has been shown to alter biofilm formation and influence infection outcomes, highlighting its importance in

the pathogenicity of *E. faecalis*.

Another important virulence determinant identified across multiple studies is the aggregation substance encoded by the *asa1* gene. Aggregation substance facilitates bacterial aggregation and promotes cell-to-cell contact, which enhances plasmid transfer and the dissemination of antibiotic resistance genes among bacterial populations [4, 5, 16]. This mechanism also contributes to the formation of dense biofilm structures that protect bacterial communities from antimicrobial agents and host immune defenses. The presence of *asa1* has been frequently associated with increased biofilm-forming capacity among clinical isolates of *E. faecalis* [4, 17].

Adhesion to host tissues represents a critical step in the establishment of infection. The collagen-binding adhesin encoded by the *ace* gene plays a crucial role in facilitating E. faecalis attachment to collagen-rich tissues, such as dentin and cardiac valves. Experimental studies have demonstrated that the Ace protein enhances bacterial adhesion and colonization within host tissues [7, 12]. In animal models of infective endocarditis, inhibition of Ace-mediated adhesion has been shown to reduce infection severity significantly, further supporting its role as a key virulence factor [12, 18].

Cytolysin encoded by the *cylA* gene represents another important contributor to the virulence of *E. faecalis*. Cytolysin is a toxin capable of lysing host cells and competing microorganisms, thereby promoting bacterial survival and tissue invasion [9]. The production of cytolysin has been associated with increased disease severity in systemic infections and may provide bacteria with additional nutrients by destroying host cells.

The enzyme hyaluronidase, encoded by *hylE,* facilitates bacterial dissemination through the degradation of hyaluronic acid within the extracellular matrix. This enzymatic activity allows *E. faecalis* to penetrate deeper into host tissues and establish more persistent infections. Similarly, the endocarditis antigen encoded by *efaA* contributes to bacterial adhesion and colonization, and its presence has been correlated with enhanced pathogenic potential in clinical isolates [5, 10].

Several studies included in this review also highlighted the role of regulatory mechanisms and environmental factors in modulating virulence gene expression. For example, alterations in quorum-sensing pathways have been shown to significantly influence the expression of virulence determinants and biofilm formation in *E. faecalis* [8]. Additionally, exposure to sub-inhibitory concentrations of antibiotics may enhance biofilm development and alter the expression of virulence genes, further complicating the treatment of persistent infections [6]. Emerging therapeutic approaches, including nanoparticle-based antimicrobial strategies and photodynamic therapy, have also been investigated as potential methods for disrupting *E. faecalis* biofilms and reducing virulence gene expression [14, 15].

The findings of the included studies collectively demonstrate that the pathogenicity of *E. faecalis* is multifactorial and involves the coordinated interaction of multiple virulence determinants. Adhesion proteins such as Ace and EfaA facilitate the initial attachment of bacteria to host tissues, while enzymes such as gelatinase and hyaluronidase promote tissue degradation and bacterial dissemination. Meanwhile, aggregation substance enhances bacterial aggregation and biofilm formation, and cytolysin contributes to host cell damage and competitive advantage within microbial communities.

Despite the valuable insights provided by these studies, several limitations should be acknowledged. Many investigations were conducted using in vitro experimental models or laboratory strains, which may not fully replicate the complex conditions encountered in clinical infections. Additionally, variations in study design, bacterial strains, and analytical methods may influence the reported prevalence and functional roles of virulence genes. Future research should focus on clinical and translational studies that examine the expression of these virulence determinants in vivo and evaluate targeted therapeutic strategies aimed at inhibiting virulence mechanisms.

Overall, the evidence synthesized in this scoping review highlights the critical role of virulence genes in the pathogenic behavior of *Enterococcus faecalis*. A deeper understanding of the molecular mechanisms governing adhesion, biofilm formation, and immune evasion may contribute to the development of novel therapeutic strategies aimed at improving the management of persistent endodontic infections and other *E. faecalis*-associated diseases.

Conclusion

This scoping review synthesized evidence from fifteen studies investigating the functional roles of major virulence genes—*gelE, asa1, ace, cylA, hylE,* and *efaA*—in the pathogenic mechanisms of *Enterococcus faecalis*. The findings demonstrate that the virulence of *E. faecalis* is not governed by a single determinant but rather by a coordinated network of genetic factors that contribute to bacterial adhesion, biofilm formation, tissue invasion, and immune evasion.

Among these determinants, the gelatinase gene *gelE* was consistently associated with biofilm maturation, degradation of host extracellular matrix components, and enhanced bacterial persistence. Adhesion-related genes such as *ace* and *efaA* play essential roles in facilitating bacterial attachment to collagen-rich tissues, including dentin, thereby promoting colonization in endodontic infections. The aggregation substance gene *asa1* further contributes to

bacterial aggregation and horizontal gene transfer, which may facilitate the dissemination of antibiotic resistance and enhance biofilm stability. In addition, cytolysin (*cylA*) and hyaluronidase (*hylE*) contribute to bacterial virulence by promoting host cell damage and enabling deeper tissue invasion.

Collectively, these virulence determinants enable *E. faecalis* to establish resilient biofilm communities that protect bacterial cells from antimicrobial agents and host immune responses. This capability is particularly relevant in persistent root canal infections, where biofilm-associated bacteria may survive conventional endodontic treatment procedures.

The evidence summarized in this review also highlights the importance of regulatory pathways such as quorum sensing in controlling virulence gene expression and biofilm formation. Emerging therapeutic strategies, including approaches aimed at disrupting biofilms or inhibiting virulence mechanisms, may offer promising avenues for improving the management of persistent *E. faecalis* infections.

However, several limitations in the current body of literature should be acknowledged. Many studies were conducted under in vitro conditions, which may not fully reflect the complexity of clinical infections. Additionally, differences in study design, bacterial strains, and analytical techniques may influence the reported prevalence and functional significance of virulence genes.

Future research should focus on clinical and translational studies that investigate the expression and regulation of these virulence determinants in vivo. Improved understanding of the molecular pathways underlying *E. faecalis* pathogenicity may support the development of targeted therapeutic strategies aimed at disrupting biofilm formation and reducing bacterial persistence in endodontic infections.

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