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Porphyromonas endodontalis, its virulence factor, nutrition, detection, epidemiology and treatment

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Abstract
Introduction: Gram-negative anaerobic microorganisms play a crucial role in endodontic and periodontal infections. *Porphyromonas endodontalis* is a rod-shaped, gram-negative anaerobic bacterium, pigmented in black that causes periapical lesions with acute symptoms.
Objective: To analyze the literature about *P. endodontalis*, as well as its virulence factor, nutrition, detection, epidemiology and treatment.
Methodology: Relevant articles were compiled and selected in PubMed about *P. endodontalis*, using key words such as *P. endodontalis*, periapical periodontitis, gram-negative anaerobic bacteria pigmented in black, among some other phrases.
Results: *P. endodontalis* lipopolysaccharide is a potent stimulator of inflammatory cytokines that participate in the formation of acute abscesses and bone destruction; To detect this bacterium with greater efficiency, the molecular technique of PCR is used. *P. endodontalis* does not need many nutrients to be able to reproduce due to its location and characteristics, so it is important to eliminate them by chemical-mechanical cleaning of the root canal followed by a hermetic seal.
Conclusions: *P. endodontalis* is one of the most frequent bacteria in endodontic lesions playing an important role in abscesses. Therefore, it is an objective in the endodontic treatment and its eradication is crucial to achieve the elimination of the infection.

Keywords: *Porphyromonas endodontalis,* periapical periodontitis, bacteria pigmented in black, gram-negative bacteria, anaerobic bacteria

1. Introduction
Gram-negative anaerobic microorganisms play a crucial role in endodontic and periodontal infections [1-3]. These microorganisms are organized in complex communities adhered to a surface and protected by a viscous layer constituted by a matrix of polysaccharides and proteins, which form a biofilm [4]. That provides protection against antagonistic microorganisms, host defenses, antimicrobial agents and environmental stress [5]. *P. endodontalis* (Pe), formerly *Bacteroides endodontalis*, is a black-pigmented, rod-shaped, gram-negative anaerobic bacterium that is associated with endodontic infections and necrosis of the pulp [6-8]. *P. endodontalis* colonization causes periapical lesions with acute symptoms, such as pain, swelling in response to a purulent inflammation and pain on percussion or palpation [9, 10]. Among the five to seven different species associated with endodontic infection is *P. endodontalis*, which is frequently associated with the initial infection of the root canal, that is, an untreated root canal [11-13]. The lipopolysaccharides of *P. endodontalis* induce inflammatory cytokines [14]. And the resulting inflammation may lead to bone resorption [8]. For this reason, it is an important bacterium in the mediation of periapical pathology and an important endodontic target [2]. In order to correctly treat endodontic infections, it is important to thoroughly know the causative agents. The objective of this review is to analyze the literature about the bacterium *P. endodontalis*, including its virulence factors, nutrition, diagnosis, epidemiology, and treatment.

2. Materials and Methods
PubMed, Google Scholar and EBSCO were searched with the following keywords and phrases: *P. endodontalis*, periapical periodontitis, gram-negative anaerobic bacteria, nutrition, virulence factor, diagnosis, treatment. The results of an exhaustive search was classified and presented along with some critical comments when necessary.

3. Results & Discussion
3.1 Virulence factor
An important virulence factor of *P. endodontalis* is the lipopolysaccharide endotoxin, which plays a critical role in the induction of proinflammatory cytokine secretion and bone destruction [8, 15, 16]. Lipopolysaccharides form the major component of the outer membrane of gram-negative bacteria and act as potent stimulators of bone destruction since they inhibit osteoblast differentiation and bone mineralization [17, 18]. Lipopolysaccharides also induce inflammatory cytokines and lipid immunomodulators, such as tumor necrosis factor-α (TNF-α), interleukins (IL), and prostaglandin E2 in osteoblasts [19, 20]. These factors participate in alveolar bone resorption and in the inhibition of bone formation [21, 23]. On the other hand, lipopolysaccharides favor osteoclastogenesis by promoting the survival of pre-osteoclasts, inducing their fusion to form active multinucleated osteoclasts and activating the nuclear factor κB (inflammatory mediator regulators) in stem cells of postnatal dental pulp [8, 24-26]. The lipopolysaccharides of *P. endodontalis* are detected in a large number of infected root canals or in samples of pus from acute abscesses (approximately 90%), so it plays an integral role as a potent stimulator of inflammatory cytokines that participate in abscess formation acute and bone destruction. Other virulence factors of *P. endodontalis* include fimbriae, capsules, outer membrane proteins, proteinases, cytotoxic metabolic products, oxygen resistance protein and iron-binding proteins [9, 27, 28].

3.2 Nutrition
Because the apical third of the root canal system is considered a critical area for the success of endodontic therapy, knowledge about the microbiota that infects this area is of paramount importance [29]. The microorganisms are located in privileged and strategic positions within the root canal. In such places, they are protected from the action of host defense cells (phagocytes) and molecules (antibodies, complement) and, on the other hand, must find resources or nutrients to survive [30, 31]. The unique anatomy of the root canal, especially the apical third, and its proximity to the hosts living tissues confer a special microenvironmental niche for the bacterial strains that colonize this region [32, 33]. The low oxygen tension in the apical third of the root canal favors the establishment of strictly anaerobic bacteria, such as *P. endodontalis*. In addition, bacteria located in the apical part of the root canal can obtain various nutrients from the tissue fluids and the inflammatory exudate present at the boundary between the periradicular tissues and the infected root canal [34]. This may favor the establishment of bacteria that use proteins as their main nutritional resource in and explain why certain bacteria, such as *Porphyromonas*, *Peptostreptococcus*, *Prevotella* and *Fusobacterium*, are commonly reported as part of the microbiota in this area [35]. The host may provide additional nutrients, such as vitamins, hormones, and blood components [36]. Therefore, bacteria located in the apical part of the root canals receive nutrients from the host and, as a consequence, can flourish and cause damage to the periradicular tissues [34]. Due to the location of these bacteria, which is mainly in the apical third, and their anaerobic characteristics, their nutrition is poor or they do not need many factors or nutrients to reproduce or survive, so they are difficult to eradicate.

3.3 Diagnosis
Molecular and culture methods have been used to detect bacterial species in root canals with either previous endodontic treatment and persistent infections or in untreated ducts with initial infection. Molecular techniques allow a more reliable identification of various bacterial species, especially some bacteria that are difficult to grow [6, 9]. Particularly, the 16S rDNA-directed polymerase chain reaction (PCR) [27, 37]. Has been used to detect black-pigmented bacteria in primary endodontic infections and in teeth with failed endodontic therapy [34]. PCR-based identification studies have reported a higher incidence of black-pigmented bacteria in endodontic infections compared to culture studies [9, 38]. The detection of *P. endodontalis* via culture technique is low [39, 40], possible due to the loss of difficult-to-grow bacteria. The detection of black-pigmented species by PCR analysis is more efficient and sensitive than culture methods.

3.4 Epidemiology
In general, the bacteria in root canal samples of teeth with apical periodontitis in order of prevalence are *P. endodontalis* (59%), *Fusobacterium nucleatum* (55%), *Dialister invisus* (50%), *Olsenella uli* (49%), and *Parvimonas micra* (48%) [27]. On the other hand, the bacteria most frequently detected in asymptomatic teeth are *P. endodontalis* (63%), *D. invisus* (58%), *O. uli* (56%), and *F. nucleatum* (51%), whereas in abscesses they are *F. nucleatum* (60%), *P. endodontalis* (53%), *P. micra* (51%), and *Streptococcus* (45%). *P. endodontalis* is significantly more prevalent in symptomatic than asymptomatic cases [27]. The prevalence of *P. endodontalis* in secondary or persistent endodontic lesions is 22.2%, which is also closely associated with purulent exudates. This gram-negative anaerobic bacterium, which is not frequently detected in cases of endodontic failure, can be associated with certain clinical characteristics and exert a synergistic relationship with *F. alocis*, *P. gingivalis* and *T. denticola*, which could be involved in the pathogenesis of endodontic treatments. Failed [6]. Also, the combination of *F. nucleatum*, *Prevotella* and *Porphyromonas* is a risk factor for endodontic outbreaks or exacerbations, because the synergy among these organisms can worsen a periapical inflammatory lesion [41]. Bram-negative black-pigmented bacteria occur in approximately 65% of cases with pain and 75% with swelling or purulent exudates [9]. Black-pigmented bacteria are detected more frequently in teeth with necrotic pulp than in teeth with failure of previous endodontic treatment. In secondary endodontic infections, black-pigmented bacteria are identified in both symptomatic and asymptomatic teeth [9, 27, 42]. It is possible that species found in both asymptomatic and symptomatic infections do not associate with the symptoms, suggesting that the development of acute signs and symptoms depends on the synergy between black-pigmented bacteria, such as *P. endodontalis* and other bacterial species, their pathogenicity, as well as the number of bacteria present in the root canal.

3.5 Treatment
Because the system of root canals varies in anatomy,

including fins, isthmuses, and accessory canals, complete elimination of bacteria in the root canals is difficult. In the treatment of the root canal, along with mechanical cleaning, various irrigators are used, such as sodium hypochlorite (the most effective antimicrobial irrigator), chlorhexidine, and intra-channel medications, such as calcium hydroxide [43, 44, 45]. However, some bacteria may remain in the root. Therefore, a tight seal of the duct space is required to bury any residual bacteria and eventually eliminate them [46]. Root canal sealants with antibacterial activity are necessary, effective and provide many advantages in the treatment of infections since they prevent the reentry of bacteria into the canal and inactivate the remnants after filling [46]. The growth of *P. endodontalis* is significantly inhibited when the concentration of the sealer cement AH Plus (Dentsply) or Sealapex (Kerr) is higher than 6.4 mg/ml. AH plus, a sealer based on epoxy resin, exhibits strong antibacterial activity against *P. gingivalis* and *P. endodontalis* through bisphenol A diglycidyl ether and formaldehyde during polymerization [47]. Gram-negative bacteria, with thin cell walls are sensitive to chemicals due to easy penetration into the bacterial cytosol. Formaldehyde penetrates into the interior of bacteria and inhibits their metabolism by reacting with cytosolic proteins, RNA and DNA [48]. The close communication between the bacteria and the living tissue of the host in the apical area is not sufficient to eliminate the infection from the root canal. Defense molecules and leukocytes hardly have access to the infection due to a bad circulation in necrotic pulp tissue [31]. Only bacteria that gain access to periradicular tissues can be effectively combated and eliminated by the host [33]. The elimination of a species must be accompanied by a parallel remission of the disease. To eradicate a bacterium such as *P. endodontalis*, both an effective chemical-mechanical cleaning and a hermetic seal of the root canal are strictly necessary, since the host defense of the host can never eliminate the infection on its own. The vast majority of endodontic infections are treated without the need for antibiotics.

4. Conclusions

P. endodontalis is an anaerobic bacterium with minimal nutrient requirements and therefore difficult to eradicate. Lipopolysaccharides form the main virulence factor. PCR is the most suitable detection method. Epidemiological aspects are difficult to evaluate, because of the synergy with other bacteria. A mechanical-chemical cleaning and sealing is the best treatment to eradicate *P. endodontalis*.

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