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## *Candida albicans*, from endodontic point of view

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### **Abstract**

**Introduction:** *Candida albicans* is a ubiquitous commensal organism that commonly colonizes the oral mucosa. In fact, up to 80% of the general population are carriers.

**Objective:** To analyze the literature about *C. albicans*, its epidemiology, diagnosis, clinical manifestations, antimicrobial resistance and treatment in relation to endodontics.

**Methodology:** Using the keywords *Candida albicans* in conjunction with epidemiology, diagnosis, clinical manifestations, antimicrobial resistance and treatment, the main public databases were searched, with emphasis on the last 5 years. It was evaluated with the PRISMA and AMSTAR-2 guidelines.

**Results:** *C. albicans* is the fungus most frequently isolated in root canal infections, it binds to the dentin to form biofilms within the dentin tubules. *C. albicans* can be detected by different diagnostic methods, the most used is cultivation. This microorganism is increasingly found in the oral cavity, it is responsible for endodontic failure, its biofilms are inherently resistant to antifungal drugs, the host's immune system, environmental stresses and biomechanical treatment. The most favourable method to eliminate is using Qmi X irritant and Endo Vac as a suction system, together with chemo mechanical debridement.

**Conclusions:** *C. albicans* is a pathogen which has been presenting itself more frequently in the oral cavity, in the endodontic area, it is the fungus that is most frequently found in the root canals, either due to primary or secondary infection.

**Keywords:** *Candida albicans*, epidemiology, diagnosis, clinical manifestations, antimicrobial resistance, treatment

### **1. Introduction**

*C. albicans* is by far the main causative agent of oral candidiasis and accounts for up to 95% of cases. Although considered a pathogen, *C. albicans* is a ubiquitous commensal organism that commonly colonizes the oral mucosa. In fact, up to 80% of the general population are carriers [1]. In the oral cavity, Candida-associated infections are referred to as oral candidosis, of which there are four main clinical presentations: chronic and acute erythematous, pseudomembranous and chronic hyperplastic candidosis [2]. An important consideration in endodontic treatment is the elimination of microorganisms, including fungi. *Candida albicans* (CA) plays an important role in endodontic treatment failure as the most important fungus isolated from the root canal system [3]. *C. albicans* frequently resides in the oral cavity as a biofilm-forming microorganism. When considering root canal infections, pathogenic yeasts have also been isolated from teeth associated with primary apical periodontitis and post-treatment disease [4]. *C. albicans* is the species most frequently isolated in endodontic infections, its prevalence in persistent infections is higher than in primary infections [5]. Root canal treatment (RCT) is the treatment of choice for these endodontic infections. RCT aims to: remove microorganisms from the root canal system to a level that promotes healing of periarticular tissues and provide a three-dimensional tight seal to prevent reinfection. During RCT, different hand and rotary instruments are used to mechanically debride the biofilm on the root canal walls [6]. In case of a failed endodontic procedure, specific fungal species grow as a result of intercommunication between certain bacteria due to changes in intracanal oxygen pressure and environment [7]. Failure in endodontic treatment is caused by bacterial colonization of the root canal system and periarticular tissues.

The literature mentions that *Candida albicans* may be one of the causes, along with other bacteria, of endodontic treatment failures because it is identified in cultivation samples taken from root canals with primary or secondary infection and its various mechanisms of resistance to some antibiotics. The aim of this article is to analyze the literature about *Candida albicans*, its epidemiology, diagnosis, clinical manifestations, antimicrobial resistance and treatment in relation to endodontics.

## 2. Materials and Methods

Articles on the subject published through the PubMed, SCOPUS and Google Scholar databases were analyzed, with emphasis on the last 5 years. The quality of the articles was evaluated using PRISMA guidelines, i.e., identification, review, choice and inclusion. The quality of the reviews was assessed using the measurement tool for evaluating systematic reviews (AMSTAR-2). The search was performed using Boolean logical operators AND, OR and NOT. It was realized with the words *Candida albicans* in conjunction with epidemiology, diagnosis, clinical manifestations, antimicrobial resistance and treatment. The keywords were used individually, as well as each of them related to each other.

## 3. Results and Discussion

### 3.1 Epidemiology

The main supply of *C. albicans* in the body is found in the gastrointestinal tract and the development of infections occurs due to dysbiosis of the residential microbiota, immune dysfunction and damage to the muco-intestinal barrier [8]. A small number of *Candida* species are part of the normal microbial flora of human mucosal surfaces and can give rise to opportunistic infections when host defenses are impaired. This pathogen is by far the most prevalent commensal *Candida* species [9]. *Candida albicans* is the most frequently isolated fungus in endodontic root canal infections. Although it is recognized by cells in the dental pulp and periradicular tissue that elicit immune responses, it evades host defenses and causes cell death. This fungus then binds to tooth dentin, forms biofilms and invades dentinal tubules to resist intracanal disinfectants and endodontic treatments [10]. Overall, 9,769 (6.09%) of the 160,357 patients examined were diagnosed with oral candidiasis on the basis of clinical manifestations and laboratory tests. The ratio of females to males was 1:0.61, and females had higher overall infection rates than males in all age subgroups [11]. Patients with long-term diabetes mellitus carried *C. albicans* in their root canals more frequently when they had a primary endodontic infection. Furthermore, this presence of *C. albicans* seems to be related to a higher frequency of apical periodontitis [12]. The frequency of yeasts was higher in teeth with primary infections compared to teeth with persistent infections. The predominant yeast species was this microorganism [13]. Failure of endodontic treatment has been associated with the persistence of microbial flora after therapy in the root canal system, and this includes this fungus, which is resistant to conventional root canal irrigants [14]. A cross-sectional study was conducted where saliva samples were collected from 48 patients who used dentures and 43 patients (control group) who did not use dentures. Among the 91 patients, *Candida* spp was isolated in 40 (83.3%) who used prostheses and in 23 (53.5%) in the control group [15].

*Candida albicans* is the most frequent fungus in root canals forming biofilms, regularly found in primary endodontic

infections than in persistent infections, in which this yeast is resistant to irrigants and causes endodontic failure.

### 3.2 Diagnosis

CHROM agar for *Candida* speciation is a differential cultivation method that facilitates the isolation and identification of some clinically important species [16]. The cultures are sensitive for detecting viable *Candida*. At the time of the first positive blood culture, the mean *Candida* concentration is 1 CFU / ml [17].

Biochemical profiling based on vibrational spectroscopy reflects the variability of chromosomal patterns and DNA content of clinical isolates of *Candida* species and can facilitate diagnosis and targeted therapy of candidiasis [18]. Restriction enzyme analysis with MwoI and BstI can be used for *Candida* species identification in situations where rapid identification is necessary or conventional methods are problematic [19]. The application of *C. albicans* microarrays in early studies on pathogenesis, cell biology, antifungal susceptibility and diagnostics confirmed their usefulness, and the results showed good correlations with data obtained with other techniques. These studies and those published in the near future will surely be the basis for a better understanding of the biology of this pathogen [20].

Presumptive identification of fungal species was performed using conventional methods like colony characteristics on CHRO Magar *Candida* medium, germ tube production and evaluation of fungal morphology on corn meal agar. Confirmation of presumptive *Candida* isolates was performed by PCR-RFLP [21]. A potential for electrochemical impedance detection of *Candida albicans* at clinically relevant concentrations was demonstrated. The developed sensor showed high sensitivity and specificity towards *Candida albicans* providing rapid and accurate detection in less than 1 hour. Future work requires optimization of the sensor functionalization protocol to ensure more reliable target binding [22]. EphA2-deficient mice demonstrated reduced inflammatory responses and IL-17 signalling, resulting in severe disease. Therefore, EphA2 PRR in oral epithelial cells is key to detect *C. albicans* and induce an immune response [23].

Currently, many laboratory methods are available for the identification of this fungus; *C. albicans* is a bacterium that is well studied, its form, behavior and the media in which it develops; therefore, it can be easily identified by different diagnostic methods.

### 3.3 Clinical Manifestations

*C. albicans* is the most common and best studied of the *Candida* spp., that naturally colonizes the skin, genital and/or intestinal mucosa in up to 70% of healthy individuals [24]. The most common oral manifestation in HIV-infected subjects taking Highly Active Antiretroviral Therapy (HAART) was hyperpigmentation. *Candida* colonization was detected in 64%, 65%, and 35% of HIV-infected subjects taking HAART, subjects without HAART pretreatment, and HIV-negative subjects, respectively. Interestingly, the group that had not received HAART was colonized more by non-*albicans* species [25]. In pediatric AIDS patients, the sample consisted of 117 children. A dental examination assessed the prevalence of dental caries. The prevalence of oral *Candida* colonization was 62%. Only seven children presented clinical manifestation of oral candidiasis despite their high viral load index and low CD4 count for their age [26]. This fungus can rarely cause clinically significant pneumonia in adults and

should be considered in the differential diagnosis of suppurative granulomas in the lung [27]. *Candida albicans* is closely associated with the occurrence of oral diseases such as childhood caries, root caries, periodontitis, root canal infection, soft tissue infection and facial space infection [28]. Similarly, this microorganism colonizes the gastrointestinal (GI) and genitourinary tract of healthy individuals [29]. Clinical manifestations included pain (82%), edema (71%), limited function (39%) and erythema (22%) with knees (75%) and hips (15%) most commonly infected. *Candida albicans* constituted 63% [30]. This pathogen is considered one of the most resistant fungal species, which are responsible for root canal treatment failures. The collagenolytic activity of this microorganism promotes colonization in the root canal, as it uses dentin as a source of nutrients, leading to its high virulence [31].

*Candida* manifests itself in different sites of the organism, mainly in patients who are immunosuppressed and is increasingly found in the oral cavity, where in the endodontic area, it is the main fungus found in the root canal and also in endodontic failure.

### 3.4 Antimicrobial Resistance

*C. albicans* biofilms are inherently resistant to antifungal drugs, the host immune system, and environmental stresses. Biofilm is a major virulence factor and an important clinical challenge [32]. The plasticity of the mycelial form is a determinant of drug resistance and is also an important form during the infection stage [33]. Once a biofilm of this fungus forms on an implanted medical device, it acts as a reservoir of pathogenic cells, is highly resistant to drugs and the host immune system, and has the potential to seed disseminated bloodstream infections (candidemia) that can lead to systemic invasive tissue and organ infections [34]. This fungus can occur and transform between the spore, hyphal and mycelial stages [35]. In addition, transformation to hyphal yeast can help fungi escape macrophage phagocytosis, which increases the likelihood of invading host tissues and causing further damage [36]. A phenomenon of increasing resistance of *Candida* spp. to azoles has been observed for several years, one of the mechanisms of lack of sensitivity to azoles is associated with CDR1, CDR2 and MRD1 genes [37]. The role of fungi in endodontic diseases is also well documented. Persistence of virulent microorganisms and their by-products in the root canal system, or surrounding tissues, after initial endodontic treatment is the main cause of treatment failure [38]. *C. albicans* and *C. glabrata* are resistant to several agents, including calcium hydroxide (Ca(OH)<sub>2</sub>), used in root canal therapy [39].

*C. albicans* is a fungus which is difficult to eradicate, due to its resistance mechanism against different antibiotics, the immune system and biomechanical endodontic treatment. The literature mentions that when it forms its biofilm, it becomes a clinical challenge, because it serves as a reservoir for other pathogens.

### 3.5 Treatment

Several treatments have been used to eliminate *Candida*, among them, NaOCl and EDTA showed a measurable antimicrobial effect, even in the presence of dentin powder, which may be promising in the reduction of *C. albicans* in root canal therapy [40]. Also, the association of 2% chlorhexidine followed by ozone gas for 24 seconds promoted the complete elimination of *Candida albicans* and *Enterococcus faecalis* [41].

A 0.0156% concentration of alexidine may be a good alternative to chlorhexidine as an irrigation solution in endodontic treatment when used for one minute against *E. faecalis* and *C. albicans* [42]. Also, probiotic organisms of *Lactobacillus* and *Bifidobacterium* species are suggested to be effective in preventing the growth of *E. faecalis* and *C. albicans in vitro* [43]. This microorganism can only be completely inhibited by direct contact with a saturated aqueous calcium hydroxide solution after 48 hours of exposure [44].

The antibacterial photodynamic therapy and calcium hydroxide therapy showed the same antimicrobial efficacy on *E. faecalis* and *C. albicans* [45].

QmiX, a root canal irrigation mixture of ethylenediamine tetraacetic acid (EDTA), chlorhexidine (CHX) and surfactant, showed inhibitory effects against *Enterococcus faecalis* and *Candida albicans*, better than Guava leaf extract, aloe vera extract, 2.5% sodium hypochlorite and 2% chlorhexidine [46].

The EndoVac irrigation/aspiration system associated with chemomechanical debridement was the most effective therapeutic protocol for reducing intra-canal levels of *C. albicans* [47].

AH 26 exhibited strong activity against this pathogen with the minimum inhibitory concentration of 12.5 mg/ml [48].

In order to eliminate *C. albicans*, the literature mentions that if it comes in direct contact with calcium hydroxide, it can be completely inhibited after 48 hours. It mentions that the most favorable irrigant to eliminate it was QmiX, and EndoVac as a suction system together with chemomechanical debridement was the most effective protocol to eliminate *C. albicans*.

## 4. Conclusions

*C. albicans* is a pathogen that primarily affects the skin and gastrointestinal tract. However, it has been increasingly found in the oral cavity, for example, in association with endodontic failures. Its diagnosis is mainly by cultivation and, due to its resistance to drugs, biomechanical treatment and biofilm formation, chemomechanical therapy is necessary for its intra-canal elimination. The literature mentions that the most effective method to suppress this fungus is by using the QmiX irrigant and the Endo Vac as a suction system.

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