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# Candida albicans: An orthodontic point of view

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**Abstract**
**Introduction:** Patients with long-term fixed and removable orthodontic treatment are susceptible toward an increase in oral microflora, especially Candida albicans, which can have repercussions by increasing the risk of periodontal lesions such as cariogenesis.
**Objective:** To analyze the literature on the relationship between C. albicans and orthodontics and its epidemiology, diagnostic methods, pathogenicity and treatments.
**Methodology:** A literature review was performed in databases with high impact such as PubMed, Scopus and Web of Science, including relevant articles from 2009 to 2022 using keywords such as: "Candida albicans", "oral candidiasis", "candidiasis", "orthodontic", "dental", "epidemiology", "diagnosis", "pathogenesis", and "treatment".
**Results:** This fungal microorganism has a mortality rate of 40%, mainly in immunosuppressed patients. Fixed orthodontic appliances generate a significant increase for invasion by C. albicans. There are different diagnostic methods, including PCR examination, cytological smears, Gram stains, calcofluor white or fluorescent antibodies. In orthodontic patients it can be detected by clinical findings and by a decrease of HBD-3 and IL-1. Pathogenicity is directly related to host defenses, which control initial growth and inhibit subsequent tissue invasion. Treatment recommends good oral hygiene, such as manual brushing, use of chlorhexidine, ultrasonic cleaning, and the use of tablets over dentures for removable orthodontic appliances.
**Conclusion:** Proper oral hygiene is needed during orthodontic treatment, as it is essential to reduce the presence of Candida albicans, decreasing the possibility of periodontal disease and cariogenic risk.

**Keywords:** Candida albicans, oral candidiasis, candidiasis, orthodontic, dental, epidemiology, prevalence, incidence, diagnosis, pathogenesis, pathogen and treatment

## 1. Introduction
Fixed orthodontic appliances can act as a reservoir for yeast and predispose to the development of oral candidiasis in the patient [1]. Candida is a pathogen found in 50-60% of healthy people and is harmful when the human immune defense is compromised [2]. It is classified as a type of fungus that is frequently found in the oral cavity of healthy individuals and is considered a member of the normal oral microbiome. They are normally harmless, but when conditions in the mouth are altered to an environment that favors the proliferation of Candida albicans, the shift to host pathology occurs. Occasionally, it can enter the bloodstream, then spread to many organs with potentially fatal infection [3].
Orthodontic treatment is associated with changes in oral microbiota, increasing Candida colonization. This can cause oral lesions and infections such as candidiasis, angular cheilitis, among others. Poor grooming facilitates colonization of these organisms [4]. Complex appliances greatly inhibit oral hygiene of patients, which predisposes to increased accumulation of dentobacterial plaque [1]. Compared to subjects without braces, patients with braces reported significant qualitative and quantitative differences in supra- and subgingival plaque throughout the treatment period. Certain components of fixed appliances (mainly bonded molar brackets, ceramics and elastomeric ligatures) showed high risks as periodontal disease and dental caries for patients [5].

Long-term use of fixed and removable orthodontic appliances creates a favorable environment for the increase of normal oral microflora, particularly Candida species, which may increase risks, e.g., periodontal lesions [6].

After the literature review, it can be observed that there are not enough articles on Candida albicans in relation to orthodontic treatment, however, it is a fungus present in a large percentage of patients. Therefore, the objective of this review is to perform a literature-based analysis of the relationship between C. albicans with orthodontics and its epidemiology, diagnostic methods, pathogenicity and treatments.

## 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 guidelines, i.e., identification, review, choice and inclusion. The quality of the reviews was assessed using the measurement tool for evaluating systematic reviews. The search was performed using Boolean logical operators AND, OR and NOT. The search was performed using Boolean logical operators AND, OR and NOT; with the keywords: "Candida albicans", "orthodontics", "dental", "epidemiology", "diagnosis", "pathogenicity", "treatment". The keywords were used individually, as well as each of them related to each other.

## 3. Results & Discussion

### 3.1 Epidemiology

Invasive candidiasis is a fungal infection caused by several types of Candida; C. albicans is the most common species, but its prevalence varies considerably depending on geographic location [7]. It occurs equally in men and women, with higher frequency in childhood and old age [8]. However, in a study of 160,357 patients, where 6.09% were diagnosed with oral candidiasis (OC), women had higher infection rates than men. Of the 11,161 Candida isolates, C. albicans is the most common species (75.37%), followed by C. tropicalis (6.06%), C. krusei (2.79%) and C. glabrata (2.02%) [9].

Over the past few decades, Candida albicans has emerged as the leading causative pathogen in invasive fungal infections, being potentially fatal with mortality rates of approximately 40% despite treatment [10, 11]. The overall prevalence of OC among HIV-infected children was 23.9% and C. albicans was the most predominant etiologic agent [12]. Patients with HIV, anemia-or radiation-related stomatitis and Sjögren's/xerostomia syndrome were highly susceptible to oral candidiasis [8]. Patients with xerostomia had a higher risk of developing oral candidiasis and oral fungal growth than non-xerostomia groups [13]. In addition, another study on the presence of local host factors, including xerostomia, orofacial clefts, dentures, fixed orthodontic appliances (FOA) and oral mucous membrane atrophy, found that these lead to a significant increase in Candida colonization [14].

C. albicans is the most common fungal infection, usually occurring in very young and older patients. It has a considerably high mortality rate of 40%, mostly in immunosuppressed patients. The presence of local host factors, such as fixed orthodontic appliances, generate a significant increase of invasion of the fungal microorganism.

### 3.2 Diagnostic Methods

Candida can be commonly found in the gastrointestinal tract of humans and as normal skin flora, apart from mucous membranes [15]. Diagnosis is based on clinical findings. A cytologic smear can help confirm the diagnosis in situations where lesions do not respond to empirical antifungal treatment [16]. In addition, there are efficient techniques used for molecular typing of Candida species, which are: multilocus enzyme electrophoresis, fragment length polymorphism, electrophoretic karyotyping, random amplified polymorphic DNA and multilocus sequence typing [17]. Other tests include Gram staining, calcofluor white or fluorescent antibodies. Differential diagnosis includes infections with organisms that cause lesions of similar appearance (viral, bacterial) or trauma [18].

The real-time PCR assay does not require prior identification of clinical isolates by yeast, such as C. albicans, by germ tube formation and accurately reports results within 2 hours. Detection of amplicons by agarose gel electrophoresis is also suitable for resource-poor settings devoid of real-time PCR facilities [19]. In recent years, data have been emerging for tests other than culture such as mannan/anti mannan, Candida albicans germ tube antibody, 1,3-β-d-glucan, PCR, and the Candida T2 panel. In most settings, positive predictive values to the nonculture test are low and those negative are high [20].

Patients with fixed orthodontic appliances are primarily colonized by C. albicans, which it is related to decreased HBD-3 expression and IL-1 levels [21]. A central role is played by IL-1 in the induction of type 17 innate immune responses to eliminate C. albicans-related infections [22].

Candida albicans has different methods to be detected, including PCR, cytologic smear, Gram stain, calcofluor white or fluorescent antibodies. In orthodontic patients it can be detected by clinical findings and by a decrease in HBD-3 and IL-1 studies.

### 3.3 Candida albicans infection - Pathogenicity

Candida albicans may be eliminated by immune cells rapidly or spread hematogenously, leading to life-threatening systemic infections [23]. The interaction between C. albicans and host cells is characterized by a complex interplay between the expression of fungal virulence factors, resulting in adherence, invasion, and cell damage. Likewise, the host immune system, which responds by secreting proinflammatory cytokines, triggers antimicrobial actions, ultimately killing the fungal pathogen [24]. For example, innate host immunity to Candida critically requires pattern recognition receptors (PRR), and defense against infection is provided by an interaction between the innate and adaptive arms of the host immune system [25]. This recognition is mediated by several classes of PRR, including Toll-like and C-type lectin receptors. C. albicans cell wall components interact with PRR that are expressed by different cells, mainly antigen-presenting cells [26]. Dectin-1, the transmembrane receptor on epithelial cells and phagocytes, plays a key role in C. albicans recognition, resulting in activation of CARD9 that stimulates differentiation of CD4+ T cells to the Th17 phenotype [27].

Central to this protection are the Th1 and Th17 adaptive cellular responses, which are considered paramount for successful immune defense against C. albicans infections, allowing tissue homeostasis to be maintained in the presence of colonizing fungi [28]. T helper 17 (Th17) adaptive immune response is primarily involved in mucosal host defense, controlling initial Candida growth and inhibiting subsequent tissue invasion. On the part of innate immunity, saliva is considered to be enriched with anti-candida peptides preventing adhesion of the fungus to epithelial cells [29]. In

another study in mice, it was shown that in the oral cavity B lymphocytes contribute to the commensal control of C. albicans carriage by secreting IgA at the foci of colonization, thus preventing imbalance of fungal colonization [30].

Candida albicans infection is characterized by a complex interplay between the expression of fungal virulence factors and the host immune system. The pathogenicity of C. albicans is directly related to host defenses, which control initial growth and inhibit subsequent tissue invasion.

### 3.4 Treatments

Oral candidiasis usually occurs secondary to immunosuppression, either due to decreased immune function in the patient's mouth or systemically, being sensitive to antifungal agents [31, 32]. Patients on antifungal treatment showed significant improvement to the oral mucosal condition. Sensation symptoms such as burning, pain, tongue flaring and xerostomia disappeared. After two weeks, a second study of the fungicide treatment was performed and the results showed a reduced presence of Candida and a reduced degree of dissemination [33].

Antifungal drugs have efficacy in the treatment of oral candidiasis [34]. Fluconazole and itraconazole are the two commonly prescribed systemic azole antifungal agents [35]. In a meta-analysis by Fang et al., itraconazole capsules (51.2%), itraconazole oral solution (75.2%), miconazole tablets (34.4%), miconazole oral gel (76.9%), clotrimazole (64. 8%), fluconazole (79.3%), ketoconazole (50.7%), nystatin (15.7%) and amphotericin B (44.4%) showed better results for the treatment of oral candidiasis than placebo (6.80%). The most effective in reducing the risk of mycologic cure rate in oral candidiasis was fluconazole [34]. Similarly, it is widely used in the clinical treatment of Candida albicans infections. However, fluconazole only has fungistatic activity in Albicans, therefore, long-term treatment could generate resistance to this active [36]. Due to resistance, there is another intravenous echinocandin-based treatment with caspofungin, micafungin and anidulofungin, which is considered as the first-choice treatment for disseminated candidiasis, especially in patients with neutropenia. Treatment with intravenous echinocandin is associated with increased survival compared to patients treated on amphotericin B and fluconazole [37].

For pregnant women, topical therapy is the recommended treatment, since oral therapy may cause side effects such as miscarriage or fetal death. Clotrimazole dissolving oral tablets or miconazole mucoadherent tablets are used over a period of 7 to 14 days with nystatin oral suspension. Topical use of these drugs has not been associated with congenital malformations and is considered safe due to limited systemic absorption [38]. In a study by Yang et al. the presence of FOA was shown to disrupt C. albicans colonization and may increase the risk of patients to Candida infections [39]. Treatment of C. albicans in orthodontic patients has several ways to be taken care of, such as manual brushing (89.9%), chlorhexidine (95.8%), ultrasonic cleaning (99.9%) and denture tablets (100%) [40].

The most applied and effective treatment for a long time has been fungicides, in which fluconazole was mostly used. However, resistance has been generated by Candida albicans, so alternative treatments such as intravenous echinocandin have been sought. For treatment in orthodontic patients, good oral hygiene is recommended; such as manual brushing, use of chlorhexidine, ultrasonic cleaning and use of denture tablets for removable orthodontic appliances.

## 4. Conclusions

Candidiasis is found in 50-60% of healthy people, it is harmful when the human immune defense is compromised. Orthodontic treatment is associated with changes in the oral microbiota, increasing Candida colonization. It can cause oral lesions and infections such as candidiasis, angular cheilitis, among others. The methods for the detection of candidiasis are PCR test, cytological smear, Gram stain, calcofluor white or fluorescent antibodies. The most widely applied and effective treatment has been fungicides such as fluconazole. However, fluconazole has generated resistance due to continuous use, so alternatives such as intravenous echinocandin have been sought. In addition, in patients with orthodontics, good oral hygiene is recommended, such as manual brushing, use of chlorhexidine and ultrasonic cleaning.

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