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**Review Article**

# Salivary Lactoferrin in HIV-Infected Children: It's Importance on Antifungal Activity against Oral *Candida Albicans* Infections

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## Abstract

Children living with HIV constitute a population highly susceptible to a variety of opportunistic infections, among which oral candidiasis is the most common oral manifestation, despite its decreased prevalence after introduction of the treatment with highly active antiretroviral therapy. Among the pathogens, *Candida albicans* is responsible for most of the oral lesions in HIV-infected patients, which, after the initial adhesion and multiplication, starts to penetrate and invade host tissues. These mechanisms are related to the production and secretion of hydrolases such as proteases and phospholipases. Its diversity and abundance is influenced by host's specific and non-specific components, such as lactoferrin, which is a multifunctional glycoprotein, from metalloproteins group, which performs iron transport. Lactoferrin is present in various body fluids such as saliva, tears, semen, sweat, colostrum, milk and nasal secretions in the innate immune system, especially for protecting the mucosal surface from microbial infections. This article aimed to review studies evaluating the role of salivary lactoferrin in the modulation of *Candida* spp infection and possible mechanisms of evasion used by *Candida* spp. in HIV-infected children. In conclusion, despite the fact that lactoferrin harbors a significant antifungal effect against *Candida* spp., the prevalence of oral candidiasis is still high among HIV-infected children, so it is important to investigate the evasion mechanisms involved on this fungus resistance to conventional treatments, in order to justify the high incidence of candidiasis among pediatric patients living with HIV.

**Keywords:** Lactoferrin; HIV; Children; Infectious disease; *Candida albicans*; Oral manifestations

## Introduction

It is estimated that 34 million people worldwide were infected with the Human Immunodeficiency Virus (HIV) in 2012, and approximately 260,000 children have been killed by the disease, only in 2009 [1]. In Brazil, it is suspected that 700,000 people were living with HIV in 2013 and among them, 21,000 cases were children up to 14 years old. Due to major advances in the disease control in the last decade, new cases continue to decline globally, but in some countries the national epidemic is still expanding [2].

The oral manifestations may be one of the first clinical indicators of HIV infection and are directly related to disease progression in children [3]. Since the mouth is readily accessible, these oral signals should be used to help diagnose, prevent and intervene in the HIV infection progression to AIDS [4]. Oral candidiasis is the most common oral manifestations in children, despite its decreased prevalence after the introduction of the treatment with highly active antiretroviral therapy (HAART). *Candida albicans* is the most frequently etiologic agent found in these lesions, but other species such as *Candida* tropicalis, *Candida* parapsilosis, *Candida* stellatoidea, *Candida* krusei, *Candida* glabrata, *Candida* guillermondii, and *Candida* dubliniensis have emerged as pathogens that cause fungal infections [5].

*Candida* spp: Have several virulence factors that influence disease development, including adhesins (molecules that modulate the microorganisms adhesion to host cells and their ligands), and hydrolytic enzymes (such as phospholipase and protease) which contribute to tissue invasion, leading to a dysfunction or a disruption of the host cell membrane, promoting the adherence and colonization of *Candida* spp [6].

Saliva plays an important role in the oral health maintenance and, among its various components, salivary lactoferrin is essential to the individual, especially for protecting the superficial mucosa from microbial infections [7]. Studies showed that salivary lactoferrin can act as an inhibitor of infection due to *Candida* spp., by modulating this fungus growth in the oral cavity [8,9]. Nevertheless, immunocompromised patients due to HIV infection, still develop oral candidiasis more frequently, when compared to healthy patients. Given this context, this article aims to review studies evaluating the role of salivary lactoferrin in the modulation of *Candida* spp. infection and possible mechanisms of evasion used by *Candida* spp in HIV-infected children.

## Background

### The HIV infection in children

Human Immunodeficiency Virus infection in children was first

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described in 1983. Although the disease course have many similarities in pediatric patients with the disease progression in adults, some differences are found, as the spectrum of the disease, natural history, risk factors, form of transmission and seroconversion patterns. In 85% of HIV pediatric cases, the virus transmission occurred through vertical transmission and can occur during pregnancy, childbirth or after birth through breastfeeding [10].

HIV infection manifests itself differently in adult and infant carriers, since pediatric patients enjoy a still immature immune system leading to a more severe deficiency of defense against infections [11]. HIV-related oral manifestations are observed, such as oral candidiasis, herpetic stomatitis, linear gingival erythema, gingivitis, hairy leukoplakia, parotid hypertrophy and aphthous ulcers. These oral lesions are reported as the first indicators of infection since they are directly related to the degree of patient's immunosuppression, which directs the disease progression [10,12].

## Oral candidiasis among HIV infected children

Immunocompromised individuals, especially those infected with HIV, constitute a population that is highly susceptible to a variety of opportunistic infections. Among the pathogens, the fungi of the species *Candida albicans* are responsible for most of the oral lesions reported in HIV-infected patients. This fungus is normally present as commensal in the oral cavity of healthy individuals and also the gastrointestinal and genital tracts, but may take pathogenic characteristics in immunocompromised individuals, changing the harmony with the host [3]. Oral candidiasis is a strong immunodeficiency indicator and is considered the first clinically observable manifestation of the disease and, therefore, has a high predictive value in the development of AIDS [3,4,12]. However, a decrease of this infection is currently observed after the introduction of HAART, primarily due to an improved immune function of patients with increased levels of CD4 T-lymphocytes, thus making them less susceptible to opportunistic infections [11,13-15].

Species other than *Candida albicans* are also emerging as causative pathogens of fungal infections, such as *Candida* tropicalis, *Candida* krusei, *Candida* glabrata, *Candida* stellatoidea, *Candida* parapsilosis, *Candida* dubliniensis and *Candida* guillermondii [13]. The best recognized form of *Candida* spp. infection and most often found in HIV-infected patients is pseudomembranous candidiasis, characterized by the presence of an adherent white plaque on the mucosa. The erythematous candidiasis is also common, despite being clinically overlooked, and may occur on the tongue, hard palate region and labial commissures, yielding to angular cheilitis. Chronic hyperplastic candidiasis is the rarest type, as this condition is a candidiasis superimposed on a preexisting oral leukoplakia. The frequency and intensity of the damage is directly related to the degree of immunosuppression.

*Candida* spp. have the ability to survive as commensal in anatomical regions with distinct characteristics and under different environmental pressures, which gives them the ability to cause a greater variety of diseases [6]. This is related to the expression of different genes that promote cell wall synthesis in different environments, such as the bloodstream, where the pH is neutral, and in the vaginal canal, a region with acidic pH [16].

The transition from a commensal organism to a pathogen may be associated with prolonged use of antibiotics or corticosteroids and radiotherapy [17], as well as folic acid and iron deficiencies, xerostomia [18], poor oral hygiene, high-carbohydrate diet, gingivitis [19], reduced flow and salivary pH, decreased salivary components (lactoferrin, histatin 5, IgA), immune system failure such as in HIV infections [13,18,19], and the presence of carious lesions [5,15].

## *Candida albicans*' virulence factors

After the initial adhesion and multiplication, *Candida albicans* starts to penetrate and invade host tissues. These mechanisms are related to the production and secretion of hydrolases such as proteases and phospholipases [20]. These enzymes provide nutrients necessary for *C. albicans* maintenance by polymer breakdown and inactivation of host defense molecules [16], furthermore, damaging the lipid and protein constituents of host cells membranes [21].

### Proteases

Microorganisms are capable of producing and secreting aspartic proteases to acquire nutrients. However, this biochemical ability provides specialized functions to pathogens in the infectious process, promoting host protein degradation, and play an important role during the fungal infection, such as adhesion, cell invasion, nutrition, evasion, cell proliferation and differentiation [22].

The major proteolytic activity described for *Candida albicans* refer to secretory aspartic proteases, which are involved in adhesion to host cells, degradation of host extracellular matrix proteins such as laminin, fibronectin, collagen, and defense proteins such as IgA, IgG, C3 and 9C3bi [22]. Matrix metalloproteinases (95kDa) are also capable of hydrolyzing the host subendothelial extracellular matrix components such as collagen type I and IV, laminin and fibronectin. This indicates that these enzymes might facilitate dissemination of *C. albicans* in tissue after its passage through the endothelial layer, thus allowing fungus invasion to target organs [23].

A greater protease expression and activity is observed among HIV-infected patients, when compared to patients without clinical signs of immunosuppression. De Brito et al [24] showed that *C. albicans* isolated from the oral cavity of HIV-infected children presented both metalloproteinase and secretory serine protease activity. C. guilliermondii isolates from HIV-infected patient showed protease activity at physiological pH, cleaving ability of a broad spectrum of protein substrates as lamina, fibronectin, serum albumin and human immunoglobulin G. However, the greatest expression of these enzymes does not lead to higher incidence of oral candidiasis [20]. Koga-Ito et al. [25] observed a greater expression of protease in oral *C. albicans* isolates from patients with denture prosthodontics with oral candidiasis. Although the expression of aspartic protease alone is not decisive for the establishment of infections caused by *Candida* spp., inhibitors of these enzymes are resources that can be used to prevent the onset and progression of these infections [26].

### Phospholipases

Specific virulence factors are required for a pathogenic organism to penetrate the eukaryotic epithelial cell barrier of the human host. An important virulent attribute of *C. albicans* is its ability to produce extracellular phospholipases, which deteriorate phospholipid constituents of the host cell membrane, leading to cell disruption,

what facilitate cellular invasion. Barrett-Beeet al. [27] showed that *C. albicans* strains with the highest phospholipase activity exhibited the highest adherence to oral epithelial cells and a greatest ability to kill mice after intravenous inoculation, when compared with yeasts with a low degree of phospholipase activity.

As phospholipids are a foremost constituent of the host cell envelope, enzymes capable of hydrolyzing phospholipids i.e. phospholipases, are likely to play a critical role in host cell invasion. By cleaving phospholipids, *candidal* phospholipases undermine the membrane and cell lysis is the end result. Another important aspect is that filamentous *candidal* hyphae are critical in this process and, together with the extracellular phospholipases, facilitate the yeast invasion of the host tissues. Therefore, both physical or enzymatic activities, or a combination of both, are associated with the pathogenesis of *candidal* disease [28].

## Host defense: salivary lactoferrin

The oral cavity surface is heavily colonized by microorganisms. The microbiota diversity and abundance is influenced by host's specific and non-specific components, such as antimicrobial proteins associated with the secretory immune system (lysozyme, lactoferrin, histatin-5, mucin, cystatin and agglutinin). Most of these proteins may inhibit the metabolism and adherence of these microorganisms in vitro [29], while maintaining and protecting the integrity of the oral mucosa [30]. Generally, the antimicrobial activity of these components depends on the disruption of the bacterial and fungal cells membranes [31], suppression of mitochondrial respiration [32], glucose utilization [33] or activation of neutrophils and macrophages [30].

Lactoferrin is a multifunctional glycoprotein, from metalloproteins group, which belongs to the transferrin family. It has a molecular weight of 80kDa and a porphirin core similar to hemoglobin, performing iron transport [34]. Lactoferrin is expressed in mucosa, endometrium, vaginal epithelium, prostate and seminal vesicle [35]. Is present in various body fluids such as saliva, tears, semen, sweat, colostrum, milk and nasal secretions in the innate immune system of the individual, especially for protecting the mucosal surface from microbial infections [35-37].

This glycoprotein possesses many properties: bacteriostatic and bactericidal activities, anti-inflammatory, fungicides, antiviral and antioxidant [38]. The main lactoferrin action mechanisms are sequestering ferrous ions, leading to elemental iron deprivation necessary for yeast metabolism [39], activation of the intracellular autolytic enzyme system subsequent to adsorption of lactoferrin [40], structural changes induced in the cell walls of the yeast and increasing the number of natural killer cells and T cells in peripheral blood by increasing the phagocytic activity of neutrophils [41].

Lactoferrin is considered a cytokine, responsible for coordinating the human cellular response, acting in the maturation and activation of macrophages and neutrophils. Its deficiency cause suppression of the immune system and its excess causes an exacerbated immune response [42]. Polymorphonuclear neutrophils are rich in lactoferrin, which act as a protective factor against various infections [43]. Lactoferrin can directly regulate the inflammatory response [7] and may bind to bacterial endotoxin [36,44]. Its antimicrobial activity is attributed to the property to chelate the iron ion, depriving thus microorganisms of its essential elements [29,44].

Whole saliva concentration of lactoferrin in adults is approximately 2.95 to 10.49 mg/L [45]. HIV-infected adults exhibit a significant reduction in the secretion of salivary glands [46], and significant variations in lysozyme concentrations and lactoferrin in the saliva occur during disease progression [9,47].

Although HIV-infected children shows higher concentration of salivary lactoferrin when compared to patients without clinical evidence of immunosuppression, oral candidiasis is still present and in high prevalence among this special patients [47].

The antifungal activity of lactoferrin was first reported by Kirkpatrick et al., in 1971 [8]. In combination with fluconazole, it was used to reduce the amount of drug needed to reach inhibitory concentration to eliminate clinical isolates of *Candida* spp., thus suggesting that lactoferrin may have a potential use in combination with drugs against resistant infections by *Candida* spp [48].

## Lactoferrin evasion strategy of *Candida albicans*

*C. albicans* has developed an excess of iron acquisition systems [49]. The siderophore uptake system, via Sit1/Arn1 (siderophore iron transport 1), is used to steal iron from siderophores produced by other microorganisms without producing its own siderophores [49,50], so *C. albicans* can further bind host ferritin with the hyphae-associated adhesion and invade host cells [49-51]. Another iron acquisition system is a reductive system, with its large gene families of reductases, oxidases and iron permeases [49], that mediates the iron acquisition from host ferritin, transferrin or, if available, free iron from the environment. *C. albicans* can also use heme-iron uptake system from host hemoglobin and hemoproteins by first expressing haemolysins that disrupt red blood cells [49,50]. Subsequently the iron acquisition is mediated by the heme-receptor gene family members RBT5, RBT51, CSA1, CSA2, and PGA7 (RBT6) [50].

*Candida* spp. can use these systems to produce resistant infections. As a treatment alternative for *Candida* infections, synergistic inhibitory effects on *Candida* growth were found for combinations of lactoferrin and fluconazole or amphotericin B. In HIV-infected patients expressing oral candidiasis infections resistant to conventional antifungal treatments, an alterantive is to oral mouthwash containing lactoferrin and lysozyme in combination with an antifungal agent as itraconazole. This indicates that for treatment of oral Candidiasis a formulation containing lactoferrin seems appropriate; results may be optimized if the formulation is provided with buffer capacity to attain pH 7.5 in the mucosal fluid. The synergistic effects between lactoferrin and 'standard' antifungals indicate that combinations should be considered in such a formulation [52].

Another alternative against systemic infection caused by *Candida albicans* is treatment with orally administered lactoferrin. Samaranayake et al. [9] demonstrated the effectiveness of lactoferrin against oral candidiasis, which has been obtained by means of food supplements. This study was made with bovine milk lactoferrin, suggesting that the cow's milk can be used as a supplement to support antifungal chemotherapy without side effects. Also, bovine lactoferrin has beneficial effects on oral candidiasis, and may be used as a dietary supplement, supporting the antifungal chemotherapy and improving

the quality of life of patients living with HIV without side effects since it is a endogenous protein.

## Conclusion

Despite lactoferrin presents a significant antifungal effect against *Candida* spp., the prevalence of oral candidiasis is still high among HIV-infected patients. Thus, it is important to investigate the evasion mechanisms involved on this fungus resistance to conventional treatments, in order to justify the high incidence of candidiasis among pediatric patients living with HIV. A promising alternative is the combined use of lactoferrin and antifungals for the treatment of *Candida* spp. infections. It is noteworthy, therefore, the important role of the pediatric dentist in the hospital health team for early diagnosis of *candida* infections in these immunocompromised patients, since mouth is the first location of appearance of these lesions, which are closely related to the progression of HIV infection.

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