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REVIEW ARTICLE

Oral candidiasis: an opportunistic disease

Candidiasis oral: una enfermedad oportunista

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ABSTRACT

Introduction: oral candidiasis is an opportunistic fungal infection of the oral mucosa caused by Candida albicans, a commensal organism adaptable to the human host, but changes in the host microenvironment can favor the transition from commensal to pathogen, causing dysbiosis in the oral cavity.
Objective: to analyze oral candidiasis as an opportunistic disease in immunocompromised patients and its relationship with various risk factors, clinical manifestations and therapeutic options.
Methods: this article was structured from a systemic review of the literature through platforms such as Scielo, Biblioteca Virtual em Saúde, Pubmed, LILACS, Science Direct, Elsevier, and Google Scholar, using as a filter tool for articles published internationally in a time period of five years, 2019-2023.
Development: it is a common opportunistic infection in individuals with weakened immune systems. The main associated risk factors include the use of drugs, ill-fitting dentures and the presence of systemic diseases. Clinical manifestations vary from mild lesions to severe forms that can compromise the patient's quality of life. Treatment is based on topical or systemic antifungals, as well as identification and correction of predisposing factors. Understanding the risk factors, clinical manifestations and therapeutic options is crucial for effective and timely management.
Conclusions: early diagnosis and a multidisciplinary approach are important to optimize clinical outcomes and improve the quality of life of patients affected by this condition.

Keywords: Oral Candidiasis; Oraldysbiosis; Soft Tissues; Oral Pathology.

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RESUMEN

Introducción: la candidiasis oral es una infección fúngica oportunista de la mucosa oral causada por la *Candida albicans*, organismo comensal adaptable al huésped humano, pero los cambios en el microambiente del huésped pueden favorecer la transición de comensal a patógeno, causando disbiosis en la cavidad oral.
Objetivo: analizar la candidiasis oral como una enfermedad oportunista en pacientes inmunocomprometidos y su relación con diversos factores de riesgo, manifestaciones clínicas y opciones terapéuticas.
Métodos: el presente artículo fue estructurado a partir de una revisión sistémica de la literatura a través de las plataformas como *Scielo*, *Biblioteca Virtual em Saúde*, *Pubmed*, LILACS, *Science Direct*, *Elsevier*, y *Google Scholar*, utilizando como herramienta de filtros para los artículos publicados internacionalmente en un periodo de tiempo de cinco años, 2019-2023.
Desarrollo: es una infección oportunista frecuente en individuos con sistemas inmunitarios debilitados. Los principales factores de riesgo asociados incluyen el uso de fármacos, prótesis dentales mal ajustadas y la presencia de enfermedades sistémicas. Las manifestaciones clínicas varían desde lesiones leves hasta formas graves que pueden comprometer la calidad de vida del paciente. El tratamiento se basa en antifúngicos tópicos o sistémicos, así como en la identificación y corrección de los factores predisponentes. La comprensión de los factores de riesgo, las manifestaciones clínicas y las opciones terapéuticas es crucial para un manejo efectivo y oportuno.
Conclusiones: es importante el diagnóstico temprano y el abordaje multidisciplinario para optimizar los resultados clínicos y mejorar la calidad de vida de los pacientes afectados por esta afección**.**

Palabras clave: Candidiasis Oral; Disbiosis Oral; Tejidos Blandos; Patología Oral.

INTRODUCTION

The terminologies candidiasis or candidiasis are synonyms and are used for fungal infections caused by the fungus Candida albicans. Oral candidiasis is a Candida albicans infection of the oral cavity, first described in 1838 by the pediatrician Francois Veilleux. The lesion is known to rank second in oral cavity incidence among other oral mucosal diseases and accounts for more than 41,7 % of all oral cavity diseases.[1,2,3]

Candida species are normal components of the oral microflora and about 30 to 50 % are carriers of these organisms. The rate of this microorganism increases with age, especially in older age where they have recovered from the mouth of the patient over 60 years of age. Other species such as C. glabrata, C. tropicalis and C. guilliermondii are isolated infrequently but consistently.[4]

Early detection of oral candidiasis, clinically, is valuable because this disease is an early stage symptom of more serious or life-threatening disease in older adult and immunocompromised patients, however, currently available detection methods include examination of smears, swabs, biopsy, imprint specimens, whole saliva, mouthwash fluid, and cell culture.[5]

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The organism under favorable conditions has the ability to transform into pathogenic hyphae and these conditions are obtained secondarily and may be local or systemic: age factor (newborns and elderly); immunocompromised diseases such as HIV / AIDS; chronic systemic use of steroids and broad-spectrum antibiotics; inhaled corticosteroids, often prescribed in the preventive treatment of asthma and chronic obstructive pulmonary disease; xerostomia; the use of invasive devices (venous catheters), organ transplantation, diabetes, use of removable prostheses.[2,6]

Other factors that are related to the appearance of lesions are: dietary problems, deficient nutrition, lack of hygiene of the oral cavity and removable prostheses, endocrine alterations, severe blood dyscrasias, oncological patients who receive radiotherapy in the head and neck area, smoking and epithelial dysplasias.[2]

The classification proposed in 1990 by Holmstrup and Axel is based on two groups: primary oral candidiasis and secondary oral candidiasis. The first group is divided into acute forms comprising erythematous and pseudomembranous candidiasis; in the chronic form we have erythematous, pseudomembranous, nodular candidiasis and the lesions associated with Candida: medial rhomboglossitis, angular cheilitis, prosthetic stomatitis and linear gingival erythema associated with HIV.[2]

The above conditions correspond to primary candidiasis of the mouth; those of the secondary group are associated with systemic manifestations traversing with mucocutaneous candidiasis, nail involvement, vulvovaginal involvement, and sometimes affecting the larynx, pharynx and esophagus areas.[2]

The diagnosis of oral candidiasis is often clinical, based on the examination performed in the dental office, the performance of the anamnesis and the evaluation of risk factors. A biopsy is recommended for certain types in addition to empirical treatment. Cultures are usually performed if antifungal therapy is ineffective. Topical antifungal therapy and oral hygiene measures are generally sufficient to resolve mild oral candidiasis, and systemic antifungal therapy is generally reserved for patients who are refractory or intolerant to topical treatment and those at increased risk of developing systemic infections.[1]

The present study aims to provide a comprehensive and updated view of oral candidiasis as an opportunistic disease, highlighting its impact on the oral and general health of affected patients; by delving into the pathogenic mechanisms, risk factors and therapeutic options, it is hoped to contribute to scientific and clinical knowledge in the field of dentistry.

METHODS

The present work was performed in a systemic literature review through digital platforms such as Scielo, Biblioteca Virtual em Saúde , Pubmed, LILACS, Science Direct, Elsevier, and Google Scholar, using as a filter tool for articles published internationally in a time period of five years, 2019-2023, limiting in English, Spanish and Portuguese languages, using a combination of keywords such as "oral candidiasis", "oral dysbiosis", "candidíase na boca", "risk factors", "candida albicans", "oral phototherapy" and other related terms. The search strategy will be adjusted to the specifications of each database to obtain relevant and complete results.

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In this search a total of 36 articles were obtained that have a close relationship to the topic, such as oral candidiasis, with the purpose of establishing and describing its manifestation in the mouth, symptomatology and treatment in these patients, where inclusion and exclusion criteria were applied.

Inclusion criteria included systemic reviews and meta-analysis, in which the final results were similar to those proposed in this review, obtaining 21 articles and clinical case reports; exclusion criteria discarded articles that presented obsolete data, excluding 15 articles.

Inclusion criteria

1. Study population: The selected articles and journals should include studies conducted in humans presenting with oral candidiasis, regardless of age, gender or general health status.
2. Type of study: Observational studies (cohort studies, case-control studies, cross-sectional studies) and controlled clinical trials (randomized clinical trials) investigating epidemiological, clinical, diagnostic or therapeutic aspects of oral candidiasis will be considered.
3. Language: Articles and journals written in Spanish, English and Portuguese will be included, since these are the main languages of access to scientific literature in the health area.
4. Date of publication: The selected articles and journals should have been published within the last 5 years to ensure that up-to-date and relevant information on the topic is included.

Exclusion criteria

1. Unrelated studies: Articles and journals that do not specifically address oral candidiasis as an opportunistic disease will be excluded.
2. Animal studies: Studies conducted in animal models are excluded, since the objective of this review is to obtain information directly applicable to the human population.
3. Non-original studies: Narrative reviews, editorials, letters to the editor and other types of articles that are not original studies will be excluded.

By applying these inclusion and exclusion criteria, we will seek to obtain a selection of rigorous and relevant studies that contribute to a complete and reliable systematic review on the topic of oral candidiasis as an opportunistic disease.

Finally, the results of this review will be presented in order to contribute to the knowledge and understanding of oral candidiasis as an opportunistic disease and its impact on the oral and general health of patients.

DEVELOPMENT

Candidiasis, or candidosis, is the most common fungal infection of the oral cavity caused by Candida species. Previously, it was thought that 35-80 % of the population had an oral Candida infection but recent studies using molecular detection methods have shown that Candida species are present as part of the normal oral flora in all people. Various systemic, local, genetic and environmental factors cause changes in the homeostasis of the oral cavity, leading to a transition from normal flora to pathogens and opportunistic infections, leading to an overgrowth of Candida species or altered expression of virulence factors.[7]

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The most common local predisposing factors for candidiasis are poor oral hygiene, use of removable dentures, orthodontic appliances, xerostomia (dry mouth), smoking and use of inhalable steroids, carbohydrate-rich diet, and oral mucosal disease. Systemic factors include age (the elderly and newborns are at risk), pregnancy, antibiotic treatment, systemic treatment with corticosteroids, cancer and its treatment, digestive tract diseases, nutritional deficiencies (iron, folic acid and vitamin deficiencies), endocrine diseases (diabetes, hypothyroidism, hypoparathyroidism), autoimmune diseases (such as Sjogren's syndrome, among others.), HIV and primary immunodeficiency.[7]

Oral candidiasis has some clinical manifestations, generally it is a change of color in the affected area that can be white or red, so it is attributed a classification: primary candidiasis and secondary candidiasis. The first affects only the oral cavity and surrounding tissues and the second is when the infection occurs as part of a systemic disease, i.e., the mucosa may already be altered which makes it susceptible to infections and fungal lesions by Candida spp. In the primary classification we find four distinct conditions: pseudomembranous candidiasis, chronic erythematous candidiasis, acute erythematous candidiasis, chronic hyperplastic or nodular candidiasis and Candida-associated diseases, while in the secondary classification it is linked to systemic manifestations.

Pseudomembranous candidiasis

It is the most common form of the disease and occurs in all ages, mainly affecting immunodeficient individuals, infants, patients with halitosis and salivary gland hypofunction, antibiotic therapy and other malignant neoplasms. It is characterized by soft, multifocal or diffuse, slightly elevated plaques in the jugal mucosa, tongue, palate and retro molar region, periodontal tissues and oropharynx.[8,9]

Among the causal factors may be poorly adapted prostheses, poor oral hygiene, inhalation of steroids plus systemic conditions can develop this pathology. Clinically, small homogeneous white plaques to white nodular lesions similar to curdled milk or cottage cheese are observed, which may or may not be removed by scraping with a swab or blunt instrument, thus exposing the underlying erythematous mucosa.[9]

A classification of this condition can be found: of the homogeneous type which is described as a smooth lesion whose symptomatology is quite mild and patients may complain only of a slight tingling sensation or bad taste; and of the heterogeneous type which manifests as a nodular lesion, thus being more prone to malignant transformation; they can affect the esophageal region, causing dysphagia and chest pains.[8,9]

Its treatment is based on the use of antifungals for 7 days, before performing a biopsy for a suspicious lesion, since its result could be interpreted as a "true" dysplasia instead of being associated with the presence of candida spp.[9]

Chronic erythematous candidiasis

Also known as chronic atrophic erythematous candidiasis or denture stomatitis or prosthetic palatitis. It is a common condition, with an incidence of up to 65 %. It is a frequent pathology in patients with removable acrylic prostheses, being the areas located under the mucosa the affected ones (frequently the palatal mucosa and less frequently the mandibular mucosa).[7]

The lesions usually present swelling and redness, limited to the area of contact with the denture. Angular cheilitis is usually seen in conjunction with chronic atrophic candidiasis.

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The clinical appearance of denture stomatitis can be divided into three types. Type I shows punctate hemorrhage and local inflammation; type II shows redness of the mucosa under the dentures; and type III shows redness in the central area of the hard palate or papillary hyperplasia of the oral mucosa under the denture.(1)

Although in many cases the condition may have no symptoms, patients may experience pain or a burning sensation in the mouth.

Acute erythematous candidiasis
Also known as acute atrophic c. atrophicus or antibiotic mouth lesion; it manifests as a side effect of systemic therapy with broad-spectrum antibiotics, immunosuppressants and corticosteroids that alter the oral flora. However, other risk factors have also been identified, including corticosteroid use, HIV infection, anemia due to iron deficiency, vitamin B12 deficiency and uncontrolled diabetes mellitus.(1)

Its clinical picture manifests as painful red lesions on the dorsum of the tongue, changes in taste perception, depapillation of the tongue, in some cases a burning sensation even when the tongue surface is whole. Patients with xerostomia are more likely to develop this type of candidiasis.(3)

Chronic hyperplastic candidiasis
This is a less common form of candidiasis. This type of lesion affects more men than women, especially smokers. The most commonly affected site is the labial commissure followed by the jugal mucosa, the dorsum of the tongue and less frequently on the palate, lateral surfaces of the tongue. This type of pathology can be of 2 types: homogeneous or plaque type and nodular or mottled or heterogeneous type.(10)

HCC of the homogeneous type presents as a smooth white plaque or spot that cannot be scraped and is usually asymptomatic, while HCC of the nodular or heterogeneous type presents in a nodular form with an erythematous background, with painful symptoms and sometimes with a burning sensation.(9,11)

A very particular characteristic of this lesion is that its evolution is prone to be malignant, especially the heterogeneous or nodular type; therefore, biopsy is mandatory for an accurate diagnosis. Ideally, systemic antifungal therapy should be started first for seven days before biopsy, because the material seen on biopsy may be interpreted as true dysplasia rather than Candida.

Management of HCC involves elimination of predisposing factors, mainly smoking, antifungal therapy (both topical and systemic) and finally surgery in cases that do not respond to pharmacologic medical treatment.(11)

Treatment

Pharmacological treatment
The antifungal agents established for the treatment of candidiasis belong to four classes of drugs: azoles, polyenes, echinocandins and pyrimidine analogues (flucytosine). Azoles and polyenes act at the fungal membrane level, echinocandins at the fungal cell wall and flucytosine alters nucleic acid synthesis. Selection of antifungal therapy is based on multiple factors, including host immune status, degree of infection, previous tolerance to the drug, and antifungal resistance.(12)

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In addition to antifungals, chlorhexidine solutions may also be prescribed for topical treatment. These solutions are an excellent complementary option, since in the oral cavity special environmental conditions, such as the washing effect of saliva and the "wiping effect" of the musculature, often make it difficult for antifungals to reach adequate therapeutic concentrations in the mouth. Clinical studies have shown that chlorhexidine affects phospholipase activity, which decreases the pathogenicity of C. albicans. [13]

As polyene antifungals we have nystatin, natamycin and amphotericin B remembering that the latter is nephrotoxic. miconazole and fluconazole. When oral candidiasis cannot be effectively treated with topical drugs, the administration of azoles is mainly resorted to, this being the exclusive responsibility of internists and dermatologists. Azole derivatives include miconazole, ketoconazole, fluconazole, clotrimazole and itraconazole.[14]

Photodynamic therapy

The disadvantages of conventional treatments are the following: possibility of fungal resistance, drug-drug interactions and side effects of topical treatments: nausea and possible vomiting. The disadvantages of systemic treatment are possible liver and kidney damage, gastrointestinal problems, and bone marrow suppression.[15]

The therapeutic approach known as photodynamic therapy to treat candidiasis and other oral and perioral diseases involves the topical local application of a photosensitizer (methylene blue, toluidine blue, rose bengal, crystal violet), methylene blue being the most commonly employed, which is a light-sensitive substance, followed by visible light exposure.[16,17]

Photodynamic therapy uses red light source (630 nm - 700 nm) because of its ability to effectively penetrate biological tissues. Photosensitizing agents preferred for this wavelength are methylene blue (MB), toluidine blue (TA) and malachite green (MV). On the other hand, blue light sources (380 nm - 520 nm) are employed, using pink bengal (RB), eosin (EOS) and erythrosin (ERI) as photosensitizers.[18]

Table 1. Conventional treatments.

Drug	Presentation and Posology - Ecuador	Lesion
Nystatin	Oral Suspension Children. - 1ml 4 times a day for 7 days. It is recommended to administer on the surface of the tongue and inside the cheeks. Adults. - 1ml 4 times a day for 7 days. It is recommended to keep the oral suspension in the mouth for a few moments before swallowing. Spray solution Children and adults: 250.000-500.000 IU/6-12 h. Infants under 1 year of age 250.000 IU/6 h. Newborns or low birth weight 100,000 IU/6 h. Continue for at least 48 h after disappearance of symptoms to avoid recurrence. If symptoms worsen or persist after 14 days, re-evaluate with the professional. Creams Apply 3-4 times daily to the affected area.	Acute and chronic candidiasis and angular cheilitis
Itraconazole	Hard capsules Adults - 100 mg twice a day for 1-2 weeks. Adults with HIV or other immunodeficiencies: 200 mg in 1-2 doses per day for 1-2 weeks.	Acute and chronic candidiasis

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	Patients with fluconazole resistance: 100-200 mg every 12 h for 2-4 weeks. Maximum dose: 400 mg daily for 14 days.	
Miconazole Tablet	Tablet 250 mg 4 times a day Oral Gel 2%. Children 6 months to 24 months. - 1.25 ml 4 times a day for 7 days. It is recommended to administer on the surface of the tongue and inside the cheeks. Children 2 years and adults. - 2.5 ml 4 times a day for 7 days. It is recommended to keep in the mouth for 2 to 3 minutes before swallowing. Patients with prosthesis, remove them at night and brush with the gel. A 14 day treatment may be necessary.	Chronic candidiasis
Fluconazole Tablet	Tablets Children: From 28 days to 11 years: 6 mg/kg/day initial dose, followed by 3 mg/kg/day. Maximum dose 400 mg/day. Adults: 200-400 mg on the first day, followed by 100-200 mg daily for 7-21 days. In chronic atrophic candidiasis 50 mg/day for 14 days. In chronic mucocutaneous candidiasis: 50-100 mg/day for up to 28 days. In cases of resistance to this drug, high doses of 800-1600 mg/day are used.	Acute and chronic candidiasis
Phototherapy	Topical form, methylene blue (0.005 % and 0.01 %) and radiation at 660nm (0.1W, 9J, 90s) and energy dose of 321J/cm2 at a distance of 1mm.	Acute and chronic candidiasis
Chlorhexidine gluconate 2 %.	Removable prosthesis should be immersed twice a week for 30 minutes.	Chronic candidiasis

Oral candidiasis is a common opportunistic fungal infection of the oral mucosa, with Candida albicans being the main causative organism. This paper reviews the evidence and results of articles on the relationship between oral candidiasis and its position as an opportunistic disease in immunocompromised patients. In addition, the risk factors, clinical manifestations and treatment methods presented in these studies are discussed.

The study has shown that oral candidiasis is a frequent infection in immunocompromised individuals, highlighting that it is an opportunistic lesion. Immunocompromised patients, such as those with HIV/AIDS, diabetes and those on immunosuppressive treatment, or undergoing antibiotic, steroid or corticosteroid ingestion are more susceptible to contracting the disease. Dysbiosis of the oral flora due to alterations in the host microbiome plays an important role in the transition of *Candida albicans* from commensal to pathogenic phenotype.

Shah N et al,[11] diagnosed oral candidiasis in a 57-year-old male patient with a significant smoking habit, which is in line with what is reported in the scientific literature indicating that most cases occur in patients aged 31-81 years, with a higher incidence in those over 50 years of age. One of the salient observations is that men appear to be more affected by oral candidiasis than women, by a ratio of 2:1.

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Interestingly, there is a significant difference in the incidence of oral candidiasis between men and women. According to the ratio reported in various studies, men are more predisposed to develop oral candidiasis, with a ratio of 2:1 compared to women. This difference in incidence according to gender could be due to several factors, such as differences in lifestyle habits, immunity and oral flora composition between men and women.

Tobacco use has been associated with an increased risk of developing oral candidiasis. Smoking can alter the immune function of the oral cavity and promote an environment conducive to Candida overgrowth, which increases susceptibility to this fungal infection.

Topical antifungals, such as miconazole, clotrimazole and nystatin, are widely used to treat mild to moderate forms of oral candidiasis. These agents act directly on the fungus, inhibiting its growth and replication. Topical application of these antifungals has been shown to be safe and effective, with rapid improvement of symptoms and resolution of lesions in many cases.

For more severe or resistant cases, systemic antifungals, such as fluconazole and itraconazole, may be necessary. These drugs are administered orally or intravenously and have the ability to reach deeper areas of the oral cavity, making them more effective in more extensive or recurrent infections. However, it is important to be aware of possible drug interactions and side effects associated with systemic antifungals.

The results obtained showed a significantly greater decrease in the number of fungal colonies and lesions in the group that received PDT associated with nystatin compared to those who were treated with nystatin alone, with no adverse effects. The combination of PDT and nystatin was shown to be more effective and in reducing the presence of fungal colonies, suggesting that this therapy may offer significant advantages in the treatment of this condition.[19]

These studies suggest that PDT in combination with antifungals may be a valuable and effective alternative for the treatment of oral candidiasis. The ability of the laser to effectively penetrate biological tissues in combination with the action of antifungals provides a therapeutic synergy that may improve treatment outcomes. It is important to keep in mind that, although these studies have provided encouraging evidence, further research is still needed to fully understand the potential of this therapeutic combination.

In addition, each clinical case may be different, and it is critical to evaluate the appropriateness of photodynamic therapy in combination with antifungals based on the specific patient characteristics and severity of oral candidiasis. The reviewed studies suggest that the combination of laser and antifungals may represent an exceptional therapeutic strategy for the treatment of oral candidiasis. PDT offers the advantage of being a non-invasive and potentially effective therapy, which could provide significant benefits to patients suffering from this condition.

CONCLUSIONS

Treatment of oral candidiasis should be approached on an individualized basis, taking into account the patient's overall health status and level of immunosuppression. Topical antifungals remain a valid option in patients with an adequate immune response, while in those with significant immunosuppression, the combination of photodynamic therapy with antifungals emerges as a promising alternative to improve therapeutic outcomes. However, further research is required to strengthen and optimize the management of oral candidiasis in patients with increased immune vulnerability.

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No conflicts of interest

Authorship contribution
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