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Review

An Overview of Oral Candidiasis in Immunocompromised Pediatric Patients

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Abstract

Oral candidiasis is a common fungal infection caused by *Candida* species, primarily affecting immunocompromised pediatric patients due to their weakened immune defenses. In children undergoing chemotherapy, living with HIV, or experiencing primary immunodeficiencies, the risk of infection increases significantly. The disrupted immune barriers and altered oral microbiota create an environment conducive to fungal overgrowth. Clinical presentations vary from classic white plaques to more subtle erythematous lesions, which can complicate timely diagnosis. Advanced diagnostic tools, such as molecular methods and species-specific testing, are crucial for accurate identification, especially with the rise of non-*albicans Candida* species resistant to standard therapies. Therapeutic strategies rely heavily on antifungal agents, with topical treatments like nystatin and systemic options like fluconazole forming the cornerstone of management. However, increasing antifungal resistance and recurrent infections pose ongoing challenges. Innovations in antifungal drug development, including liposomal amphotericin B and novel agents like ibrexafungerp, offer promising solutions. Additionally, immunomodulatory therapies and probiotics are being explored as adjuncts to enhance host defenses and restore microbial balance. Emerging insights into *Candida* biofilms and resistance mechanisms underscore the need for combination therapies and targeted interventions. Preventive measures, including oral hygiene education and prophylactic antifungal use in high-risk populations, play a pivotal role in reducing infection rates. Multidisciplinary approaches integrating clinical expertise, advanced diagnostics, and novel therapeutic strategies are essential to address the complex needs of this vulnerable population. The continued exploration of host-pathogen interactions and therapeutic innovations offers hope for improved management and outcomes in immunocompromised pediatric patients.

Keywords: *Oral candidiasis, immunocompromised pediatric patients, antifungal resistance, therapeutic strategies, diagnostic challenges*

Introduction

Oral candidiasis, commonly known as oral thrush, is a fungal infection caused by Candida species, predominantly *Candida albicans*. This opportunistic infection is a significant concern in immunocompromised individuals, particularly pediatric patients. The immune system plays a critical role in maintaining a balance between host defenses and commensal microorganisms in the oral cavity. In immunocompromised children, however, this balance is disrupted, predisposing them to opportunistic infections such as oral candidiasis (1). Understanding the factors that contribute to this imbalance and the subsequent development of oral candidiasis is critical for improving diagnostic, preventive, and therapeutic approaches.

Pediatric patients who are immunocompromised may include those undergoing chemotherapy for malignancies, those with primary immunodeficiencies, or those infected with HIV. In these populations, the reduced ability to mount an effective immune response allows Candida species to overgrow, leading to the characteristic lesions and discomfort associated with oral candidiasis (2). In infants and young children, the condition may present with symptoms ranging from mild mucosal irritation to severe pain and difficulty eating or swallowing, further complicating their already fragile health status. The diagnosis of oral candidiasis in children can be challenging due to overlapping symptoms with other conditions and the variability in clinical presentation. Typical findings include white, curd-like plaques on the mucosal surfaces, but erythematous or hyperplastic lesions may also occur, depending on the subtype of the infection. Early and accurate diagnosis is essential to initiate timely treatment and prevent complications (3). However, reliance on clinical examination alone may result in underdiagnosis or misdiagnosis, underscoring the need for improved diagnostic methodologies.

Treatment of oral candidiasis typically involves antifungal agents, such as topical nystatin or systemic fluconazole, depending on the severity of the infection and the immune status of the patient. However, recurrent infections and the emergence of antifungal resistance present significant challenges. Prophylactic measures, including good oral hygiene and the judicious use of antimicrobials, are crucial in reducing the incidence of this condition in at-risk populations (4). Advances in immunotherapy and antifungal drug development hold promise for addressing some of these challenges, but their application in pediatric patients requires further investigation. Despite advances in our understanding of Candida pathogenesis, significant gaps remain in the comprehensive management of oral candidiasis in immunocompromised pediatric patients. Improved understanding of host-pathogen interactions, enhanced diagnostic tools, and innovative therapeutic strategies are essential to optimize outcomes for these vulnerable patients.

Review

Oral candidiasis in immunocompromised pediatric patients represents a significant challenge due to the interplay of host immune deficiencies and the pathogenicity of *Candida* species. Immunosuppression, whether caused by primary immunodeficiencies, chemotherapy, or HIV infection, disrupts the oral mucosa's defense mechanisms, allowing fungal overgrowth (5). Children undergoing treatments such as chemotherapy experience neutropenia and mucositis, which further increase their susceptibility to infection. The clinical manifestations, ranging from asymptomatic colonization to painful lesions, often complicate the management of their already vulnerable condition.

Diagnostic challenges arise due to the nonspecific nature of symptoms and overlapping presentations with other oral pathologies. While white plaques are a hallmark, variations such as erythematous or hyperplastic candidiasis may obscure clinical recognition. Culture and molecular diagnostic methods, though more definitive, are not always readily accessible, particularly in resource-limited settings (6). Treatment strategies emphasize antifungal agents, with topical therapies like nystatin often preferred for milder cases. However, systemic antifungals, such as fluconazole, are

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necessary for severe infections. The risk of antifungal resistance and drug interactions underscores the importance of judicious antifungal use. Prophylactic measures, including improved oral hygiene and nutritional support, can reduce incidence, but gaps in effective management persist, requiring further research and innovation (5, 6).

Pathophysiology and Risk Factors in Immunocompromised Pediatric Patients

The pathophysiology of oral candidiasis in immunocompromised pediatric patients involves a complex interplay between host immunity and the pathogenic mechanisms of *Candida* species. The oral cavity serves as an ecological niche for *Candida*, where its growth is typically kept in check by host defenses. In immunocompromised children, these defenses are diminished, allowing the fungus to proliferate, adhere to epithelial cells, and invade tissue. The epithelial barrier, innate immune responses, and adaptive immunity are pivotal in preventing fungal colonization and subsequent infection. Any disruption in these systems heightens susceptibility, particularly in vulnerable pediatric populations (7).

At the cellular level, innate immunity represents the first line of defense against *Candida* infection. Pattern recognition receptors, such as Toll-like receptors and C-type lectin receptors, recognize fungal components like β-glucans and mannan, initiating immune responses. In immunocompromised children, the function of these receptors or downstream signaling pathways may be impaired, resulting in an inadequate immune response. Chemotherapy, for instance, reduces neutrophil counts, compromising the ability to contain fungal growth. The neutropenic state is further exacerbated by damage to mucosal barriers caused by cytotoxic agents, providing an entry point for fungal invasion (8). Adaptive immunity plays a critical role in long-term control and prevention of fungal infections. T-helper 17 (Th17) cells, which produce cytokines such as interleukin-17 and interleukin-22, are essential in mounting protective responses against *Candida*. In children with HIV or primary immunodeficiencies, impaired Th17 cell function is a common finding, which diminishes the ability to recruit neutrophils to infection sites and promotes fungal persistence. Additionally, defects in other immune pathways, such as those involving regulatory T cells or B cells, can also compromise mucosal immunity, leading to recurrent or severe infections (9).

Beyond immune deficits, several risk factors increase the likelihood of oral candidiasis in immunocompromised pediatric patients. Prolonged use of broad-spectrum antibiotics alters the oral microbiota, reducing bacterial competitors and favoring *Candida* overgrowth. This dysbiosis is particularly evident in hospitalized or critically ill children receiving antibiotic therapy. Similarly, malnutrition—a frequent complication in immunocompromised children—further undermines mucosal integrity and immune defenses. Deficiencies in micronutrients like iron, zinc, and vitamin A impair epithelial repair mechanisms and immune cell function, creating a favorable environment for fungal colonization and invasion (10). Another significant risk factor is the presence of indwelling medical devices, such as feeding tubes or central venous catheters, which can serve as reservoirs for *Candida* (11). Biofilm formation on these surfaces enhances fungal persistence and resistance to antifungal agents. This poses a unique challenge in pediatric populations requiring long-term parenteral nutrition or intensive care. Furthermore, the use of corticosteroids, either as part of chemotherapy regimens or for other chronic conditions, suppresses immune responses at multiple levels, facilitating fungal growth.

Environmental and genetic factors may also play contributory roles. Geographic regions with higher prevalence of fungal infections or poor access to healthcare can result in delayed diagnosis and treatment of oral candidiasis. Genetic polymorphisms affecting immune signaling pathways, such as mutations in the *CARD9* gene, have been associated with increased susceptibility to fungal infections. Such hereditary factors are particularly relevant in children with unexplained recurrent candidiasis or severe disease presentations. Collectively, these pathophysiological mechanisms and risk factors

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underscore the complexity of managing oral candidiasis in immunocompromised pediatric patients. The interplay between host immune dysfunction, microbial factors, and external influences creates a multifaceted challenge, requiring tailored approaches to diagnosis and treatment to improve patient outcomes (7-10).

Clinical Presentation and Diagnostic Challenges in Pediatric Populations

Oral candidiasis manifests in various forms, each influenced by the immune status of pediatric patients and the specific strain of *Candida*. In immunocompromised children, the presentation often differs from that seen in healthy populations. Commonly, pseudomembranous candidiasis, characterized by white, curd-like plaques that can be wiped away to reveal erythematous mucosa, is observed. However, alternative forms such as erythematous candidiasis, marked by painful red lesions, or hyperplastic candidiasis, presenting as thick, adherent plaques, are frequently encountered in this population. These variants can complicate the recognition of the disease, especially in non-verbal or pre-verbal children who cannot adequately describe their symptoms (12).

The clinical course of oral candidiasis is often exacerbated in children with severe immunosuppression, as seen in those undergoing chemotherapy or suffering from advanced HIV. In such cases, lesions may become extensive, involving the palate, tongue, and buccal mucosa. This widespread involvement can interfere with feeding and oral hygiene, further compounding the risk of secondary infections. The presence of angular cheilitis, an inflammatory condition at the corners of the mouth, may also coexist, adding to the diagnostic complexity. These factors can mask the primary fungal infection, leading to delayed or missed diagnoses in busy clinical settings (13). Accurate diagnosis of oral candidiasis remains a challenge due to overlapping presentations with other oral conditions, such as mucositis, lichen planus, and viral infections like herpes simplex. Clinical examination alone may not always differentiate these entities, particularly in cases where candidiasis manifests atypically. Moreover, healthcare providers may attribute symptoms such as oral discomfort or erythema to the side effects of medications, overlooking fungal etiology. This diagnostic uncertainty is further heightened by the variability in the clinical skills and experience of practitioners across healthcare settings (14).

Laboratory confirmation of oral candidiasis can be invaluable but is not without limitations. Direct microscopic examination of potassium hydroxide preparations allows rapid identification of fungal elements but lacks specificity in distinguishing *Candida* species. Culture methods, while more definitive, require longer processing times, which may delay treatment. Advances in molecular diagnostics, such as polymerase chain reaction, offer greater accuracy and sensitivity, but their availability in pediatric clinical settings is limited, especially in resource-constrained regions. These barriers highlight the need for more accessible, point-of-care diagnostic tools tailored for pediatric use (15). Another layer of complexity in diagnosis arises from the diverse spectrum of *Candida* species implicated in infections. While *Candida albicans* is the most prevalent, non-albicans species like *Candida glabrata* and *Candida krusei* are increasingly reported in immunocompromised children. These species often display intrinsic resistance to commonly used antifungal agents, making species-level identification critical for guiding treatment. Despite this, routine fungal species identification is not always performed in clinical practice, leading to suboptimal therapeutic outcomes in cases of resistant infections (15).

The role of biofilm formation by *Candida* further complicates the clinical picture. Biofilms, which are structured communities of fungal cells embedded in an extracellular matrix, are highly resistant to antifungal therapies and host immune responses. In pediatric patients with medical devices like feeding tubes, biofilm-related candidiasis is a significant concern. These infections are challenging to diagnose due to their subtle and often nonspecific presentation, and standard diagnostic methods may fail to detect biofilm-associated fungal cells (12). Early and accurate diagnosis of oral candidiasis in pediatric populations requires a multidisciplinary

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approach that integrates clinical expertise with advanced diagnostic techniques. Understanding the clinical nuances of the disease and the limitations of current diagnostic practices is crucial to improving outcomes for this vulnerable population.

Therapeutic Strategies and Emerging Treatments

The management of oral candidiasis in immunocompromised pediatric patients hinges on the careful selection of antifungal therapies, tailored to the severity of the infection and the patient's overall health status. Topical antifungal agents such as nystatin and clotrimazole remain the first line of treatment for localized infections due to their minimal systemic absorption and safety in children. These agents act by disrupting fungal cell membranes, effectively reducing fungal load. However, their efficacy is often limited in cases of severe immunosuppression or when poor compliance affects the duration or consistency of use, especially in younger patients unable to retain topical applications for extended periods (16).

Systemic antifungals, such as fluconazole and itraconazole, are preferred for moderate to severe infections or when topical agents fail to provide adequate relief. Fluconazole, a triazole antifungal, inhibits fungal ergosterol synthesis, a critical component of the fungal cell membrane. Its favorable pharmacokinetic profile, including excellent oral bioavailability and tissue penetration, makes it a commonly prescribed agent in pediatric populations. However, the increasing prevalence of fluconazole-resistant *Candida* strains, particularly *C. glabrata* and *C. krusei*, poses a significant therapeutic challenge. In such cases, echinocandins, such as caspofungin and micafungin, are employed as second-line therapies. These agents target fungal cell wall synthesis and have demonstrated efficacy in treating refractory or invasive candidiasis in pediatric patients (17).

Emerging treatments are gaining attention as the limitations of current antifungal regimens become apparent. Liposomal amphotericin B, a lipid formulation of the traditional amphotericin B, has shown promise due to its reduced nephrotoxicity and enhanced efficacy against multidrug-resistant *Candida* species. This formulation allows for higher doses to be administered safely, addressing severe cases where other therapies fail. In addition, recent advancements in immunotherapy aim to bolster the host's immune response to fungal infections. Recombinant cytokines, such as granulocyte colony-stimulating factor and interferon-gamma, have been investigated for their ability to enhance neutrophil function and improve antifungal defenses in immunocompromised patients (18). The potential of combination therapies is also being explored to overcome resistance and improve outcomes in severe infections. Combining azoles or echinocandins with other antifungal agents or immunomodulatory treatments may provide a synergistic effect, enhancing fungal clearance while reducing the likelihood of resistance development. Preliminary studies have shown that pairing fluconazole with echinocandins can achieve better outcomes in refractory candidiasis compared to monotherapy. However, the increased complexity of such regimens necessitates careful monitoring for drug interactions and adverse effects, particularly in pediatric patients with underlying comorbidities (19).

The development of novel antifungal agents remains a critical area of research. Ibrexafungerp, a glucan synthase inhibitor with a mechanism similar to echinocandins, has recently emerged as an effective treatment option for resistant *Candida* infections. Unlike traditional echinocandins, ibrexafungerp can be administered orally, providing a more convenient option for pediatric patients who may struggle with intravenous therapies. Other agents in development include manogepix, a drug that targets fungal GPI-anchored protein maturation, showing promise in preclinical studies for its broad-spectrum activity against *Candida* species (16, 19). Adjunctive therapies focusing on probiotics and microbiome modulation offer additional avenues for managing oral candidiasis. Probiotics, such as *Lactobacillus* and *Bifidobacterium* species, have been shown to inhibit *Candida* growth by competing for adhesion sites and producing antifungal metabolites. Incorporating these into preventive strategies may help maintain

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oral microbiota balance and reduce the incidence of fungal infections in at-risk pediatric populations. Lastly, exploring the role of dietary modifications and micronutrient supplementation in enhancing mucosal immunity could complement conventional antifungal therapies, providing a holistic approach to treatment (18).

Conclusion

Oral candidiasis in immunocompromised pediatric patients remains a multifaceted challenge, requiring tailored therapeutic approaches and a deeper understanding of host-pathogen interactions. Advances in diagnostics, antifungal therapies, and emerging treatments offer hope for improved management and outcomes. Addressing gaps in early detection and resistance prevention is crucial for effective care. Future research must prioritize innovative strategies to safeguard this vulnerable population.

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Conflict of interest

There is no conflict of interest.

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Data availability

Data that support the findings of this study are embedded within the manuscript.

Author contribution

All authors contributed to conceptualizing, data drafting, collection and final writing of the manuscript.

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