ХІРУРГІЧНА СТОМАТОЛОГІЯ

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MODERN ASPECTS OF THE PRINCIPLES OF ORAL CANDIDIASIS TREATMENT

Purpose of the study. *Fungal infection is currently a grave cause of morbidity and mortality, despite significant achievements in clinical practice and scientific research. The success of the strategy for liquidating fungal lesions of the oral mucosa is always the result of a comprehensive and multidisciplinary approach in diagnostics and treatment tactics, and requires correction of risk factors or underlying diseases, aimed at preventing candidemia and recurrent disease attacks.* **Research methods.** *With full knowledge of the arsenal of antifungal drugs, the clinician must determine the appropriate role of currently available treatment methods, the potential advantages of new antifungal drugs and the disadvantages and complications in the clinic progressing in case of candidal lesions. When using antifungal drugs, it is necessary to monitor the patient's condition on a daily basis in order to assess the clinical effectiveness of treatment, record possible adverse reactions and determine the optimal treatment duration.* **Scientific novelty.** *When choosing a treatment regimen, the patient's immune status, the features of oral mucosa candidiasis (clinical picture, etiology, sensitivity to antifungal drugs, positioning, process spread), and the pharmacological characteristics of available antifungal drugs (indications, metabolism, excretion, interaction with other drugs, toxicity) should be taken into account. It is recommended to prescribe general antimycotics in a clinical situation, when oral mucosa candidiasis is a consequence of the use of antibiotics, cytostatic drugs, as well as somatic diseases with immunodeficiency states and endocrinopathies.* **Conclusions.** *The effectiveness of the treatment of oral candidiasis consists in a thorough study of the past medical history and implementation of relevant recommendations. Therapy with antifungal drugs for systemic use should be prescribed only if the patient has a laboratory-confirmed/reasonably suspected fungal infection. In order for a decision to be made on the appropriateness of starting empirical antifungal treatment, it is necessary to use methods of rapid identification of the virus.*

Key words: *candidiasis, treatment, antifungal drugs.*

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СУЧАСНІ АСПЕКТИ ПРИНЦИПІВ ЛІКУВАННЯ КАНДИДОЗНОГО УРАЖЕННЯ РОТОВОЇ ПОРОЖНИНИ

Мета дослідження. *Натепер грибкові інфекції залишаються серйозною причиною захворюваності та смертності, незважаючи на значні досягнення у клінічній практиці та наукових дослідженнь. Успіх стратегії ліквідації грибкового ураження слизової оболонки порожнини рота завжди є результатом комплексного та мультидисциплінарного підходів як у діагностиці, так і в тактиці лікування, потребує корекції чинників ризику або основних захворювань, що спрямовано на запобігання кандидемії та рецидивуючого перебігу захворювання.* **Методи дослідження.** *За наявності ґрунтовних знань про арсенал протигрибкових препаратів клініцист має визначити відповідну роль доступних натепер методів лікування, потенційні переваги нових протигрибкових препаратів і недоліки й ускладнення у клініці, що розвиваються за кандидозного ураження. У разі застосування антифунгальних засобів необхідно щоденно контролювати стан пацієнта з метою оцінювання клінічної ефективності лікування, реєстрації можливих побічних реакцій і визначення оптимальної тривалості лікування.* **Наукова новизна.** *Під час вибору схеми лікування варто враховувати імунний статус пацієнта, особливості кандидозу слизової оболонки порожнини рота (клінічна картина, етіологія, чутливість до протигрибкових препаратів, ділянка ураження, поширення процесу) та фармакологічні характеристики доступних протигрибкових засобів (показання, метаболізм, виведення, взаємодія з іншими лікарськими засобами, токсичність). У клінічній ситуації, коли кандидоз слизової оболонки порожнини рота є наслідком застосування антибіотиків, цитостатиків, а також соматичних захворювань з імунодефіцитними станами й ендокринопатіями, рекомендовано призначати антимікотики загальної дії.* **Висновки.** *Ефективність лікування кандидозного стоматиту зумовлена ретельним вивченням історії хвороби та дотриманням відповідних рекомендацій. Терапію антифунгальними лікарськими засобами для системного застосування варто призначати суто за наявності в пацієнта лабораторно підтвердженої обґрунтовано підозрюваної грибкової*

інфекції. Для ухвалення рішення щодо доцільності початку емпіричної антифунгальної терапії необхідно використовувати методи пришвидшеної ідентифікації збудника інфекційної хвороби.
Ключові слова: *кандидоз, лікування, протигрибкові препарати.*

Scientifically justified therapeutic and preventive measures aimed at eliminating candidal lesions of the oral mucosa have been the subject of a sufficient number of specialized domestic and international literary sources [3; 11; 16; 22; 28].

The success of strategies for eliminating fungal lesions of the oral mucosa is invariably the outcome of comprehensive and multidisciplinary approaches, both in diagnosis and treatment tactics. This success also requires correcting risk factors or underlying diseases in order to prevent candidemia and recurrent disease progression [2; 13; 24; 27].

When choosing a treatment strategy for patients with oral infections caused by *Candida* fungi, various authors [3; 4; 6] recommend the following therapeutic measures:

a) to prevent relapses, eliminate local and general factors that predispose to the disease;

b) strictly observe oral hygiene practices to reduce the concentration of *Candida* on the surface of the oral mucosa, the esophagus, and the genital organs;

c) correctly and promptly recognize the clinical form of oral candidiasis;

d) provide differentiated treatment (local therapy alone or in combination with systemic therapy), depending on the clinical form and severity of the disease.

Therapeutic interventions for oral candidiasis **aim** not only to achieve an immediate effect (eliminating clinical and bacteriological signs of disease) but also to prevent relapses, especially in patients with somatic comorbidities [22; 25].

An important aspect of achieving this goal is the complete eradication of *Candida* not only from the lesion focus but also from the infection reservoir [13]. At the same time, there is a viewpoint suggesting that the goal of treating overgrowth of *Candida* is not to eradicate the fungal infection in humans but to restore correct and balanced ecological relationships between humans and microorganisms. Saliva contains a range of antimicrobial substances – lactoferrin, amylase, proline-rich glycosylated protein (PRP), lysozyme, and specific antibodies against *Candida* – that interact with the oral mucosa and protect against *Candida* infection [15].

Therapy for oral mucosa candidiasis should be comprehensive, encompassing etiological, pathogenetic, and symptomatic treatments. It should be combined, including both local interventions and systemic treatment. A differentiated approach is mandatory, taking into account: the extent of the lesion (generalized or localized); the disease course (acute or chronic); relevant background pathology and the patient's level of immunological reactivity.

When formulating a treatment regimen, it is necessary to consider the patient's immune status, the specific characteristics of oral mucosa candidiasis (clinical presentation, etiology, antifungal sensitivity, lesion sites, process spread), and the pharmacological characteristics of available antifungal agents (indications, metabolism, excretion, drug interactions, toxicity).

A common mistake made by dentists is to consider the process as localized only when changes are found on the oral mucosa, without paying attention to other causal factors or clinical signs of disease that can result in unsatisfactory treatment and persistence of the infection [24]. It has been established that approximately 20% of patients with oral candidiasis experience recurrence, and in about 30% of these recurrent cases, the newly isolated strain differs from the one responsible for the initial infection episode. Sometimes, the question arises whether the recurrence is a secondary infection or is caused by persistent *Candida* cells [13].

Patients who have been treated by a dentist for oral mucosa candidiasis should undergo continuous follow-up. A major component of this follow-up includes monitoring these patients, ensuring timely sanitation and appropriate oral hygiene, and implementing therapeutic, preventive, and social measures to prevent relapses and complications.

After obtaining test results and establishing a definitive diagnosis, when prescribing a therapeutic regimen, the physician should rely on an existing algorithm but should also recognize that clinical guidelines do not always account for patients' individual differences. They are not designed to replace a clinician's judgment regarding specific patients or particular clinical scenarios. Therefore, the final decision on how to apply such guidelines is made by the treating physician, considering the unique circumstances of each patient, overall medical status, and local dental status [22]. In determining the management tactics for candidiasis, it is important to take into account the form of the disease and to consult with other specialists – dermatologists, gastroenterologists, endocrinologists, and in some cases allergists.

Therapeutic measures for uncomplicated candidiasis are carried out for up to 14 days, and for complicated forms up to 30 days, with mandatory follow-up

at intervals of 2–5 days, including microscopic examinations (smears from the oral cavity) to evaluate treatment efficacy. Effective therapy is indicated by the absence of dryness, burning sensation, hyperemia, edema, or plaque in the affected oral mucosa areas. The measure of success is recovery manifested by the elimination of clinical and bacteriological signs of disease, accompanied by a lack of relapses. Patients with chronic oral candidiasis should be monitored dynamically for 2 years, with examinations 3 months after disease resolution and then every 6 months thereafter.

During treatment, monitoring of its effectiveness is performed by assessing clinical signs and using laboratory parameters that reflect disease progression. If the treatment response is found to be poor, as confirmed by monitoring data, appropriate adjustments should be made to the treatment plan and follow-up. In cases of chronic candidiasis, treatment courses are periodically repeated to prevent recurrence [9].

According to clinical practice guidelines [3; 21; 22; 25], the management of candidal lesions includes:

General treatment:

– *treatment in collaboration with physicians of other specialties;*

– *prescription of therapeutic nutrition (diet);*

– *direct impact on the etiological factor by prescribing antimycotics (azole group, antifungal antibiotics);*

– *general health-enhancing therapy;*

– *use of immunotropic agents;*

– *correction of intestinal flora composition;*

– *desensitizing therapy;*

– *use of hepatoprotectors, if indicated.*

Local treatment:

– *sanitation of the oral cavity;*

– *strict adherence to oral hygiene rules;*

– *normalization of oral fluid pH (use of alkaline solutions);*

– *application of antifungal agents (azole group) locally; antifungal antibiotics locally;*

– *use of antiseptics with antifungal activity locally;*

– *local application of immunomodulators; use of topical eubiotics.*

In patients presenting with fungal lesions of the oral mucosa (in cases of acute disease and exacerbation), treatment starts with pain relief. Local anesthetics in the form of baths, applications, etc. are prescribed. For this purpose, 1–2% lidocaine solution, 0,5–1% etonium solution, and others may be used [8; 10; 12].

A critical requirement of local therapy is the sanitation of the oral cavity – removal of mechanical irritants (e.g., sharp tooth edges, root remnants, poorly fitting dentures), along with necessary antiseptic and hygienic treatment of the oral cavity. One must remember that tooth extraction or surgical intervention on the oral mucosa in the acute stage or during an exacerbation is hazardous because it can lead to systemic spread of infection and the development of candidal sepsis.

If a patient requires surgical procedures on the oral mucosa or needs treatment for concomitant dental diseases (pulpitis, periodontitis, periodontal disease, etc.) while also exhibiting signs of oral candidiasis, therapeutic and preventive measures should be differentiated and carried out in tandem with antifungal therapy.

Special attention must be given to the hygienic cleaning of the oral cavity and to instructing patients in oral hygiene techniques. The thoroughness and correctness of oral hygiene practices should be monitored. Where plaque is tightly adhered to the mucosa, special scrapers are prescribed for its removal.

An important element in the treatment of fungal lesions is the therapeutic diet designed to inhibit fungal growth (e.g., carrots, lemon, seaweed, cinnamon, foods containing micronutrients, fermented dairy products). Fresh vegetable juices (carrot, cucumber, parsley, or combinations thereof) are especially beneficial, for instance, in candidiasis occurring against the backdrop of kidney, reproductive system, or cardiovascular diseases. Patients are advised to exclude irritating foods and alcohol from their diets, and to restrict carbohydrate intake. In cases of severe diarrhea related to enteritis or colitis, it may be necessary to start with strong tea plus pomegranate juice, or an infusion of chamomile, mint, St. John's wort, or other herbs, as well as blueberry, blackcurrant jelly, or fruit broths (excluding fruit chunks). Broths (meat or fish), boiled vegetables, lean boiled meat, fish, and various cereals (buckwheat, oatmeal, rice, barley) are allowed; baked apples, raspberries, and blueberry broth are recommended.

In accordance with the medical care standard "Rational Use of Antibacterial and Antifungal Drugs for Therapeutic and Preventive Purposes" approved by the Ministry of Health of Ukraine (Order № 1513 of August 23, 2023) [7], systemic antifungal agents are to be prescribed only if a patient has a laboratory-confirmed or reasonably suspected fungal infection. Rapid identification methods for the infectious agent should be used to determine whether empirical antifungal therapy is warranted.

The aforementioned document stipulates that in a patient with no signs of infectious inflammation,

the isolation of commensal fungal strains (based on microbiological examination) does not constitute grounds for prescribing antifungal therapy (i.e., antifungal drugs must not be used for treatment), except for certain fungi identified by relevant national medical standards as requiring mandatory eradication.

Persistence of fungi in the range of 10^2–10^3 CFU/mL at a non-sterile locus, or the isolation of a new fungal strain from a non-sterile locus without clinical signs of infection, must not serve as justification for starting, continuing, or modifying antifungal therapy. Detecting microorganisms in a sterile locus in the absence of clinical signs may indicate sample contamination; in such cases, additional material should be obtained for microbiological tests.

Isolation of *Candida* spp. or other agents of invasive mycoses from sterile loci (e.g., blood, cerebrospinal fluid, biopsy specimens) requires the mandatory use of systemic antifungal therapy (antifungal treatment with echinocandins or azoles). Azoles should be prescribed only when the patient's condition is stable and microbiological testing confirms infection by *Candida* albicans.

The prescription of antifungal therapy must be individualized, taking into account the pharmacokinetic properties of each medication for each patient. The route of administration for antifungal drugs should be selected to achieve fungicidal tissue concentrations in the region of the fungal infection.

Justification for prescribing antifungal therapy must include:

– a confirmed or highly suspected diagnosis of fungal infection (with criteria substantiating the need for antifungal treatment);

– the international nonproprietary name (INN) of the antifungal agent to be used;

– dosage, formulation, frequency, and route of administration of the antifungal drug;

– the duration of antifungal therapy;

– the date for re-evaluation and/or discontinuation of the prescribed antifungal therapy (within 48–72 hours).

Risk factors for the development of invasive candidiasis in patients (which, in themselves, do not constitute grounds for prescribing antifungal prophylaxis or therapy) include:

– previous detection of fungal colonization;

– use of broad-spectrum antibacterial agents;

– presence of intravascular devices (e.g., catheters, sensors, ports);

– hemodialysis;

– chronic renal failure (glomerular filtration rate <30 ml/min);

– decompensated diabetes mellitus; pancreatic necrosis;

– neutropenia;

– abdominal surgery or radiation therapy.

Current approaches to treating oral mucosa candidiasis recommend prescribing polyene antibiotics and azoles [3; 5; 21; 28]. The azoles constitute the largest group, which is subdivided into imidazoles (miconazole, ketoconazole) and triazoles (fluconazole, isavuconazole, itraconazole). The choice of an antifungal agent for oral candidiasis depends on drug absorption, systemic effects, toxicity, and the emergence of resistant strains [26]. Prophylactic antifungal therapy for patients undergoing antibiotic therapy, in the absence of risk factors for invasive candidiasis, is prohibited. Polyene antifungals that are not absorbed in the gastrointestinal tract (e.g., nystatin, natamycin), fluconazole at daily doses below 400 mg, and oral ketoconazole are not recommended for preventing invasive mycoses. Empirical prescription of azoles or echinocandins is indicated in neutropenic patients with fever unresponsive to antimicrobial therapy. In non-neutropenic patients, indications for empirical antifungal therapy (echinocandins, fluconazole if it has not already been used prophylactically, or posaconazole) include:

– fever of unknown origin lasting more than four days with no response to empirical antimicrobial therapy;

– widespread Candida colonization (three or more loci);

– presence of two or more risk factors for invasive candidiasis.

When administering antifungal agents, one must monitor the patient's condition daily to evaluate clinical efficacy, record possible adverse reactions, and determine the optimal duration of treatment.

In clinical scenarios where oral mucosa candidiasis has resulted from antibiotic or cytostatic therapy, or from somatic diseases with immunodeficiency states and endocrinopathies, the prescription of systemic antimycotics is recommended (Table 1) [17].

Systemic antifungal therapy is prescribed for patients with resistance to local therapy and for individuals at increased risk for systemic infection [19], in line with the sensitivity profile of the isolated fungal pathogen (Table 2).

In most cases of superficial candidiasis, topical antifungal agents are used (Table 3).

Topical administration of antifungals is the cornerstone of treatment for localized forms of candidiasis. Unlike other forms of fungal infection, in these cases, nonspecific antiseptics – compounds with minimal

Table 1

Antifungal drugs for systemic use in the treatment of oral candidiasis (adapted from Guillermo Quindós, 2019)

Antifungal Drugs	Advantages	Drawbacks
Polyene Group		
Amphotericin B deoxycholate Amphotericin B lipid complex (ABLC) Amphotericin B liposomal (ABL)	Clinical efficacy and broad spectrumSafe in hepatic insufficiencyActive against fungal biofilms	Nephrotoxicity and other infusion-related side effects. Nephrotoxicity is very low with ABLC and ABL
Triazoles		
Fluconazole	Clinically effective, good safety profile, and low cost. Can be combined with other antifungals.	Low activity against *C. glabrata* and none against *C. krusei*.No activity against fungal biofilms.Drug interactions.
Isavuconazole 1Itraconazole 1, 2, 3, 5Posaconazole1, 3–5Voriconazole 1, 3–5		1. Not available in many countries. 2. Low activity against *C. tropicalis*, *C. glabrata*, *C. krusei*. 3. Drug interactions. 4. Serum concentration monitoring required in certain situations. 5. IV form is contraindicated in severe renal failure.No activity against fungal biofilms.
Echinocandins		
AnidulafunginCaspofunginMicafungin	Broad spectrum, excellent safety profile.Usable in renal failure and neutropenia. Active against fungal biofilms. Minimal drug interactions.	*C. parapsilosis* may be less susceptible.

Table 2

In vitro activity of key antifungal agents against the main Candida species causing candidal stomatitis (adapted from Guillermo Quindós, 2019)

Antifungal drugs	Species of Candida						
	Candida albicans	Candida glabrata	Candida parapsilosis	Candida tropicalis	Candida krusei	Candida dubliniensis	Candida spp.
Nystatin	●●	●●	●●	●●	●●	●●	●●
Amphotericin b	●●	●●	●●	●●	●●	●●	●●
Miconazole	●●	■ ○	●●	●●	○	●●	●
Clotrimazole	●●	■	●●	●●	○	●●	●
Fluconazole	●●	■ ○	●●	●●	○	■ ○	●
Isavuconazole	●●	●●	●●	●●	●●	●●	●●
Itraconazole	●●	■ ○	●●	○	○	■ ○	●
Posaconazole	●●	●●	●●	●●	●●	●●	●●
Voriconazole	●●	●	●●	●●	●	●●	●●
Anidulafungin	●●	●●	●	●●	●●	●●	●●
Caspofungin	●●	●●	●	●●	●●	●●	●●
Micafungin	●●	●●	●	●●	●●	●●	●●

Note: Antifungal activity: ●● – very active; ● – active; ■ – variable activity; ○ – resistant.

Table 3

Topical Antifungal Agents

Group	International Nonproprietary Name	Trade Name
Polyenes	Natamycin, Nystatin	Pimafucin, Nystatin
Azoles	Miconazole, Clotrimazole	Mikospor, Nizoral, Miconazole,Clotrimazole, Canesten, Candid

selectivity that interact with microbial cell proteins (leading to coagulation and other disruptions causing cell growth cessation or cell death) – are widely used alongside specific antimycotics. Antiseptic mouth rinses employed against fungal infection are considered an adjunct or alternative antifungal therapy. Since localized forms of candidiasis are often complicated by superimposed bacterial infection, the activity of antiseptics is particularly beneficial. For oral mucosa candidiasis, the recommended therapeutic and preventive regimen often includes antiseptic agents such as chlorhexidine and its analogs, 1–2% fuchsin solution, decasan, povidone-iodine, givalex, miramistin, 1% iodinol solution, Candid solution, 3% potassium iodide solution, fucorcin, 2% boric acid solution, 20% sodium tetraborate solution (borax in glycerol), 5–10% decamine, 2% methylene blue solution, Daktarin gel, and Micostatin. To treat the oral cavity of infants after every feeding, alkaline solutions (1–2% sodium bicarbonate) may be used; these solutions can also be used for soaking removable dentures overnight. Among plant-based preparations used to eliminate fungal infections, 1% aqueous sanguirythrine solution, 4% propolis, and "Stomatofit A mini" are notable [4; 9; 10].

An essential strategic complement to therapeutic interventions is the combined use of local and systemic therapy aimed at maintaining symbiotic flora and administering comprehensive immunomodulators of bacterial origin – such as vaccines, biologically active supplements, eubiotics, probiotics, synbiotics, and bacteriophages. These are effective due to their role in modulating intestinal microbiota and its interaction with the immune response, ultimately preventing disease relapse [1; 8; 11; 16]. The probiotic drugs most frequently used in clinical practice contain attenuated (lyophilized) live strains of normal intestinal microflora, primarily *Lactobacillus spp.* and *Bifidobacterium spp.*, with lesser use of *Saccharomyces spp.*, *Bacillus spp.*, and *Escherichia spp.* [18, p. 49].

Systemic antifungal therapy for systemic mycoses is sometimes constrained, often expensive, and associated with significant toxicity. Nanotechnology has become an intriguing strategy to enhance the efficacy and specificity of conventional antifungal agents, offering reduced toxicity, improved biodistribution, high activity, and a broad antifungal spectrum. Particularly promising is the evaluation of different nanomaterials as novel antimicrobial agents: silver, gold, and iron nanoparticles have demonstrated potential antifungal activity via multifaceted mechanisms in *C. albicans* cells and biofilms, which may help minimize the emergence of antifungal resistance [14; 20; 23].

Therefore. To successfully treat candidal stomatitis, it is vital to thoroughly analyze the patient's medical history and adhere to appropriate guidelines for antifungal therapy – both by the dentist and the patient. Given the presence of various predisposing factors that are challenging or even impossible to eliminate, prophylactic antifungal treatment may be required.

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