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Research paper

The dietary modification and treatment of intestinal *Candida* overgrowth – a pilot study

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ABSTRACT

Objective. – The aim of this study was to evaluate the effectiveness of an alternative treatment in a form of recommended diet modification during and after conventional treatment with antifungals in patients with a chronic form of intestinal *Candida* overgrowth (ICOG).
Methods. – The study included patients with ICOG divided in two subgroups: patients treated with nystatin and recommended diet regime (study group-SG) and the patients treated only with nystatin (control group-CG). After treatment, the mycological control examination and follow-up were performed two times: the first one within ten days after the completion of antifungal treatment, and the second one three months after the treatment initialization.
Results. – A total of 120 patients finished the study: 80 from the SG and 40 from the CG. At the first mycological control examination of SG patients stools, we noted satisfactory antifungal and symptomatic effect in 56 out of 80 (70.0%) patients and 29 out of 40 (72.5%) in CG, with no statistically significant difference. However, at the second control stool examination, significantly higher percent (85%) of cured patients was recorded after three months of the recommended diet comparing with CG–17 out of 40 (42.5%).
Conclusion. – Results of this pilot study showed that patients who adhered to diet modification during and after treatment with nystatin had better outcomes of ICOG and strongly suggest the need for diet modification in these patients which recommendation could reduce excessive prescription of antifungals.

1. Introduction

The mycobiome is fungal biota of various human body sites such as the oral cavity, vaginal mucosa, skin and gut. It is well known that *Candida* spp. represent the part of normal flora (mycobiome) in healthy people, but in certain cases, these commensal fungi can switch from non-pathogenic to pathogenic ones [1]. So far, significance and role of these yeasts in the occurrence of skin, nail, oral, vulvovaginal, balanopreputial, and perianal infections are defined [2]. However, in light of existing knowledge the role of *Candida* spp. as causative agents of intestinal mucosal infections is still hot topic of debate [3]. It is difficult to make clear borderline between *Candida* overgrowth (COG) and *Candida* infection (CI) on intestinal mucosa (IM). Contrary to vulvovaginal and oral candidosis where mucosal inflammation could be established trough clinical examination, for CI of IM clarification, beside mycological analysis of stool, endoscopic and histopathological examination of mucosa are also required. However, these diagnostic procedures are very rarely performed [4]. In these circumstances, in patients with mycological findings of *Candida* spp. as dominant isolates in stool without endoscopic and histological examination we can consider it as a *Candida* overgrowth, but not as infection. This fact is in accordance with traditional theory which is based on the attitude that in changing of the mucosal environment, *Candida* yeasts, as a part of the normal mycobiota, may prevail and dominate leading to dysbiosis and

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diarrhoea [4–6]. On the other hand, possibility of *Candida* yeast to cause superficial fungal infection of skin and mucous membranes leaves potentiality for the assumption that overgrowth, aside from dysbiosis, can also cause infection of intestinal mucosa [7]. This assumption is also supported by the results of many previous studies which have clearly showed that the presence of *Candida* spp. induce a much profound damage (larger defect) and increased inflammation [8–12] of the digestive tract mucosa in humans and in different animal models with inflammatory diseases of the gastrointestinal tract.

Additionaly, the reason of inconsistent viewpoint regarding significance of *Candida* spp. in pathogenesis of digestive tract infection is a fact that the high percent of patients with symptoms and signs of digestive tract infection has laboratory proved yeasts in stool [13]. This is a reason why is very difficult to determine the prevalence of intestinal candidosis. In our previously conducted study, it was shown that more than 63% of patients have positive findings of *Candida* isolates in mycological analysis of stool [14]. However, based on our routine laboratory work, the percent of patients with COG is significantly lower (11%) [unpublished data].

In vivo and in vitro studies that have evaluated the effectiveness of antifungal treatment by polyenes (nystatin) and azole/triazole derivatives in patients with intestinal COG (ICOG) have showed satisfactory results [4,6]. However, limitations of current treatment options are reflected in the lack of general considerations and guidelines regarding the treatment of sporadic and recurrent forms of ICOG that often leads to a misunderstanding or even dismissing by healthcare professionals [4–6].

Some efforts have been made to find an adequate alternative to the conventional treatment with antifungals [15]. In spate the fact that the structure and activity of the fungal gut mycobiota can be changed in response to food, whereby *Candida* abundance has been reported with recent consumption of carbohydrates [3], there are still no evidence-based guidelines to support an anti-*Candida* diet. Nevertheless, it has been shown that *Candida* abundance negatively correlates with a diet high in amino acids, fatty acids and proteins [16]. In addition, decrease in *Candida* species in the gastrointestinal tract has also been noted following pistachio and almond consumption [17]. Likewise, it has been shown that the probiotic bacteria *Lactobacillus acidophilus* and *Lactobacillus casei* induce protection against systemic candidosis in mice [18]. Weak organic acids such as acetic, propionic, and butyric acid, which are primarily produced in intestines by anaerobic bacteria, have the potential to inhibit *Candida albicans*(*C. albicans*) growth in various body sites [19]. Moreover, positive probiotic yeasts, such as *Saccharomyces cerevisiae* var. *boulardii*, may enhance survival of probiotic bacteria, thus leading to a synergistic effect. Besides, it is important to emphasize that probiotic yeasts also express disease-fighting proteins known as killer toxins, or mycocins, against opportunistic yeasts such as *Candida* spp [18].

Additionally, promising in vitro anticandidal activity was obtained in the case of resveratrol [20], goldenseal extracts (*Hydrastis canadensis* L.) [21], lactoferrin (both in vivo and in vitro) derived from bovine and human sources [22], coconut oil [23], as well as thermally processed garlic extracts [24].

Based on in vitro results from our previously conducted studies, we can point out that almost 100% of *Candida* species isolated from stool of patients with ICOG were susceptible to nystatin [6,14]. Contrary, high percentage of *Candida* spp. isolates were sensitive (S), in a dose-dependent (DD) manner [higher minimal inhibitory concentration (MIC)], to itraconazole (ITZ) (MIC = 0.25 μg/mL) (67.20%) and to fluconazole (FCZ) (MIC = 0.25 μg/mL) (59.79%) [14]. In addition to this, previously published data about the impact of consumed food, probiotics and/or supplements on *Candida* growth on intestinal mucosa [16–19,25,26] inspired us to make an alternative/supplementary treatment protocol that would include dietary modification in order to prevent the ICOG recurrence and improve the clinical outcome. Consequently, we designed this first pilot study to evaluate the effectiveness of an alternative treatment in a form of recommended diet modifications during and after conventional nystatin-antifungal therapy in patients with the recurrent form of ICOG.

2. Materials and methods

2.1. Patients

This pilot study was conducted at the Department of Microbiology and Immunology, Medical Faculty, University of Niš, and the Public Health Institute of Niš, Serbia. Our prospective study involved the study group (SG) of 80 patients with ICOG treated with nystatin (2 × 500.000 IU, three times a day for 10 days) and who accepted the dietary regime recommendations for ICOG during the 3-month period (Table 1). The control group (CG) consisted of 40 patients who underwent antimycotic treatment prescribed by their physicians (nystatin 2 × 500.000 IU, three times a day for 10 days).

2.2. Inclusion and exclusion criteria

The inclusion criteria for the patients included in the study were: patient age should be more than 18, they should be non-smokers, and with a minimum of two episodes of mycologically

Table 1
Recommendations for dietary intake in study group-SG of patients.

Not recommended food and beverages	Avoid	Recommended
All simple sugar containing foods	Honey, jam, candy, ice cream with sugar added	Artificial sweeteners and stevia were allowed in beverages and meals
All simple sugar containing foods	and types of fruit with high sugar content, such as grapes and watermelon	Taking one, possibly two fruit servings per day is allowed, excluding those with high sugar content
Cured and fatty meats hard to digest	Foods containing a lot of starch, such as	Food made from whole grain wheat flour (bread and pasta), whole potatoes cooked, brown rice
Milk and dairy products	products made of white flour (white bread and	Fish, preferably sea originating (mackerel, hake, tuna, salmon, sardines), seafood, low fat-white chicken meat – minimum 2 times a week
The usage of alcohol and alcoholic vinegar is prohibited	rolls, cakes, biscuits, pasta), white rice, lentils, white beans and potatoes	Yogurt and acidophilus drinks (yogurt with inulin and other probiotics)
	Meat products (homemade or commercial), ham, bacon, salami, sausages, roasts, broil, red meat (pork, beef, mutton, chicken), entrails	Dietary supplements: Omega-3 fatty acids (alone or with omega-6 and omega-9 fatty acids), linseed oil, evening primrose oil (1 teaspoon or 3 capsules) twice a day, propolis drops, multivitamin complex with selenium, AD drops for 5 days, zinc (one effervescent tablet daily), *Lactobacilli acidophilus* or probiotic Bifidus capsules or any other probiotic, tea against fungal diseases (*Candida*) – "Institute for plants Josif Pancic", Debutir
	Milk, yellow cheese, cheese spread and moldy cheese	

proved COG on intestinal mucosa accompanied with symptoms and clinical signs of a digestive tract infection during the previous year (nausea, disgust, flatulence, bloating, mushy stool, appearance of mucus in faeces) and without bacterial or viral infection of digestive tract, who had satisfactory antifungal and symptomatic outcome in previously episodes to proscribed antifungal drugs. In referent literature, yeast carriage rates are reported to be approximately 10^3–10^5 CFU/g of stool in healthy infants [18], while in more than half of the adult population fungi of genus *Candida* can be normally detected from 10^2 to 10^4 CFU/g of stool [27]. Given that we included only adult population of patients in this study, at the beginning, we established the threshold of $\geq 10^5$ CFU/g of stool on solid media as COG during the first mycological examination. The excluding criteria were: the presence of systemic, endocrine, or malignant diseases, immunodeficiency, pregnancy, the non-existence of control microbiological/mycological examinations and the information that the patient at some time point had ceased with the recommended diet.

During the follow-up period, patients had two control microbiological (bacteriological, virological and mycological) stool examinations, the first one after the completion of antifungal treatment, and the second one 3 months after the treatment initialisation. Also, for each patient included in the study, the anamnestic data were collected and entered into a database in order to obtain information about symptoms and signs of gastrointestinal tract infection and to verify that they followed the diet recommendations.

This research was approved by the Ethical Committee of the University of Niš, Faculty of Medicine (decision No. 12-6316-2/1-2016).

2.3. Laboratory analyses

A pea-sized amount of each human stool sample (about 1 g) was inoculated for fungal growth on Sabouraud Dextrose Agar (SDA) (Liofilchem Diagnostici, Teramo, Italy) and Chromogenic Candida media (Liofilchem/Bacteriology products, Italy) (incubated at 37 °C for up to 7 days), and *Candida* spp. were isolated following standard mycological procedures. *C. albicans* was differentiated from other species using a germ-tube test [28] and chromogenic media (Liofilchem/Bacteriology products, Italy), while non-*albicans* species were identified using chromogenic media and Auxacolor™ Kit (BioRad, France). A semi-quantitative method was applied for the determination of *Candida* spp. CFU number/g of stool on solid media. In order to exclude the presence of gastrointestinal bacterial infections in patients, stool samples were also inoculated on nutrition media such as selective Salmonella-Shigella (SS) agar, Selenite F-broth (Oxoid, Basingstoke, UK), CIN agar (Oxoid, Basingstoke, UK), *Campylobacter* selective medium (Oxoid, Basingstoke, UK), *Clostridium difficile* selective agar (Oxoid, Basingstoke, UK) for isolation and identification of *Salmonella* spp., *Shigella* spp., *Yersinia* spp., *Campylobacter* sp., and *Clostridium difficile*, respectively. The presence of *Helicobacter pylori* infection was excluded using the commercial ELISA kit (Oxoid, Basingstoke, UK) for detection of bacterial antigen in stool. Virological analyses of stool were carried out using commercial direct ELISA kits for antigen detection of astrovirus (RIDASCREEN, R-Biopharm GmbH, Darmstadt, Germany), rotavirus (Institute Virion/Serion GmbH, Würzburg, Germany), norovirus (RIDASCREEN, R-Biopharm GmbH, Darmstadt, Germany) and adenovirus (Institute Virion/Serion GmbH, Würzburg, Germany) in order to exclude the presence of gastrointestinal viral infections in patients.

2.4. Dietary recommendations

Dietary modifications were consisted of nutrition recommendations on the type of groceries, probiotics and supplements to be consumed. Also, the recommendations included a list of foodstuff not recommended in patients suffering from ICOG; the patients were forbidden to smoke and consume alcohol, as well as use antimicrobial and corticosteroid drugs on their own (self-medication). Table 1 contains the list of food and beverages included in the dietary modification.

2.5. Statistical analysis

The data presented as frequency distribution tables, expressed as percentages, were analysed using SPSS (ver. 16.0). The frequency comparison of some categories of attributive characteristics was done using chi-squared or Fisher's tests in the cases when some of the expected characteristic frequencies were less than five. Probability values (p) less than 0.05 were considered to be statistically significant.

3. Results

The total number of patients with ICOG was 120 (58 males and 62 females), of an average age of 38.3 ± 22.3 (ranging from 18 to 82-years old patients). The distribution of the isolated species from the patients' stools is presented in Table 2. The dominant stool-isolated species was *C. albicans* 61 (50.8%), followed by *C. glabrata* 34 (28.3%) and *C. krusei* 22 (18.3%). *C. tropicalis* 3 (2.5%) was detected in only a limited number of patients (Table 2). The distribution of *C. albicans* vs. non-*albicans* species-ICOG between different groups was similar, with no statistically significant difference ($X^2 = 1.91$; $P = 0.387$).

By the means of a semi-quantitative method, during the first mycological analysis of the patients' stools, *Candida* spp. OG on solid media, or approximately 10^5 CFU/g, was found in all samples.

The results of mycological analyses of two control stool examinations and patients' anamnestic data related to persistence of digestive tract infection symptoms are presented in Table 3.

The first control examination of SG patients' stools revealed a satisfactory antifungal (no-*Candida* isolates) and symptomatic effects in 56 of 80 patients (70.0%). Additionally, at the first control among 80 SG patients, 20 (25%) had positive *Candida* isolates $> 10^4$ CFU/g of faeces, with a subjective feeling of condition improvement and/or an absence of symptoms, while 4 (5%) of them still ended up with positive mycological findings and low-to-moderate intensity symptoms. The comparison between the results of stool mycological examinations and anamnestic data obtained at the first control examination revealed that there was no statistical difference in the number of patients without symptoms and negative mycological findings between SG and CG [SG = 56/80 (70.0%), CG = 29/40 (72.5%)] patients. However, although they had a significant *Candida*-growth (*Candida* isolates $> 10^4$ CFU/g of faeces), statistically significantly ($X^2 = 20.82$, $p < 0.001$) more SG patients were without symptoms (Table 3).

However, in the subsequent three-month period, statistically significantly more patients who continued with the diet were

Table 2
Candida species distribution in patients with ICI/OG confirmed by mycology examinations.

Candida species	Number of patients (%) 120 (100)	Group subdivision Number of patients (%)	
		SG 80 (100)	CG 40 (100)
C. albicans	61 (50.8)	42 (52.5)	19 (47.5)
C. glabrata	34 (28.3)	22 (27.5)	12 (30.0)
C. krusei	22 (18.3)	16 (20.0)	6 (15.0)
C. tropicalis	3 (2.5)	0	3 (7.5)

SG: Study group; CG: Control group.

Table 3
Comparison of *Candida* growth and symptom intensity between study group-SG and control group-CG of patients.

Parameters	SG $n=80$ (100%)	CG $n=40$ (100%)	Statistical comparison
First control			
No growth/no symptoms	56/80 (70%)	29/40 (72.5%)	$X^2=0.087$, $P>0.05$
Growth $>10^4$ CFU	24/80 (30%)	11/40 (27.5%)	
No symptoms	20/80 (25%)	0	$X^2=20.82$, $P<0.001$
Low intensity symptoms	4/80 (5%)	11/40 (27.5%)	
Second control			
No growth/no symptoms	68/80 (85%)	17/40 (42.5%)	$X^2=23.31$, $P<0.001$
Growth $>10^4$ CFU	9/80 (11.3%)	17/40 (42.5%)	
Low intensity symptoms	0	17/40 (42.5%)	$X^2=49.83$, $P<0.001$
Low to moderate intensity symptoms	9/80 (11.3%)	0	
Growth $>10^5$ CFU with high intensity symptoms	3/80 (3.7%)	6/40 (15%)	

CFU: colony forming units; SG: Study group; CG: Control group; Low intensity symptoms – nausea, disgust, flatulence, bloating; Moderate intensity symptoms – stomach cramps, mushy stool, appearance of mucus in faeces; High intensity symptoms – persistent diarrhea with weight loss.

cured (85.0%; $X^2=23.31$, $p<0.001$ compared to CG 42.5%) (Table 3).

At the second control examination (after three months), 9 patients (11.3%) from SG with positive mycological findings (*Candida* growth $>10^4$ CFU/g of stool) had moderate intensity symptoms, while only three patients from this group (3.7%) had high intensity symptoms and *Candida* growth $>10^5$ CFU/g of stool. Conversely, in the CG, positive mycological findings (*Candida* growth $>10^4$ CFU/g of stool) were obtained in 17 patients (42.5%) who had low intensity symptoms, while statistically significantly higher percent of patients had *Candida* growth $>10^5$ CFU/g of stool and the high intensity symptoms compared to SG [6 patients (15%) vs. 3 patients (3.7%)] (Table 3).

4. Discussion

4.1. Short summary of results of this pilot study

To date, there are no recommended therapy, established diet, and valid guidelines for the intestinal candidosis especially for treatment of recurrent form [29]. Moreover, there are no general attitudes regarding the role of *Candida* in digestive tract infections and criteria for differentiation of COG from CI of IM. Therefore, the results of our pilot study are encouraging for future efforts and attempts in improving the treatment for intestinal candidosis. The results obtained in our pilot study, where patients alongside nystatin therapy also carried out specific dietary recommendations over a period of 3 months, revealed a better ICOG outcome expressed in no *Candida* growth and absence of digestive tract infection symptoms. Out of total 80 patients who accepted these dietary modifications (including the avoidance of smoking, alcohol, simple sugar containing foods, cured and fatty meats, milk and dairy products, but with recommended use of suggested artificial sweeteners, whole grain bread and whole grain pasta, fish, seafood, low-fat white meat, acidophilus drinks and supplements), 85% had satisfactory outcomes after the 3-month period. On the other hand, on the second control, which was carried out after three-month period, 42.5% patients who were treated with nystatin without dietary modifications had low intensity symptoms and a laboratory evidence of *Candida* growth.

4.2. Advantages and disadvantages of this new approach which combines diet with antifungal treatment

The increase in ICOG prevalence and low antifungal susceptibility of *Candida* species present in the intestines makes the treatment of this patient's problem a daily challenge for physicians [14]. In this circumstances, the recommendation of diet modification, which could be of significance for better outcomes in patients with intestinal candidosis, also influences treatment shortening with antifungals and prevents the onset of side-effects that can occur due to long-term use of systemic agents. However, this new approach carries aggravating circumstances and disadvantages. Nowadays, people live in an era characterized by a stressful and fast way of modern life which is accompanied by poor dietary habits. Additionally, regarding economic status and fact that some national nutrition habits are very different from recommended healthy-diet, this dietary approach could be difficult to execute due to patients' financial difficulties and/or inability to organize such a diet regime during longer period of time.

To date, a small number of studies have been conducted in order to examine the efficacy of new dietary approaches to face this pathology. In some of them, it has been shown that dietary composition, modification, and interventions in particular have marked impact on *Candida* abundance in the intestines. More specifically, it was noted that *Candida* abundance positively correlates with recent consumption of carbohydrates and negatively correlates with a diet high in amino acids, fatty acids and proteins [16–18].

4.3. Limitations of this pilot study and perspectives for future studies

Given the fact that this is the initial study dedicated to the monitoring of the effectiveness of modified diet on COG, certain limitations have to be highlighted.

In spate the fact that the tests for detection of pathogenic bacteria and viruses in digestive tract were performed in our study, it must be emphasized that we could not carry out the complete examination of the microbiome. Additionally, there was no recommended baseline diet for the patients with COG in digestive tract which could be used for treatment and survey of diet modification efficacy to microbiota. Moreover, there is the lack of guidelines and instructions for an antifungal drug selection that could be used as a standard in comparison with a new approach in the treatment of IC. In this first pilot study, we decided to have endpoint three months after the beginning of the treatment to evaluate possible reduction in compliance after this period of time. Nonetheless, these encouraging results could be the beginning of the consideration and design of anti-*Candida* medical nutrition therapy which could be helpful not only in patients with chronic/recurrent form of ICOG, but also in hospitalized patients at high risk for fungaemia and invasive fungal infections, where digestive tract *Candida*-colonization is consider as potential reservoir of yeasts [30]. Besides, once established diet could be personalised for each patient in terms of dietary plan specification (how many calories, proteins, carbohydrates etc.). Adoption, application and diet testing in longer then three-month period of time with a

constant patient monitoring and their education could be the next research step in order to investigate potential effectiveness of nutritional healthy habits implementation in solving the problem of intestinal candidosis.

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Disclosure of interest

The authors declare that they have no competing interest.

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