MICROBIOME ASSOCIATED WITH RECURRENT VULVOVAGINAL CANDIDIASIS: KEY CHARACTERISTICS AND POTENTIAL THERAPEUTIC TARGETS

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Recurrent vulvovaginal candidiasis (RVVC) is one of the most complex forms of urogenital infection in terms of its clinical burden, impact on quality of life, and difficulty in preventing relapses. The aim of this study was to comprehensively characterize the taxonomic composition and functional potential of the vaginal microbiome associated with RVVC. This case-control study included patients with RVVC and conditionally healthy women. Vaginal samples were analyzed using shotgun metagenomic sequencing, followed by taxonomic and functional annotation of the microbiome using data quality control, taxonomic classification (Kraken2, MetaPhlAn4), and functional annotation (HUMAnN 3.9). At the community structure level, the RVVC microbiome exhibited pronounced interindividual variability and did not represent a uniform microbiota configuration. The taxonomic profile of the microbiome in RVVC was characterized by an increased relative abundance of *Lactobacillus iners* and anaerobic taxa (*Prevotella bivia*, *Dialister microaerophilus*), forming a compact "core" of intergroup differences. Functional analysis revealed a limited but reproducible set of metabolic pathways associated with RVVC; these included pathways of purine metabolism, central carbohydrate metabolism, and biosynthesis of cofactors and cell wall components. RVVC is associated not only with changes in the taxonomic composition of the microbiota but also with a stable reconfiguration of its functional potential. The identified shifts in metabolic pathway patterns reflect a transition of the vaginal microbial community to an alternative functional state, thus highlighting the need to develop new therapeutic strategies alternative to traditional antifungal-based approaches.

Keywords: vaginal microbiome; recurrent vulvovaginal candidiasis; metagenomics; shotgun sequencing

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INTRODUCTION

The human microbiota is a complex, dynamic symbiosis of diverse bacteria, archaea, viruses, and fungi; it is involved in both metabolism of biomolecules (lipids, carbohydrates, and proteins) and production of secondary metabolites (including metabolites critical to the human body) and plays an important role in maintaining macroorganism homeostasis [1–3]. The vaginal-cervical microbiome accounts for approximately 9% of the total human microbiota and determines a woman's reproductive health, including predisposition to premature birth and the development of infectious pathologies [4–7]. It is unique in that its less diverse composition, dominated by bacteria of the *Lactobacillaceae* family, is associated with the maintenance of homeostatic balance by suppressing the growth and adhesion of other microorganisms and the physiological anti-inflammatory environment (through production of secreted metabolites such as lactic acid, biosurfactants, bacteriocins, and H_2O_2). Vaginal dysbiosis is associated with increased species diversity due to facultative anaerobes such as *Gardnerella*, *Prevotella*, and *Atopobium*, which stimulate production of proinflammatory cytokines [8–10]. Importantly, changes in the composition of the vaginal microbiome are closely linked and correlate with the transcription of genes involved in the molecular mechanism of inflammation and activation of neutrophils in the vaginal mucosa, thus inducing reprogramming of innate immune responses [11, 12].

Fungi of the *Candida* genus are a part of the resident human microbiota; they asymptomatically present in the urogenital tract of healthy women in 30–98% of cases [13]. However, in 75% of women of the reproductive age, yeast fungi can cause an acute infectious process (at least once in their lifetime) known as sporadic vulvovaginal candidiasis (VVC). Its development is due to various risk factors, including the use of antibiotics and contraceptives,

new sexual partners, and allergic reactions to fungal antigens [14, 15]. In 8–10% of cases, VVC takes an idiopathic recurrent form (RVVC) (≥ 4 episodes per year), resistant to therapeutic treatment [16, 17].

According to clinical guidelines, a single dose of oral fluconazole is sufficient for treating sporadic VVC in 90% of cases; however, treatment of recurrent cases requires long-term antifungal therapy [18]. However, 6-month fluconazole treatment has a negative impact on the diversity of the microbiota of both the female reproductive organs and the gastrointestinal tract; it causes the development of drug resistance in the fungal pathogen, and is accompanied by various side effects, failing to lead to a complete cure in most cases [19].

According to current concepts, RVVC is a multifactorial disease, underpinned by a complex of interrelated factors, including dysregulation of the vaginal mucosal immune response, the acquisition of virulent properties by a previously non-pathogenic commensal yeast, and disruption of the vaginal microbiome ecology [13]. The relationship between RVVC and the bacterial component of the microbiome has long remained ambiguous. For example, in a study by Zhou et al. (based on 16S sequencing), no clearly "abnormal" bacterial communities were detected in women with frequent episodes of VVC, thus indicating the absence of gross taxonomic shifts [20]. In RVVC, dysfunctions of the vaginal microbiota are associated not only with a decrease in the total number of *Lactobacillus* [21], but also with a change in their species composition: different types of lactobacilli can both enhance and suppress the growth of *Candida* [10, 22]. Some studies have shown RVVC association with a decrease in "health-associated" lactobacilli (e.g. *Lactobacillus crispatus*) and a relative increase in *Lactobacillus iners*; the presence of *L. iners* is often interpreted as a marker of an unstable, transient state of the microbiome and/or dysbiosis [13, 23].

With the development of omics approaches, it has become clear that for understanding the protective potential of the microbiome against *Candida* infection, it is important not only to perform taxonomic marker gene analysis but also characterize the functional characteristics of the microbial community. These include metabolic pathways, the potential for adaptation to the microenvironment (e.g., genetic variants associated with substrate utilization, resistance to an acidic environment, oxidative stress, antimicrobial compounds, etc.), as well as microenvironmental metabolites that can influence the growth, virulence of *C. albicans*, and local immune homeostasis. Summarizing the data of recent years, Delavy et al. emphasize that using the combination of metagenomics and metabolomics it is possible to identify bacterial species and metabolic factors that can limit or, conversely, support the colonization of *C. albicans* in various niches, including the vaginal one [24].

In this context, shotgun metagenomic analysis is becoming a key tool because, in contrast to 16S/ITS amplicon sequencing, it can simultaneously characterize the entire spectrum of organisms in a sample with more taxonomic details, including an assessment of the functional potential of communities and the identification of subtle shifts that may be "invisible" with more coarse typing methods [25]. Despite the emergence of such studies [26], they are still rare in RVVC and do not provide answers to all the questions posed.

Currently, treatment of infectious pathologies caused by human commensals is being reconsidered worldwide with the goal of reducing the negative impact of antimicrobial drugs on the composition and diversity of microorganisms in the female reproductive tract. In this aspect, therapeutic approaches to the treatment of RVVC are actively discussed, aimed at restoring the normal microecology of the vagina, disrupted by the infectious process, and preventing relapses [27]. Particular attention is paid to the development of fundamentally new therapeutic algorithms based on the study of microevolutionary processes that trigger the transition of the commensal to the pathogen, factors of biome translocation, molecular mechanisms of interaction between its individual representatives and the local immune response.

The aim of this study was to characterize the vaginal microbiome associated with RVVC by using a shotgun metagenomic approach, assessing both the taxonomic composition and functional potential of the microbial community to identify reproducible patterns associated with recurrent disease and potential targets for intervention.

MATERIALS AND METHODS

Study Design. Collection of Biological Material

The single-center, comparative case-control study included 101 women of reproductive age (25–45 years): 51 women with suspected RVVC and conditionally healthy controls (n = 50) who applied to the ambulatory care at the Kashkin Research Institute of Medical Mycology outpatient clinic from July 2024 to October 2025.

RVVC was diagnosed based on the following criteria: ≥ 4 episodes of the disease within a year, lack of response to initial antifungal therapy, and the presence of yeast fungi on microscopic examination and culture (more than 10^5 CFU/swab). Exclusion criteria included comorbid vulvovaginitis with a predominance of bacterial over fungal biota and

RVVC caused by non-*albicans Candida*. The control group included healthy, non-pregnant women with no signs of inflammation or vaginal infections of any etiology, with a vaginal pH of 4.8 or less. Exclusion criteria for the two groups also included: pregnancy, use of hormonal contraceptives, severe endocrine pathology, including those associated with severe menstrual dysfunction (polycystic ovary syndrome (PCOS), other neuroendocrine syndromes), and the presence of sexually transmitted infections.

The diagnosis of RVVC and selection into the control group were based on the following tests: (1) microscopy with Nugent scoring; (2) cultural mycological and bacteriological studies (microbiological culture for myco- and bacteriobiota, species identification of *Lactobacillaceae* bacteria and fungi, determination of fungal pathogen sensitivity to antifungal drugs); (3) molecular biological analysis (PCR method) of the vaginal microbiome (Femoflor-16). The flowchart for the study group formation algorithm is shown in Figure 1.

Vaginal swabs for metagenomic analysis were collected using sterile disposable swabs. Samples were collected using gentle, rotating movements along the lateral vaginal walls to minimize trauma to the mucosa and ensure a representative sample of the microbiota. After collection, the swabs were eluted in phosphate-buffered saline. The resulting samples were stored at -80°C until nucleic acid extraction.

DNA Extraction

Total microbial DNA was isolated using the commercial QIAamp DNA Microbiome Kit (Qiagen, Germany) according to the manufacturer's instructions. This protocol includes selective lysis of eukaryotic cells and degradation of host DNA, which ensures enrichment of the microbial fraction and increases the sensitivity of subsequent molecular analysis.

Double-stranded DNA concentration was determined fluorimetrically using a Qubit Fluorometer (Thermo Fisher, USA) and a Qubit dsDNA HS Assay Kit (Thermo Fisher). Purity and the possible presence of inhibitors were assessed spectrophotometrically by measuring the A260/280 and A260/230 optical density ratios.

Library Preparation and Sequencing

Libraries for shotgun sequencing were prepared using the Illumina DNA Prep kit (Illumina, USA) according to the manufacturer's instructions. DNA fragmentation and simultaneous attachment of adapter sequences were performed using magnetic particle tagging with a bead-linked transposome (BLT). Following the tagging step, limited cycle PCR was performed to amplify the libraries while simultaneously introducing adapters containing unique dual indices, minimized the risk of cross-contamination and demultiplexing errors. The resulting libraries were purified and normalized according to the standard kit protocol.

The indexed libraries were quantitatively equalized by concentration, pooled equimolarly, and used for paired-end sequencing with 2×150 bp reads on the Illumina NextSeq 550 platform.

Bioinformatic Analysis

Quality analysis of short reads was performed using FastQC (v. 0.11.9) [28]. Data were cleaned of adapter sequences and low-quality nucleotides using fastp (v. 0.23.2) [29]. KneadData v. 0.12.4 was used to clean the microbiome data of human

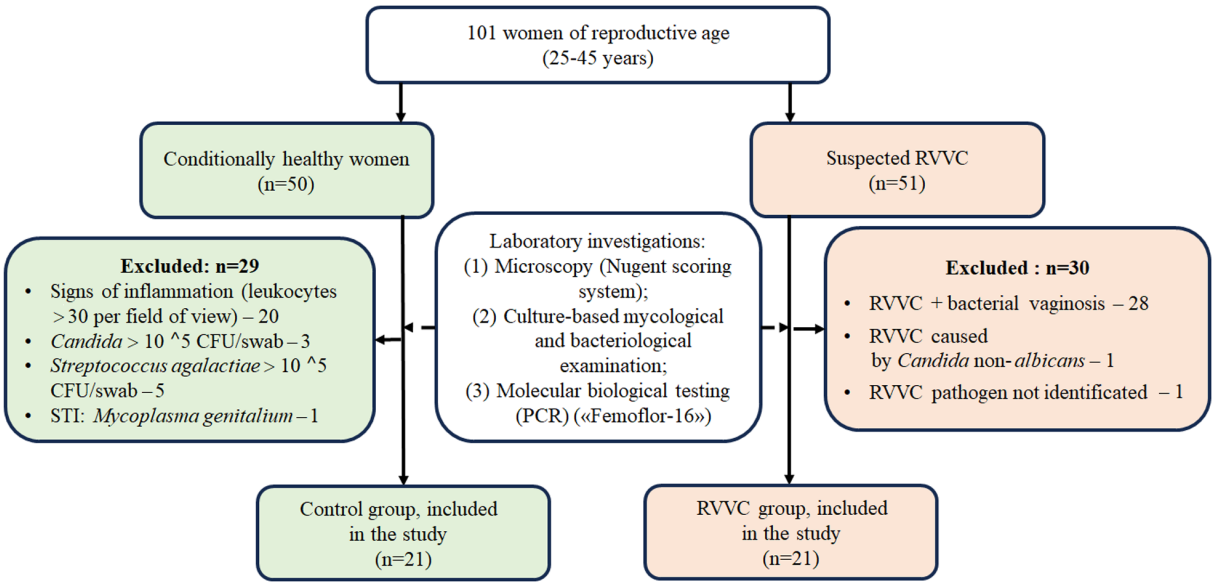

Figure 1. Flowchart of the group formation algorithms.

sequences [30]. Before calculating alpha diversity, reads, classified as *Homo sapiens*, were removed, as they are not related to the microbiome and may distort the Shannon index by artificially inflating the "species" composition. All comparisons between data operations were performed after unified host filtering. To control for the potential level of host reads based on diversity metrics, the Shannon index was additionally calculated on unfiltered data.

For comprehensive characterization of the taxonomic composition of microbial communities, two complementary approaches based on different classification principles were used: Kraken2 [31] (k-mer-based) and MetaPhlAn4 [32] (marker-gene-based). The combination of these two approaches minimizes the limitations of each individual method and provides a more complete and reliable picture of the taxonomic composition of the studied samples. Differences in the taxonomic structure of the microbiome at the species level between the patient groups and the healthy control group were analyzed using the nonparametric Mann-Whitney test with correction for multiple comparisons using the Benjamini-Hochberg method (False Discovery Rate, FDR). Functional profiling of the vaginal microbiome was performed using HUMAnN 3.9 [33].

RESULTS

Clinical and Demographic Characteristics of the Study and Control Groups

Based on the study results, 21 patients with a confirmed diagnosis of RVVC were included in the RVVC group, while 21 conditionally healthy women were included in the control group. Fifty-nine women were excluded from the study as they did not meet the inclusion criteria.

Clinical and demographic characteristics are summarized in Table 1. For the RVVC group, clinical parameters of the disease course were additionally assessed: mean disease duration and relapse rate. The studied parameters were comparable between the groups; no statistically significant differences were observed using the Student's *t*-test, Pearson's chi-square test, and Fisher's exact test for various parameters ($p \geq 0.05$).

All RVVC patients included in the study had a history of antifungal therapy according to the standard regimen. The main medications used were systemic triazoles and topical azole antifungals (clotrimazole, miconazole, sertoconazole, and ketoconazole). Antiseptics, combination topical antimicrobials, systemic antibiotics, and probiotics were also used during treatment.

Microbial Community Structure in RVVC Patients and in Control Group

The vaginal microbiome structure in RVVC patients and control group women was assessed using the Shannon index, an integrated metric that takes into account taxonomic diversity and the distribution of taxa within a sample. Even at this level, it is clear that women in both groups are characterized by a wide range of values, while the differences between the groups in the overall distribution pattern are moderate (Fig. 2A).

After excluding *Homo sapiens* reads, the median Shannon index in the control was approximately ~0.45, while in the RVVC group it was approximately ~0.40, with similar mean values (Fig. 2A). Both groups

Table 1. Comparative characteristics of patients included in the group of RVVC and control

Characteristics	RVVC patients (n = 21)	Conditionally healthy women (n = 21)	*p*-value
Age range (years)	32.2±6.1 [25–44]	31.6±6.0 [25–43]	0.724
Body mass index (kg/m^2)	20.9±3.47	22.7±4.2	0.124
Smokers (n)	6/21	7/21	1.000
Age range of menarche	13.4±1.33 [11–16]	12.8±1.44 [10–16]	0.154
Menstrual cycle duration, days	29.0±2.6	28.4±2.6	0.314
Menstrual bleeding duration, days	5.6±1.12	5.3±0.99	0.295
Pregnancy in anamnesis (number of women)	11/21	9/21	0.758
Number of women in labor	6/21	9/21	0.520
Constant sexual partner	17/21	18/21	1.000
Vaginal pH range	5.6±0.46 [5.0–6.0]	4.5±0.23 [4.2–4.8]	< 0.0001
Duration of the disease, years	5.2±4.38	Not applicable	—
Relapses per year	9.0±2.76	Not applicable	—

Quantitative data are expressed as M ± SD.

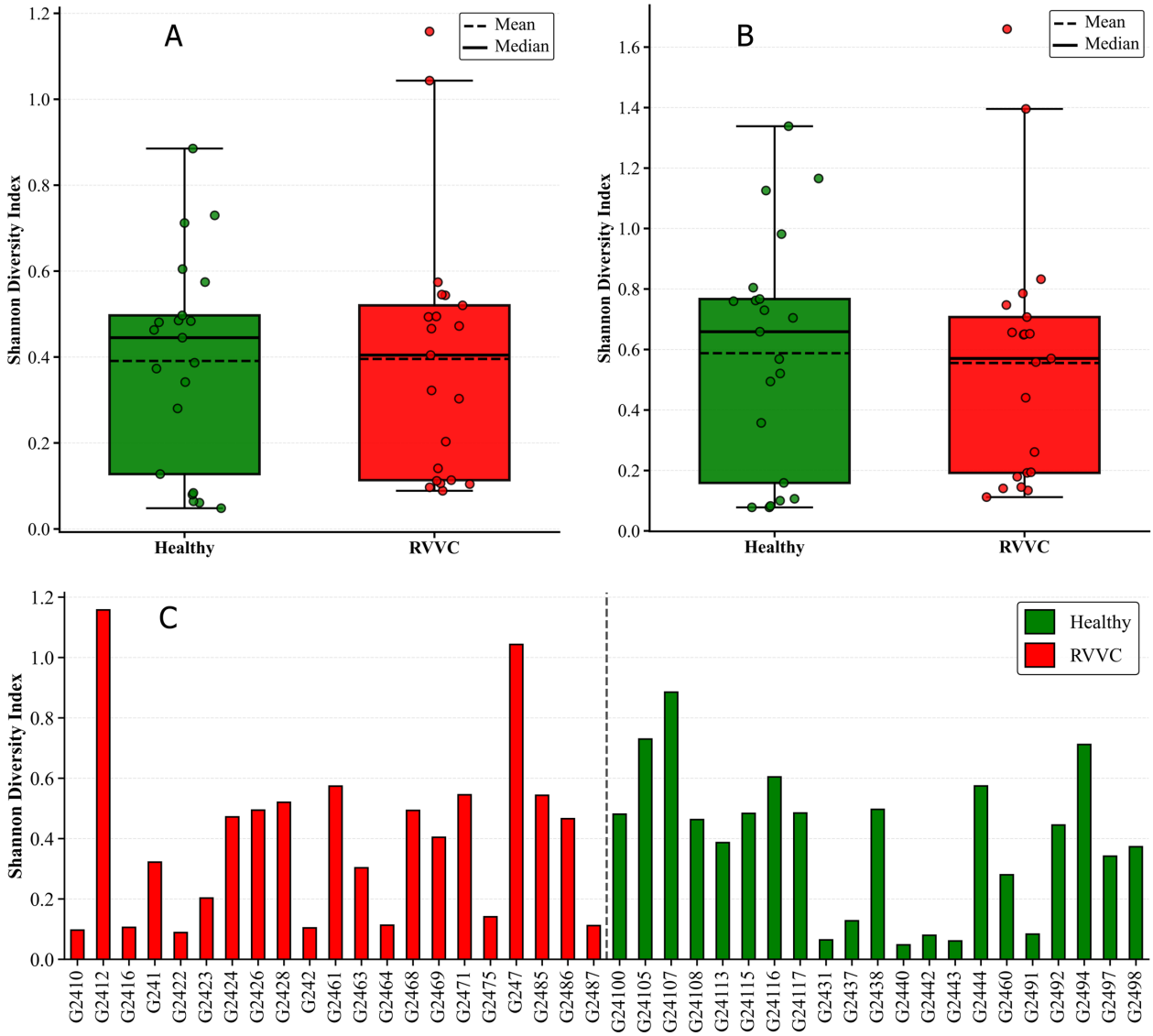

Figure 2. (**A**) Comparison of the α-diversity of the microbial community between the "RVVC" and "Healthy" groups using the Shannon index after exclusion of *Homo sapiens* sequences. (**B**) Comparison of the α-diversity of the microbial community between the "RVVC" and "Healthy" groups using the Shannon index with inclusion of *H. sapiens* sequences. (**C**) The Shannon index for each sample in the "RVVC" and "Healthy" groups with exclusion of *H. sapiens* sequences.

contained samples with extremely low values (~0.05–0.15), reflecting the predominance of a single taxon in the sample. However, in the RVVC group, a subgroup of samples with higher Shannon index values (up to ~1.16) was observed, thus resulting in a wider range of variation in the RVVC than in the control (up to ~0.89) (Fig. 2A).

Presentation of individual Shannon index values for each sample (after removing *H. sapiens*) demonstrates that the RVVC group includes both samples with a pronounced dominant taxon and samples with higher diversity (Fig. 2B). Therefore, at the level of community structure, RVVC manifests itself not as a single microbiota configuration, but as a set of different microbial states united by a clinical phenotype.

Furthermore, inclusion of *H. sapiens* in the calculation of metrics leads to a systematic increase in Shannon index values in both groups and expands the upper range (Fig. 2B). Therefore, the main results are presented for data after filtering of host reads (Fig. 2A,B), and the analysis without removing *H. sapiens* is considered a control for the influence of preprocessing (Fig. 2B).

The Taxonomic Profile of the Vaginal Microbiome in RVVC

At the species level, the vaginal microbiome of both groups retained characteristic a "lactobacillary" architecture: the majority of the signal was generated by members of the genus *Lactobacillus* (Fig. 3).

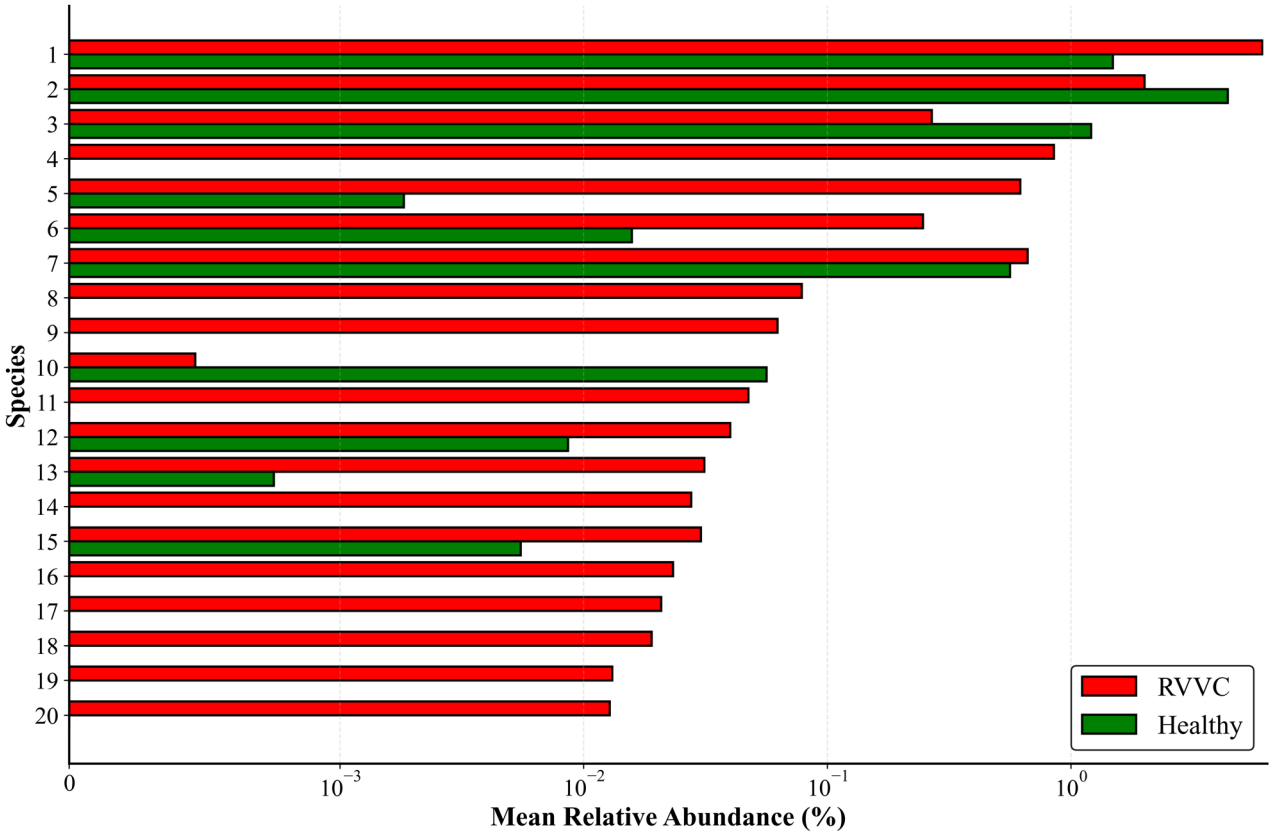

Figure 3. Top 20 species with the largest absolute differences in average relative abundance between the "RVVC" and "Healthy" groups: 1. *Lactobacillus iners*; 2. *Gardnerella swidsinskii*; 3. *Lactobacillus jensenii*; 4. *Fannyhessea vaginae*; 5. *Gardnerella pickettii*; 6. *Gardnerella vaginalis*; 7. *Lactobacillus crispatus*; 8. *Prevotella bivia*; 9. *Aerococcus christensenii*; 10. *Lactobacillus paragasseri*; 11. *Prevotella veroralis*; 12. *Lactobacillus mulieris*; 13. *Dialister micraerophilus*; 14. *Lancefieldella parvula*; 15. *Lacticaseibacillus rhamnosus*; 16. *Peptostreptococcus anaerobius*; 17. *Lancefieldella sp Marseille Q7238*; 18. *Winkia neuii*; 19. *Shuttleworthella satelles*; 20. *Lancefieldella rimae*.

Intergroup differences affected both the dominant taxon and the involvement of the anaerobic component. In both cohorts, *L. iners* remained the dominant species; however, its average representation was higher in the RVVC group, whereas in the control group, the contribution of species associated with the stable lactobacillary dominant, including *L. crispatus* and *Lactobacillus jensenii*, was relatively more pronounced (Fig. 3).

Under these conditions the RVVC group was characterized by an increased abundance of taxa typical of anaerobic-enriched vaginal communities, including *Gardnerella vaginalis*, *Fannyhessea vaginae*, and members of the genus *Prevotella* (including *Prevotella bivia*) (Fig. 3).

After correction for multiple comparisons, a limited set of taxa was identified that differed between groups at a statistically significant level (FDR < 0.05) (Fig. 4). These included *C. albicans*, *P. bivia*, *L. iners*, and *Dialister microaerophilus*; for all four taxa, mean levels were higher in the RVVC group compared to the control (Fig. 4). Importantly, the list of significant differences was compact: the statistical signal was concentrated in a small number of species, forming a reproducible "core" of intergroup differences.

A comparison of the differential analysis results (Fig. 4) with the overall species composition (Fig. 3) demonstrates consistency in the direction of the effects. For example, an increase in the proportion of *L. iners* in the RVVC group is observed under conditions of a prevalence of the anaerobic component, represented by *P. bivia* and *D. microaerophilus* (Figs. 3, 4). As a result, the RVVC profile at the data level is determined by a compact core of differences, including a shift toward the *L. iners*-associated state and the involvement of the anaerobic block through *P. bivia*, *D. microaerophilus*, and ecologically similar taxa, demonstrating an increasing trend in group mean values (Figs. 3, 4).

Metabolic Pathways Associated with RVVC

A comparative analysis of the functional profile of the vaginal microbiome revealed a limited set of metabolic pathways between patients with RVVC and women with a normal microbiota

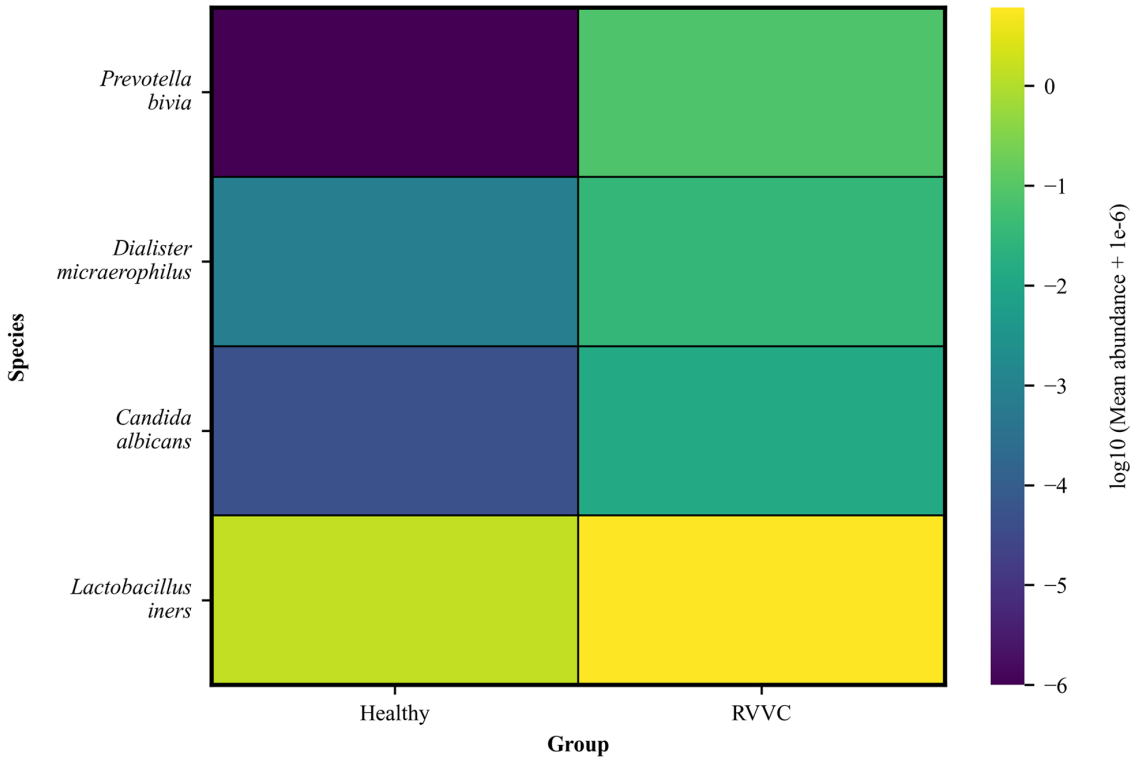

Figure 4. A heatmap of the most significantly different species (FDR < 0.05) between the "RVVC" and "Healthy" groups.

(Mann-Whitney test, q < 0.05) (Fig. 5). The most pronounced differences were associated with purine metabolism pathways, including inosine-5′-phosphate biosynthesis and related steps in the formation of 5-aminoimidazole ribonucleotides. These pathways were detected predominantly in samples from RVVC patients and were virtually absent in the control group. Increased purine biosynthesis suggests a higher demand for nucleotide precursors by the microbial community, which is characteristic of states of increased cellular turnover and intense biosynthetic activity. In parallel, a systematic increase in the abundance of central carbohydrate metabolism pathways was noted in the RVVC group compared to the control group, including alternative glycolysis pathways and fatty acid biosynthesis. These metabolic pathways are related to processes potentially involved in the energy and recovery support of anabolic reactions and demonstrate coordinated changes with nucleotide synthesis pathways. The combination of the identified shifts indicates the formation of a metabolic profile characterized by increased biosynthetic activity of the microbial community. Furthermore, increased abundance of pathways associated with the biosynthesis of cell membrane components, including phospholipids and peptide glycan precursors, was detected in samples from RVVC patients. The observed shifts indicate an increase in processes associated with the renewal and maintenance of microbial cell structures, which may be associated with adaptation to altered conditions of the vaginal environment.

Additional differences affected pathways involved in the biosynthesis of vitamins and cofactors, including thiamine- and folate-dependent metabolic pathways. These pathways are related to reactions associated with one-carbon metabolism and nucleotide synthesis; they demonstrated coordinated changes with other metabolic pathways that differentiated the RVVC group patients from healthy controls.

Taken together, the data demonstrate that the vaginal microbiota in RVVC is characterized by a metabolic profile with increased abundance of the pathways associated with energy metabolism, nucleotide synthesis, and the formation of cellular structures. This profile differs from the more limited and functionally stable metabolic regime observed in normal vaginal microbiota.

DISCUSSION

RVVC remains one of the most challenging forms of urogenital infection in terms of its clinical burden, impact on quality of life, and difficulty in preventing relapses. It requires a revision of therapeutic strategies. At the population level, the disease affects hundreds of millions of women during their lifetime, and the annual global burden is estimated to be extremely high [16]. The development of new, effective therapies for RVVC requires a deeper understanding of the pathophysiology of the disease. Based on accumulated knowledge, the key scientific question has now shifted from "how to eliminate

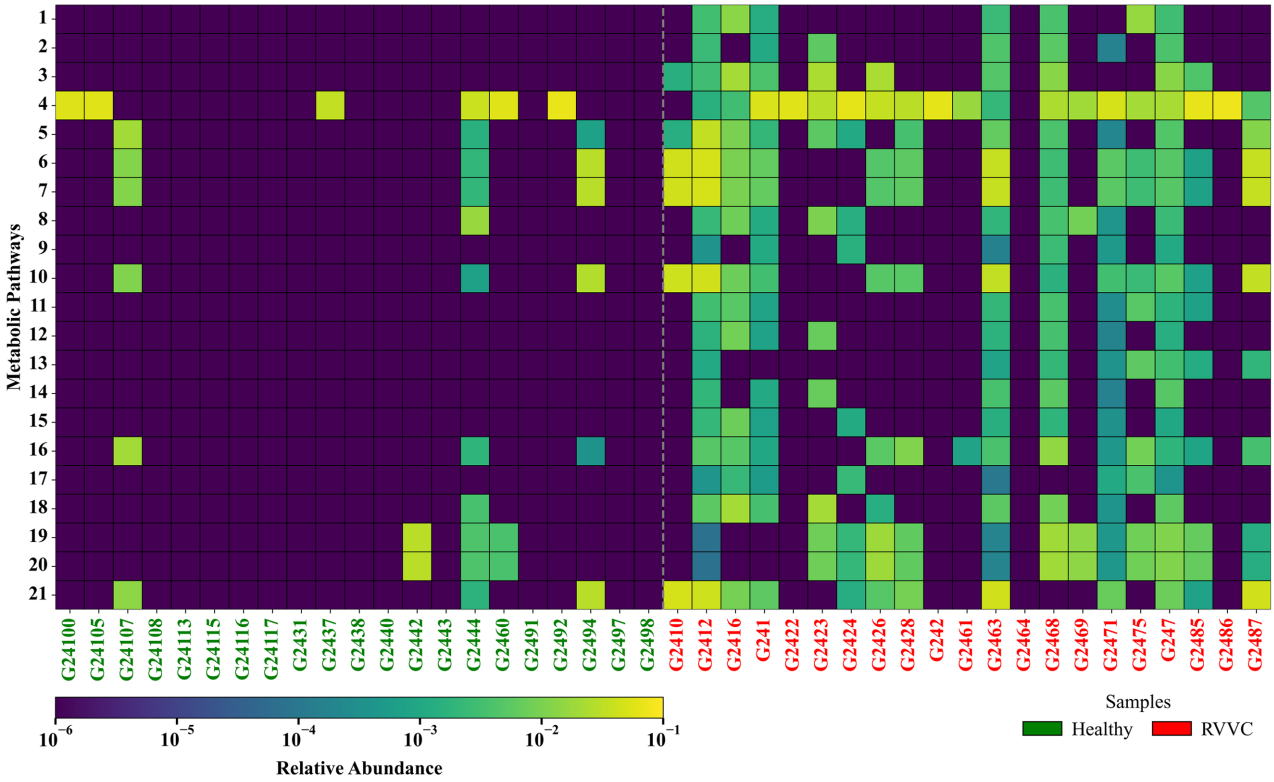

Figure 5. A heatmap of metabolic pathways statistically significantly different between groups (Mann-Whitney test, $q < 0.05$; $n = 21$ per group): *1.* PWY-2942: L-lysine III biosynthesis; *2.* PWY-5695: Inosine 5′-phosphate degradation; *3.* PWY-5484: Glycolysis II (from fructose-6-phosphate); *4.* PWY-6147: 6-Hydroxymethyl-dihydropterin diphosphate biosynthesis I; *5.* PWY-6163: Chorismate biosynthesis from 3-dehydroquinate; *6.* PWY-6277: 5-Aminoimidazole ribonucleotide biosynthetic superpathway; *7.* PWY-6122: 5-Aminoimidazole ribonucleotide biosynthesis II; *8.* PWY-5973: *Cis*-vaccenic acid biosynthesis; *9.* PWY-5989: Stearate biosynthesis II (bacteria and plants); *10.* PWY-6121: 5-Aminoimidazole ribonucleotide biosynthesis I; *11.* PWY-6897: Thiamine diphosphate recycling II; *12.* PWY-6703: Biosynthesis of preQ0; *13.* PWY-7282: Biosynthesis of 4-amino-2-methyl-5-diphosphomethyl-pyrimidine II; *14.* PWY-6608: Degradation of guanosine nucleotides III; *15.* PWY-7663: Gondoic acid biosynthesis (anaerobic); *16.* PWY-7357: Formation of thiamine phosphate from pyrithiamine and oxythiamine (yeast); *17.* PWY66-389: Phytol degradation; *18.* PWY-7953: Biosynthesis of UDP-N-acetylmuramoyl-pentapeptide III (contains meso-diaminopimelate); *19.* PWY4FS-8: Phosphatidylglycerol biosynthesis II (non-plastid); *20.* PWY4FS-7: Phosphatidylglycerol biosynthesis I (plastid); *21.* PWY-6124: Inosine 5′-phosphate biosynthesis II. Pathway variant numbers (Roman numerals) correspond to the nomenclature of the MetaCyc database.

the fungal pathogen" to the causes of the recurrent clinical phenotype, including the interactions between human mucosal immunity and vaginal bacterial and mycobiota.

Our data support the concept of RVVC as a multifactorial impairment of the local ecology, rather than a monoetiologic infection. In the context of RVVC, a combination of an increase in the yeast component (*C. albicans*) and bacterial community restructuring has been observed: the dominance of *L. iners* and an enrichment of anaerobic taxa (*P. bivia*, *Dialister*, *Gardnerella*, *Fannyhessea*/*Atopobium*). These changes are accompanied by an increase in pH, which also indicates a change in the physicochemical "niche", in which the recurrence of fungal infection occurs.

RVVC should be considered as an alternative stable state of the vaginal microbiome rather than a transient dysbiosis. In this state, the microenvironment exhibits its own stability parameters, formed by a complex of factors, including periodic antifungal therapy, which acts as a selective pressure [34]. In such models, systemic parameters rather than individual microorganisms are important: acidity, substrate availability (e.g., glycogen metabolism products), the rate of recovery from stress (menstruation, sexual intercourse, antimicrobial therapy), and the "threshold" for switching between states. In this regard, *L. iners* is often interpreted as a sign of a transitional/less stable type of microbiota, which maintains an acidic environment less strongly than *L. crispatus* and coexists more easily with anaerobes of the dysbiotic spectrum [35].

Importantly, this "transitional" microbiota type is not pathological in itself, but it can reduce the ecosystem resilience and, therefore, increase the relapse probability during repeated exogenous and endogenous exposures. Pathogenesis components

are also associated with trans-domain interactions between bacteria and fungi, as well as disruptions of stable microbial associations. Current concepts of RVVC emphasize that the recurrence of episodes can support not only the persistence of *Candida* but also the organization of the microbial community, in which bacterial components influence adhesion, morphogenesis, and the formation of biofilm structures in *C. albicans*; in turn, these structures themselves determine the availability of substrates to prevent relapses and limit sensitivity to antimicrobial therapy [36]. The detection of enrichment with anaerobic taxa (*Gardnerella*, *Prevotella*, *Fannyhessea*, *Dialister*) during RVC can be considered as a factor capable of changing the properties of the surface, as well as the characteristics of the local microenvironment to account for the formation of polymicrobial communities, metabolic interactions and the production of biologically active metabolites that indirectly contribute to the persistence of fungi [37].

Since RVVC is considered an immunopathological condition, the clinical manifestation of the disease is determined not only by the fungal load, but also by the characteristics of the inflammatory response of the vaginal mucosa, including both the protective immune response: dysregulation of the neutrophil response, the adaptive immune response along the Th17/IL-17 axis, hyperactivation of inflammasomes, and the mechanisms of immune tolerance [38, 39]. Moreover, the microbiome shifts in RVVC become potential regulators, rather than a "passive consequence" of the inflammatory response: through pH-dependent mechanisms, metabolic products, and signaling molecules that interact with the epithelium. For example, indole-3-aldehyde (3-IAld), a *Lactobacillaceae* metabolite, modulates the immune response by stimulating the aryl hydrocarbon receptor (AhR) on innate lymphoid cells, promoting IL-22 production, which initiates phosphorylation of the NLRC4 protein and subsequent limited bioactivity of the NLRP3 inflammasome via the production of an IL-1 antagonist (IL-1Ra) [40, 41]. Disruption of the critical IL-22/NLRC4/IL-1Ra axis is considered as the cause of the lack of antifungal resistance, and IL-22 deficiency is a risk factor for the development of VVC.

The functional shifts identified in our study are important primarily because they move from describing "which taxa are present" to the question of "what metabolic regime the community operates in": this regime obviously determines the system propensity for recurrence. Results of modern metagenomic and multiomic studies on VVC/RVVC emphasize that clinical phenotypes differ not only in the composition of the microbiota, but also in the set of functional programs associated with carbohydrate processing, cell wall biogenesis, and changes in the profile of metabolites that shape the local environment [26, 42]. From this perspective, changes in the abundance of central carbohydrate metabolism pathways and pathways associated with the biosynthesis of membrane lipids and peptide glycan precursors can be interpreted as a sign of the microbiota transition to a metabolic regime with increased central metabolism and enhanced biogenesis of cellular structures. This is of fundamental importance for the vaginal niche, since the processing of epithelial glycogen products determines the composition of organic acids and other low-molecular-weight metabolites that directly affect the pH and physicochemical characteristics of the environment. Accordingly, altered carbohydrate utilization pathways and the associated metabolite profile may contribute to conditions, in which the acid barrier and lactobacilli-mediated functional stability are less effectively restored, potentially reducing the probability of the system return to a protective state between disease episodes [43, 44]. Enhancement of purine metabolism pathways in vaginal inflammatory conditions has been previously described in panoramic studies as part of the general functional profile of dysbiotic conditions, including bacterial vaginosis and vulvovaginal candidiasis, when comparing different clinical phenotypes [45, 46]. In this context, the identified signal should not be considered as a specific marker of candidal infection *per se*. In the logic of RVVC, activation of purine metabolism obviously reflects increased demands of the microbial community for nucleotide supply associated with the need to maintain replication processes, DNA repair, and transcriptional activity in conditions of functional instability of the microenvironment. The relapsing course of the disease involves repeated cycles of disruption and partial restoration of the microbiota during therapy and inflammation, which prevents the formation of a long-term stable state. In such a dynamic system, nucleotide metabolism may be the ultimate limiting step, as it is necessary both for the proliferation and restructuring of bacterial communities and for the implementation of competitive strategies in the presence of *C. albicans* and hyperinflammation. Accordingly, the various pathways of purine metabolism reflect functional adaptation of the microbiota to repeated episodes of destabilization and metabolic stress rather than RVVC specificity. Thiamine- and folate-dependent pathways are rarely discussed in the context of the clinical picture, but in metagenomics, they are a typical marker of the high biosynthetic demands: the metabolism of single-carbon fragments and thiamine-dependent reactions provide a link between carbohydrate metabolism and nucleotide and lipid synthesis. In a balanced lactobacillus-dominant niche, many of these functions may be less variable, while in dysbiotic/inflammatory conditions, they become critical for the competitiveness of the consortium

(and therefore more often appear as distinguishing features in statistical analysis). This is consistent with the observation that, in different vaginitis, shotgun profiles differ not by a single "marker function", but by a combination of central metabolic pathways and cofactor axes [45].

Thus, in the context of RVVC treatment, it is advisable to consider not only the eradication of *Candida* but also the need to restore the functional balance of the vaginal environment. Azole therapy regimens can reduce the frequency of episodes, but do not always lead to a lasting change in the microbial and inflammatory picture, which is consistent with the clinical phenotype of frequent relapses in most patients [13]. Therefore, combined approaches aimed at correcting associated bacterial shifts and maintaining a lactobacillus-mediated acidic niche, as well as strengthening the barrier functions of the vaginal epithelium, appear promising [47]. Further in-depth research using metagenomic, metatranscriptomic technologies, and metabolomic profiling is needed to develop these approaches.

CONCLUSIONS

Results of this study demonstrate that RVVC should be considered not only as an infectious process caused by the persistence of *C. albicans*, but also as a state of sustained functional reorganization of the vaginal microbiota. A shotgun metagenomic approach has shown that differences between RVVC and normal vaginal conditions are formed at the level of the metabolic potential of the microbial community, rather than being limited to changes in taxonomic composition or the dominance of individual microorganisms. The functional profile of the microbiota in RVVC is characterized by coordinated changes in pathways associated with purine metabolism, central carbohydrate metabolism, cofactor biosynthesis, and the formation of cellular structures. These changes indicate a transition of the microbial community to a functional regime oriented toward maintaining high metabolic flexibility and adaptation in the conditions of repeated ecosystem destabilization, inflammatory pressure, and trans-domain interactions with *Candida* species. This regimen differs fundamentally from the more stable and functionally limited metabolic state characteristic of a healthy lactobacillus-dominant microbiota. The findings support the concept of RVVC as an alternative, stable state of the vaginal ecosystem, in which repeated episodes of clinical exacerbation and partial recovery prevent a return to a protective microbiome. In this context, the identified functional shifts reflect a systemic adaptation of the microbiota to a chronically unstable environment rather than specific "candidal metabolism".

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COMPLIANCE WITH ETHICAL STANDARDS

The protocol was approved by the Local Ethics Committee of North-Western State Medical University named after I.I. Mechnikov (protocol no. 06 dated June 19, 2024). All study participants were informed about the study goals and methods and signed voluntary informed consent.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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МИКРОБИОМ, АССОЦИИРОВАННЫЙ С РЕЦИДИВИРУЮЩИМ ВУЛЬВОВАГИНАЛЬНЫМ КАНДИДОЗОМ: КЛЮЧЕВЫЕ ХАРАКТЕРИСТИКИ И ПОТЕНЦИАЛЬНЫЕ МИШЕНИ КОРРЕКЦИИ

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Рецидивирующий вульвовагинальный кандидоз (РВВК) — одна из наиболее сложных форм урогенитальной инфекции по совокупности клинической нагрузки, влиянию на качество жизни и трудности профилактики рецидивов. Цель исследования состояла в комплексной характеристике таксономического состава и функционального потенциала вагинального микробиома, ассоциированного с РВВК. В исследование по типу “случай-контроль” были включены пациентки с РВВК и условно здоровые женщины. Анализ вагинальных образцов выполняли методом панорамного метагеномного секвенирования с последующей таксономической и функциональной аннотацией микробиома с использованием контроля качества данных, таксономической классификации (Kraken2, MetaPhlAn4) и функциональной аннотации (HUMAnN 3.9). На уровне структуры сообщества микробиом РВВК характеризовался выраженной межиндивидуальной вариабельностью и не представлял собой единую конфигурацию микробиоты. Таксономический профиль микробиома при РВВК отличался повышенной представленностью *Lactobacillus iners* и анаэробных таксонов (*Prevotella bivia*, *Dialister microaerophilus*), формирующих компактное “ядро” межгрупповых различий. Функциональный анализ выявил ограниченный, но воспроизводимый набор метаболических путей, ассоциированных с РВВК, включая пути пуринового метаболизма, центрального углеводного обмена, биосинтеза кофакторов и компонентов клеточной стенки. РВВК ассоциирован не только с изменениями таксономического состава микробиоты, но и с устойчивой перестройкой её функционального потенциала. Выявленные сдвиги в паттернах метаболических путей отражают переход вагинального микробного сообщества к альтернативному функциональному состоянию, что подчёркивает необходимость разработки новых терапевтических стратегий альтернативных традиционным подходам с использованием противогрибковых лекарственных средств.

Полный текст статьи на русском языке доступен на сайте журнала (http://pbmc.ibmc.msk.ru).

Ключевые слова: вагинальный микробиом; рецидивирующий вульвовагинальный кандидоз; метагеномика; панорамное секвенирование

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