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SHORT COMMUNICATION

Autovaccines – potent tool against chronic vulvovaginal candidiasis

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ABSTRACT
OBJECTIVE: Our aim was to determine the effect of immunomodulatory therapy in women with chronic and recurrent vulvovaginal candidiasis (RVVC).
BACKGROUND: We present recent highlights in the research into vaginal microbiome and consequences of chronic inflammation such as vulvovaginal candidiasis (VVC). VVC is a widespread vaginal infection primarily caused by *Candida albicans*. Experience of more than three episodes per year is defined as RVVC.
METHODS: The strains were isolated from women suffering from the above infections as for the period of 2017 to 2021 and subsequently used in immunomodulatory treatment. The preparation and administration of autovaccination therapy was performed using standard methodology and procedures cited in the manuscript.
RESULTS: In total, autovaccines were produced for 73 patients of whom 30 (41 %) were successfully cured by this treatment, 29 (40 %) experienced a partially successful treatment, and in the remaining 14 (19 %), the autovaccination therapy was ineffective.
CONCLUSION: We provide current knowledge about alternative (autovaccine) treatment options for female patients with VVC and RVVC diseases and our experience with the outcomes after autovaccine administration that currently has a promising therapeutic potential *(Tab. 2, Ref. 18)*. Text in PDF *www.elis.sk*
KEY WORDS: autovaccines, chronic infections, vulvovaginal candidiasis, recurrent vulvovaginal candidiasis, *Candida albicans.*

Introduction

The recent period has enormously expanded the insight into the structure of the human microbiome, i.e., into the genomic composition of microbial populations harbored by the human body. Up to now, the investigations of the human collection of microorganisms living together have been mostly aimed at specifying the arrangement of "regular" communities and recognizing connections between microbial residents' features and illness conditions. The majority of examinations were focused on the bowel microbial communities, although other host habitats have also been surveyed, including the female genital tract (1).

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The vulva may be inhabited by *Enterococcus* spp., coagulase-negative staphylococci (CoNS), *Candida* spp., *Escherichia coli* and other enterobacteria in a well-balanced community. The vaginal flora is important for the reproductive system of a woman of child-bearing age. Due to this reason, the vaginal physiological flora or microbiota should be stable as well as protective against pathogenic microorganisms. Lactobacilli, which make up about 95 % of vaginal microbial population, are particularly relevant in protecting and preserving acidic pH. *Lactobacillus* spp. (especially *L. acidophilus*) express an attributable defense mechanism of H_2O_2 production, some strains form bacteriocins (lactitins) and/or produce biofilms. The penetration of bacteria through the cervix into the uterus is blocked by a mucus plug which, however, can be biochemically broken down by enzymes. After the menopause, the composition of the vaginal microbiota is alike that before puberty and the pH rises over 6.5 (2). *Lactobacillus* spp. are the prevailing residents that are inherently regarded as favorable because *they* support the health of the microenvironment by their ability to decrease the inflammation and vulnerability to infection. Nevertheless, appropriate activity differs among *Lactobacillus* species, with some being more host-advantageous than others. For instance, *Lactobacillus crispatus* generates the highest levels of lactic acid among Lactobacilli in the vagina and may aid to prevent conditions with other microbes without promoting inflammation, driving it greatly beneficial (3). There are numerous worldwide investigations that

Tab. 1. Chronic and recurrent infections of genitourinary tract as indications for autovaccine treatment or stock vaccine (treatment success rate in range of 70–90 %) (10).

Localization of chronic and recurrent infection	Presumed bacterial cause of the infection
Chronic cystitis Subacute and chronic vaginitis Subacute and chronic vulvitis Candidiasis of vulva and vagina Chronic prostatitis	*Escherichia coli* and other Gram-negative causative agents of urinary tract infections *Enterococcus faecalis* *Candida albicans*

In: Czirfuszová et al (2021) (10), Lanzafame (2011) (7) and Troiano et al (2018) (12)

explore vaginal bacterial resident communities in distinct race and ethnicity groups including various socio-demographic and lifestyle dissimilarities (4–6). Notably, it is not entirely clear why the usage of hygiene items, birth control, fertility phase, sexual activities and foodstuffs impact the vaginal microbiota. Moreover, surveys proceed to determine the vaginal microbiome's relation with the resistance or predisposition to infectious diseases. For explanation, current multiple studies presented that women with microbiomes composed predominantly of *L. iners* or non-Lactobacillus species are exposed to a threefold to fivefold increase in threat for human papillomavirus (HPV) morbidity that can proceed to cervical malignity as opposed to women with *L. crispatus*, i.e., the prevailing bacterial resident. Given that the underlying tools for microbiome-illness relations are not comprehended, such associations could demonstrate to be clinically advantageous parameters for concern stratification and disease protection (1), particularly in chronic diseases such as vulvovaginal candidiasis.

According to Lanzafame (2011), vaginal fungal infections account for more than half of all vaginitis cases and approximately one-third of cases of vulvovaginal candidiasis may result in recurrences, and sometimes even progress into chronicity. Treatment and prolonged prophylaxis resulted in a failure of around 20 % (7). Rosati et al (2020) reported that vulvovaginal candidiasis (VVC) has long been regarded as the impact of insufficient host protection against Candida colonization, as in primary immunodeficiencies related to long-lasting mycotic infection and inadequate elimination of microorganisms. In line with these authors, even 9 % of women in various populations encounter over three or four cases per year, which is considered as a recurrent vulvovaginal candidiasis (RVVC) (8). Rosati et al (2020) refer to the Clinical Practice Guidelines for the Management of Candidiasis (2016 update by the Infectious Diseases Society of America) when stating that VVC is treatable with local or/and peroral antimycotic drugs containing azoles (e.g., miconazole, clotrimazole, ketoconazole, and fluconazole) which are the most administered medication despite not preventing the recurrent post-treatment episodes. This suggests the importance of antimycotic immunotherapy based on autovaccines. RVVC is not related to the mortality rate, but on the other hand, as morbidity increases, the costs associated with health care rise correspondingly. Consequently, harder effort is required to arrive at understanding of immunopathogenesis in order to be able to treat VVC effectively and eliminate recurrences (8).

Cellular-specific and nonspecific types of immunity are usually considered to be the providers of the primary protection against mycotic agents. The significance of cellular immunity is approved by the clinical sighting that the majority of invasive mycotic diseases arise in patients with deficient cell-mediated immunity. T lymphocytes are essential in human protection against various fungal agents such as *Candida albicans*. Mainly CD4+ lymphocytes account for important defense while their basic means is the creation of cytokines. Additionally, their further crucial efficient tool is cytotoxicity. CD8+ T lymphocytes can destroy the hyphal form of *C. albicans*. Several investigations revealed that secretory IgA (sIgA) blocks *C. albicans* from attaching to the epithelium and similar immunity feature can provide defense in rat vaginal thrush. Vaginal immunization by monoclonal antibodies specific against yeast killer toxin stimulated the production of sIgA anti-idiotypic reply which rescued rats from the flare-up of *C. albicans*; passive defense was proved with vaginal secretion comprising antibodies against the mannan component and aspartyl proteinase of *C. albicans*. In medical recordings, numerous antibacterial and antiviral vaccines are licensed but none have been approved for preventing human medically important fungi (7, 9). In advance of preparing fungal vaccines, it is meaningful to specify requirements for the expected efficacious fungal vaccine. The first purpose is to design a vaccine that would restrict the ability of the fungus

Tab. 2. A total of 73 autovaccines manufactured for the treatment of *vulvovaginal candidiasis* as for the period of 2017 to 2021.

No	Diagnosis	n	(%)
1	Other vulvar vaginitis	17	(23.3)
2	Recurrent colpitis	9	(12.3)
3	Chronic colpitis	4	(5.5)
4	Mycotic colpitis	4	(5.5)
5	Recurrent mycotic colpitis	5	(6.9)
6	Mycotic and bacterial recurrent colpitis	4	(5.5)
7	Chronic vaginal and vulvar inflammations	1	(1.4)
8	Gynecological infections	1	(1.4)
9	Other inflammatory diseases of female genital organs	2	(2.7)
10	Candidiasis	2	(2.7)
11	Recurrent candidiasis	3	(4.1)
12	Fungal gynecological infections	1	(1.4)
13	Mycosis	1	(1.4)
14	Recurrent mycoses	2	(2.7)
15	Recurrent vaginal infections	1	(1.4)
16	Recurrent gynecological fungal infections	2	(2.7)
17	Vulvovaginitis	1	(1.4)
18	Vulvovaginitis recurrence	3	(4.1)
19	Chronic vulvovaginitis	2	(2.7)
20	Vulvovaginitis fungal recurrent	4	(5.5)
21	Vulvovaginal candidiasis	2	(2.7)
22	Vulvovaginal ulcerations and inflammation in chronic infections classified elsewhere	1	(1.4)
23	Inflammation of the fallopian tubes and ovaries	1	(1.4)

n – number of autovaccines, % – percentage of autovaccines

to go into a latent state. Human hosts are successful in confining the propagation of mycotic infections, but small patches of infection may persist for years. These niches can become locations of reinfection if the host immunity becomes unbalanced. Hence, each immunogenic substance aimed at mycotic agents has to protect the host from the formation of concealed forms and consequently prevent their repeated activation. In cases of recurring vulvovaginal candidiasis and well as in those of invasive mycotic infections, the dormant form of mycotic agents harbored by the host is often involved, which is commonly coupled with impaired vaginal immunity (7).

There is a long medical history of autologous vaccines being used in the therapy of chronic infections (7). Autovaccines are usually prepared after running out of available targeted antimicrobial options of treatment. The immunomodulatory therapy using host-specific microbial strains repeatedly isolated from the patient's biological sample is in many cases more clinically effective than therapy based on mass-produced immunomodulatory substances. The clinical success of immunomodulatory treatment with microbial autovaccines ranges from 70 % to more than 90 % (10). The treatment can generally be considered successful when the finding of microbes targeted by autovaccination treatment in the control microbiological swabs or biological specimens taken from the affected site is negative. On the other hand, the success of the treatment is partial when it is achieved in approximately 50 % of the corresponding procedures with individually prepared oral microbial lysates, while the evaluating period can be extended up to three to six months, depending on the patient's state of health as well as on the efficacy of the mentioned therapy (10, 11). The most common chronic and recurrent infections of the genitourinary tract and presumed causative agents are listed in Table 1.

Biological materials suitable for capturing microorganisms for preparation of autovaccines / stock vaccines include vaginal swab, cervical swab, urine, and urethral swab. Isolated microbial strains are used in strict compliance with the principles of aseptic handling and prevention of sample contamination in the environment and usage of devices. In Slovakia, autovaccines are prepared based on standard procedures approved by healthcare authorities of the Slovak Republic (10).

Applied autovaccination therapy

At the Department of Microbiology, Medical Faculty Comenius University in Bratislava, a total of 73 autovaccines were prepared for the treatment of vulvovaginal candidiasis as for the period of 2017 to 2021. The treatment was successful in 30 patients (41 %), partially successful in 29 patients (40 %) while in 14 patients (19 %) the inflammation was still present with the persistence of bacteria such as *Streptococcus agalactiae* and *Escherichia coli*. During the autovaccination therapy, the patients were neither prescribed with antifungal treatment, nor were they administered with probiotics. This rate of the efficacy of immunomodulatory therapy, as well as the level of improvement as a result of autovaccination treatment can be considered relatively successful (Tab. 2).

Discussion and conclusion

Autovaccination involves strengthening of the innate immune mechanisms through a regular administration of antigenic complex of microorganisms isolated from the infection site. In view of that, antigens of microorganisms are the most natural immune system stimulators potentiating cellular and humoral forms of immunity, while autovaccine is a suitable immunostimulating substance. Autogenous vaccination is also individually specific because it is prepared from a strain isolated from the treated patient. The concentration of microbial antigens is standard and the dosage is adjusted to the clinical condition of the patient as well as to their immune system disposition (13). The therapeutic efficiency of immunomodulatory treatment depends on many factors, including appropriate indication, composition of autovaccine, or individual dosage. The advantage of autovaccine application lies not only in significantly reducing the number of disease flare-ups, and shortening and alleviating the course of the disease, but also in reducing the consumption of antibiotics and antifungal drugs (7, 14). Therefore, the autovaccination treatment method should not be forgotten in the era of growing resistance to a wide range of antimicrobial drugs and consequences of adverse reactions induced by their repeated administration. For this reason, immunomodulatory treatment with microbial lysates should be initiated much earlier than the antimicrobial therapy unsuccessfully repeated for several years. Moreover, another utility of autovaccines lies in minimum side effects and importantly also in being tolerated in combination with other medications. Our results and used methods are in line with recent research and recommendations (10, 15–17) related to adequate administration of immunomodulatory therapy and treatment of recurrent as well as chronic persistent infections. In addition, autovaccination treatment can serve as an alternative option for treating chronic infections (18) while avoiding the emergence and development of antimicrobial resistance.

Finally, in our view, autovaccination treatment has not yet found its way into current medicine as a therapy deserved by many patients suffering from the above infections. Moreover, according to our results, it was confirmed that immunomodulatory therapy has a great potential for becoming a beneficial and successful treatment.

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