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VAGINAL CANDIDIASIS: AN INCOMPREHENSIBLE CHALLENGE

CANDIDÍASE VAGINAL: UM DESAFIO INCOMPREENSIVO

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RESUMO

A infecção recorrente da mucosa vaginal pela Candida albicans foi abordada realçando-se os mecanismos de interação entre o fungo e o epitélio vaginal, com ênfase para os aspectos imunológicos que controlam a proliferação fúngica. Destaca-se o papel da imunidade celular mediada neste processo de equilíbrio entre agente e hospedeiro, reforçando a importância via Th_1 de resposta imune, onde há uma liberação de citocinas como interferon-gama, interleucina-1 e 12. Por outro lado, a via Th_2 que libera citocinas estimulantes da produção de anticorpos (interleucinas-4, 5 and 10), terá valor limitado na defesa da mucosa contra este agente. Comenta-se também os aspecto fisiopatogênicos envolvendo resposta imune ligada aos processos alérgicos individuais e em decorrência de interação com o parceiro sexual.

O diagnóstico, principal "arma" para o tratamento adequado, é enfocado com ênfase na prática, reforçando-se o uso de bacterioscopias simples, sem esquecer que técnicas sofisticadas, como o PCR, podem vir a ser útil para determinados casos.

O tratamento da fase aguda e de manutenção foi sugerido na tentativa de diminuir as recorrências, alertando-se principalmente para nessecidade de tomar atitudes que visem não somente o combate ao fungo, mas que também e fundamentalmente, priorize a identificação e eliminação de possíveis alergenos.

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ABSTRACT

Recurrent infection of Candida albicans in the vaginal mucous was dealt with highlighting the mechanisms of interaction between the fungus and the vaginal epithelium, emphasizing the immunological aspects which

control fungal proliferation. The role of cell immunity, which is a process of balance between agent and host, is pointed out stressing the importance, through Th_1 of an immune response, which releases cytokines (gamma interferon, interleukin- 1 and 12). On the other hand, a Th_2 way, which releases interleukin-4, 5 and 10 leading to antibodies production, will play a limited role regarding the defense of the mucous against this agent. Pathophysiogenic aspects, involving an immune response linked to individual allergic processes and those due to interaction with a sexual partner, are also dealt with.

Diagnosis, the main means towards adequate treatment is focused on, using a practical approach, stressing the use of simple exams, but also commenting on how helpful sophisticated techniques such as PCR can be useful for certain cases.

The treatment for the acute stage and for maintenance is to avoid recurrence, stressing the necessity of taking attitudes that not only fight the fungus but which also give priority to the identification and elimination of possible allergens.

INTRODUCTION

Treatment of Vaginal Candidiasis for gynecologists and other physicians, is not generally considered to be troublesome, when the issue is acute and not complicated episodes. Nevertheless, it can become extremely difficult, if it is recurrent and with chronic evolution. This kind of infection should be addressed by the specialist in this field and not by the general practitioner.

The terms "chronic" and "recurrent" vulvovaginitis are frequently misinterpreted. This could, at times, confuse the interpretation of the pathophysiology in a particular patient and lead to inadequate treatment. Chronic infection implies, nearly always, an active, persistent infectious process for prolonged periods. This does not seem to be the case in recurrent candidal vulvovaginitis, which usually occurs in repeated acute short-term episodes of variable intensity. Therefore, candidal vulvovaginitis can be recurrent but is not chronic. The recurrences are chronic in a subgroup of women who have acute episodes, which repeat themselves over a long period of time.

An approach, combining anamnesis, gynecological exam and microbiological tests, should be used all the time, as none alone seem to be enough to lead to a correct diagnosis.

Also, it is important to differentiate between colonization and infection of the vaginal epithelium. Many asymptomatic women are continually colonized with Candida albicans in their vaginas, but this does not imply that there is a current, chronic or even a latent infection. The lay press has popularized the unproven idea that Candida infections are the underlying cause of a multitude of symptoms in every body part. Consequently, most women who seek help for recurrent symptoms of vaginitis will claim to have a "yeast infection". Unfortunately, most of these self-attempted diagnoses are incorrect with evidence of Candida being detected in subsequent examination only 30% of the time. It's not surprising, therefore, that those antifungal medications have no effect on most of these conditions.

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Of private patients at our institution, about 5% with an initial episode of candidal vaginitis will have recurrent infection after apparently successful treatment with antifungal medications. To prevent frequent episodes, we must identify underlying factors predisposing to Candida growth and take measures to reduce these risks.

Immunedefense and Candida

Although all women have antibodies to Candida, these antibodies are nonprotective and do not prevent its growth. Moreover, women with defective B-cell immunity don't have an increased rate of vaginal candidiasis. Cell-mediated immunity appears to be the major, if not the only, immune mechanism limiting vaginal proliferation of C albicans. Polymorphonuclear leukocytes aren't noticeably present in the vagina. Rather, mononuclear lymphoid cells, macrophages and T lymphocytes, appear to be the major regulators of vaginal Candida

growth. Women with genetic defects that affect T lymphocyte or macrophage functions have an increased rate of candidal mucous membrane infections.

More than 95% of candidal vaginal infections are caused by C albicans, and the remainder primarily by C glabrata and C tropicalis.

More than 95% of candidal vaginal infections are caused by C albicans, and the remainder primarily by C glabrata and C tropicalis. In healthy women with normally functioning immune systems, infection of mucosal surfaces by Candida is readily treated and rarely recurs. Conversely, a defective in vitro cellular immune response to Candida is readily demonstrable in many women with recurrent candidal vaginitis. It is sometimes not appreciated that recurrent C albicans vaginal infections are often opportunistic and secondary to a transient deficiency in cell-mediated immunity.

An immune response by T helper (h) lymphocytes can occur along two pathways. A Th_1 response results in release of cytokines that activate cell-mediated immunity (interferon-gamma, interleukin-1, interleukin-12) while a Th_2 response results in release of different cytokines that stimulate antibody production (interleukins-4, 5 and 10). Women whose T cells manifest a Th_2 response upon exposure to Candida, due to genetic and /or environmental (allergic) factors, will be less likely to limit vaginal Candida proliferation and so will be increasingly susceptible to repeated episodes of candidal vaginitis.

In about 20% of cases, a vaginal allergic response can be implicated as a predisposing factor for recurrent candidal vaginitis. Semen components, contraceptive spermicides, vaginal douches, other chemicals or medicines that may come into contact with the vagina, or C albicans itself can serve as allergens in sensitized women. The vagina's immediate hypersensitivity response causes release of histamine, which stimulates macrophages to produce prostaglandin E2. The PGE_2 inhibits production of interleukin-2 by T lymphocytes, thereby transiently paralyzing the cell-mediated immune response. Under these conditions, the low levels of Candida normally present in many women's vaginas are able to proliferate and trigger a clinical infection.

Allergy-related candidal vaginitis can also be induced in nonallergic women if the male partner has a genital tract allergic response. In these cases, immunoglobulin E antibodies are transferred to the woman by coitus and bind to her basophils and mast cells. The allergen, also present in the ejaculate, then reacts with the bound IgE, initiating an allergic response.

Candidal vaginitis most often reappears during the late luteal phase of the menstrual cycle, when the elevated level of progesterone down-regulates cellular immune response and lessens inhibition of Candida growth. Similarly, women with endocrinopathies may also be especially susceptible to recurrent candidal vaginitis.

Infectivity of C albicans is associated with ability of the yeast forms to germinate. Recent evidence indicates that germination, too, may be regulated by cellular immune system components. Compounds such as PGE_2, which increase the intracellular level of cyclic adenosine monophosphate (cAMP), promote Candida germination. Thus, medications that increase cAMP levels may also increase susceptibility to candidal vaginitis. Conversely, gamma interferon, a product of activated T lymphocytes, inhibits it.

Candida albicans can sometimes be present also in the male genital tract. However, this does not mean that recurrent infection in women results in failure to eliminate the male reservoir. Even being controversial, there is no formal current recommendation for treatment of partners of women with recurrent candida vulvovaginitis.

Diagnosis

Recurrent candidal vaginitis may show the classical symptoms of pruritus, inflammation, and curdlike, cheesy discharge. Sometimes, intense pruritus may be the only symptom. Unfortunately, many patients have been treated by numerous physicians, nutritionists, and other health-care providers and have tried various home remedies that often complicate and mask presenting symptoms. Therefore, the gross appearance of vaginal secretions is not diagnostic. In a recent study (not published yet),

the vaginal contents of 100 asymptomatic patients were tested for Candida sp diagnosis (not acute infection), using appropriate microbiological exams and then comparing them to clinical aspects. The culture plus wet mount and Gram stain were able to confirm candidal infection in only 41 %(7/17) of cases suspected of being typically Candidiasis. On the other hand, were positive in 15.4% (4/26) when the clinical aspect suggested Bacterial Vaginosis although the microscopic exams were normal. It was also positive for Candida, in 10.5% in cases of atypical clinic aspects of vaginal secretion and 5.9% when visual observations pointed to absolute normality of the vaginal epithelium. These findings confirm other papers showing evidence that the candidal infection can not be made, based only on history and physical examination without the corroboration of laboratory tests. Microscopy, using saline solution, detects yeast presence in approximately 30% to 50% and can be higher when 10 % potassium hydroxide is performed. Specific culture for Candida is not always necessary in most of cases of uncomplicated candidiasis, although, as one third of patients with symptomatic candidiasis will have negative findings by microscopy only, it is strongly recommended in difficulties cases of chronic recurrent vulvovaginitis.

Even for infected women the culture can be negative, if sampling is inadequate. It can be helpful to avoid 24h previous intercourse and close post- menstrual period at the time of collection.

You can confirm diagnosis in some cases by finding branched budding pseudohyphae on wet mounts of vaginal secretions in 10% potassium hydroxide. In many symptomatic patients in whom Candida infection is suspected but wet mounts are negative, a more sensitive and specific test is to inoculate Sabouraud agar slants with a vaginal swab. Identify the yeast as C albicans by inoculating a small colony into serum or glucose beef extract and examining for germ tube formation after 90 to 120 minutes.

Use of the polymerase chain reaction (PCR) to detect Candida in vaginal specimens of symptomatic women is also helpful. There is no relation between yeast concentration and clinical symptoms. Some women with high colony counts may be asymptomatic while others may have symptoms and yet the organism is detectable only by PCR. This highlights the importance of host factors in candidal infections and mostly, the individual immuneresponse for each person.

Patients should be questioned about such classic risk factors as frequent antibiotic or steroid usage, pregnancy, diabetes or other endocrinopathies, poor perianal hygiene.

If Candida is not detected, the patient should be screened for bacterial vaginosis as well as for Chlamydia trachomatis, human papillomavirus and mycoplasma infections.

Patients should be questioned about such classic risk factors as frequent antibiotic or steroid usage, pregnancy, diabetes or other endocrinopathies, poor perianal hygiene, or wearing of tight clothing or nylon or silk undergarments. Typically, most patients will be negative for all these risk factors.

Ascertain the relationship between sexual activity and vaginal symptoms. Are the symptoms temporally related to coitus with just the present partner or with all partners? Does the sexual partner have symptoms of genital, oral, or digital Candida infection? Was he taking any medication or drug to which the woman might be sensitized? What is the means of contraception?

Women with recurrent vaginitis are tested for evidence of a vaginal allergic response. We obtain a vaginal wash sample by instilling 5 to 10 ml of sterile saline into the vaginal with a needle and syringe, directing the injection flow against the sidewalls, withdrawing the solution, and separating it into pellet and supernatant fractions by centrifugation. ELISA is used to test the supernatant for IgE antibodies to Candida and semen and the pellet for bound IgE. In coitus-related vaginitis, we obtain cultures for Candida from semen samples and test for total IgE and specific IgE antibodies to the vaginal wash pellet.

Although not performed routinely, a lymphocyte proliferation assay on a sample of peripheral-blood mononuclear cells isolated from heparinized blood may be useful when immunosuppression might be suspected, such

as in women with concomitant oral thrush or condyloma. In such instances, a defective proliferative response to Candida and plant mitogens might indicate a more serious underlying disease.

Many different approaches have been suggested for the treatment of women with chronic recurrent candidal vulvovaginitis.

TREATMENT

It is not always possible to use the same option of treatment for different patients. It needs to be individualized towards specific findings in each sick woman. The best treatment option for each patient with presumed chronic recurrent vaginal candidiasis is to have a correct diagnosis. The goals of treatment are to alleviate acute infectious symptoms, but mainly, to avoid subsequent recurrences.

Many different approaches have been suggested for the treatment of women with chronic recurrent candidal vulvovaginitis. However, none are universally successful in every case. Various treatment options are shown in Table I. Resistance to antifungal agents does not seem to be a problem for candidal vaginal infections. The majority of commercial products successfully treat acute fungal infections in most patients. At the present time there is no medication for clinical use that is completely fungicidal. Treatment with antifungal agents greatly reduces the number of vaginal organisms to a level undetectable by culture, but complete organism irradiation in the vagina is not achieved.

Treatment consists of first alleviating the current acute infection and secondly of preventing its clinical recurrence. If the second maintenance phase is not initiated, between 25-40% of patients will have a clinical recurrence within 6 weeks? Most patients will be symptom-free for at least 6 months while on maintenance treatment.

If candidal vaginitis is associated with coitus with one particular partner, it's important to find out if he is ingesting any medications or drugs that may enter his semen and elicit a vaginal response. Reports exist of vaginal allergic reactions to semen that contained

Table 1

Therapy for Chronic Recurrent Candidal Vulvovaginitis

	Drugs[a]	Dose regimen[b] (Vaginal-V or Oral-O)	Circumstance	Time duration
	Miconazol	V-5mg 1/d 10-14d		
	Clotrimazole	V-5mg 1/d 7-14 d		
Current infection[c]	Fluconazole	O-150 mg 1/d	Acute infection	Every episode
	Itraconazole	O-200 mg bid		
	Ketoconazole	O-200 mg bid		
	Miconazole	V-5mg 1/d 3 to 5 d	Every pre-menstrual period	
	Clotrimazole	V-5mg 1/d 3 to 5 d		
	Fluconazole	O-100 mg 1/d		
Maintenance[c] (Post infection)	Miconazole	V-5mg 1/d	Weekly	Six months
	Clotrimazole	V-5mg 1/d		
	Itraconazole	V-100 mg 1/d		
	Ketoconazole	V-100 mg 1/d	Daily	

[a]Other antifungus agents can also be used (Butoconazole, Econazole, Tioconazole, Terconazole, etc).
[b]Treatment of acute infection should be longer than 2-3 days.
[c]Use one drug only.

products of ingested penicillin or thioridazine. Change or eliminate the offending medication, if possible. Similarly, evaluate the effect on vaginitis recurrence of changing the contraception method or spermicide brand.

If the woman has vaginal fluid IgE antibodies to her partner's semen, or the man has IgE antibodies in his ejaculate, using a condom will eliminate vaginal contact with the allergen. An untested alternative is the use of an oral antihistamine before intercourse.

Vaginal allergic responses to Candida appear to be relatively common in women with recurrent candidal vaginitis. In one study, we reported that 18% of 64 patients tested had anticandidal IgE in their vaginal washes. In women who are hypersensitive to Candida or to an unidentified component of a vaginal wash sample, the best treatment at present is to prevent growth of Candida by aggressive use of antifungal agents plus use of oral antihistamines to obtain symptomatic relief of vaginal symptoms and reduce the incidence of histamine-mediated immunosuppression.

Hyposensitizing the patient to Candida, semen, or any other allergen associated with a vaginal allergic response may ultimately provide the best therapy. However, improved methodology and standization along with controlled clinical trials are needed to evaluate the effectiveness of these experimental immunizations. Recent anticandida strategies might include immunotherapy with cytokine antagonists, vacination for cell-mediated immunity and antigen-specific immunotherapy to induce tolerance to disease-promoting epitopes.

Many clinical and *in vitro* experiments, have been tried with regards to CRVV, to revert the focus of therapy against the vaginal microorganisms to improve resistance of the hostess, however without great success. The majority of reports show improvement to the therapeutic results, but were never sufficiently convenient to establish a commercial treatment routine, probably due to the lack of double-blind placebo-controlled trial in matched groups of women.

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