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Allergic Predisposition in Recurrent Vulvovaginal Candidiasis

Marjorie Crandall, PhD

ABSTRACT: Evidence is presented that atopic women synthesize large amounts of anti-Candida IgE antibodies in the vagina, and vaginal allergic reactions to Candida release histamine which suppresses host cellular defense mechanisms, creating a greater susceptibility to recurrent vulvovaginal candidiasis (RVC). The allergic diathesis is further demonstrated by the fact that hyposensitization with Candida antigen is effective in preventing recurrences in the face of multiple failures of antifungal therapy to achieve a permanent cure. It is also proposed that vulvovaginal inflammation, caused by persensitivity reactions to chemicals and exogenous allergens, triggers latent infection to develop into symptomatic yeast overgrowth. Hence, the term "allergic vulvovaginal candidiasis" (AVC) is suggested for this clinical entity.

Introduction

Candida vulvovaginitis (CVV) is related to many, well-recognized, risk factors including antibiotics, corticosteroids, exogenous estrogen, and pregnancy (1). For most women, vulvovaginal yeast infections resolve after using only a single prescription of vaginal antifungal medication. But for some women, their first yeast infection marks the beginning of an ever-increasing frequency of CVV associated with progressively worsening physical and psychosocial sequelae.

Sobel (1) presented evidence that RVC is attributable to endogenous relapse rather than reinfection. While exogenous reinfection does occur by sexual transmission in some cases, vaginal recolonization by Candida occurs in many patients without sexual exposure. Sobel also demonstrated that RVC is not an indication of subclinical diabetes, and he emphasized the need to identify the mechanisms of individual susceptibility in this enigmatic disease.

Clearly, the immunological characteristics of the woman are important determining factors in fighting genital Candida infections (2). For example, some women tolerate the presence of *C. albicans* as part of the normal vaginal flora, and never develop symptoms, whereas other women have repeated, acute episodes of CVV. This paradox may be explained, in part, by proposing that RVC has an allergic diathesis.

Marjorie Crandall, Ph.D. is the founder of Yeast Consulting Services in Torrance, California. From 1980 to 1988, Dr. Crandall was an Associate Research Mycologist on the faculty in the Division of Infectious Diseases at Harbor-UCLA Medical Center in Torrance.

Address correspondence to Dr. M. Crandall, Yeast Consulting Services, P.O. Box 57, Torrance, CA 90510.

Hypothesis

During the initial Candida infection, yeasts and hyphae invade the submucosal layers of the vagina and grow intracellularly inside vaginal epithelial cells (VEC). There, Candida is protected from antifungal agents, and is unaffected by host resistance. It is hypothesized that this latent intracellular infection sets in motion a self-perpetuating cycle (Fig. 1) in which the chronic release of Candida antigens stimulates the production of anti-Candida IgE antibodies in atopic women.

Vaginal allergic reactions to Candida, chemicals and foreign antigens trigger the release of histamine, which not only produces symptoms, but also inhibits neutrophil chemotaxis and T-lymphocyte proliferation. Thus vaginal cellular defenses are suppressed and Candida is not eradicated from mucosal tissues.

It is further hypothesized that chemicals or exoantigens contacting the vulva or vagina can trigger allergic reactions which precipitate recrudescence of CVV. Vaginal hypersensitivity reactions cause microscopic intracellular edema which ruptures VEC. The liberated yeasts can then overgrow, utilizing the increased amounts of blood glucose and nutrients generated *in situ* by vaginal inflammation. Success in treating RVC patients by hyposensitization with Candida antigen further indicates that this disease is both an infection, and an allergy to the infective agent. Hence, this clinical entity is named AVC.

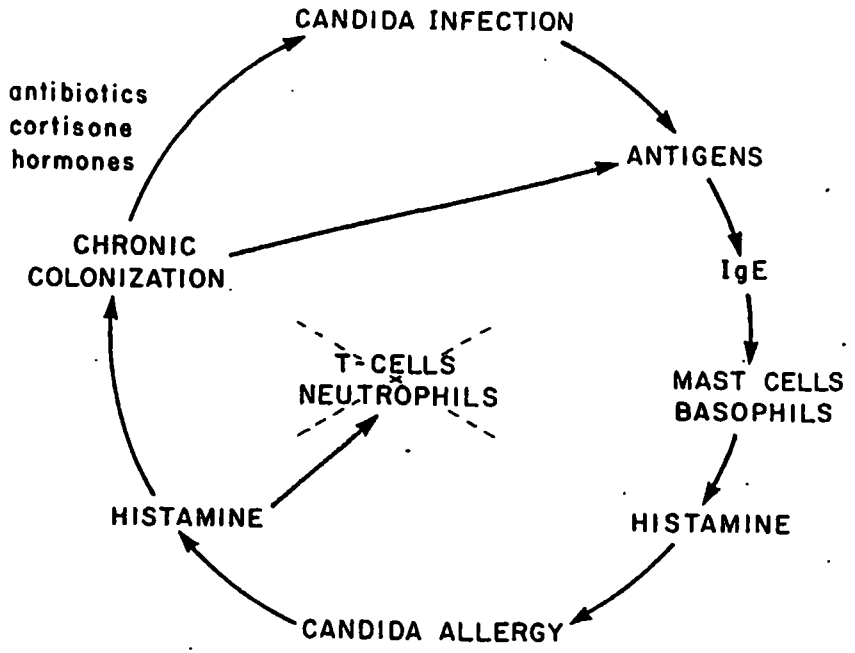

FIGURE 1

A Self-Perpetuating Cycle

Latent Intracellular Infection

CVV is considered a superficial infection. But yeast cells are not limited to the surface of the vaginal epithelium. Both yeasts and hyphae penetrate down through many layers of the vaginal mucosa and grow intracellularly inside VEC as shown by ultrastructural studies.

Schnell and Voight (3) took vaginal scrapings from women with yeast infections and examined them by electron microscopy. Yeast cells with buds were found within VEC, indicating intracellular growth. Similar studies (4) revealed blastospores within cervical stratified squamous epithelial cells as well as inside VEC.

Apparently, human VEC are capable of endocytosis because intracellular yeasts were seen inside vacuoles (5). Invasion of host cells, with intracellular localization and lysis of tissues surrounding the fungus, were also observed by Montes and Wilborn (6) in vaginal biopsy specimens. Studies of experimental vaginal yeast infections i mice also demonstrated hyphae and yeast cells penetrating into th submucosal tissue (5, 7-10).

Topical antifungals kill Candida on the surface of the vaginal mu cosa, and negative swab cultures are obtained after a few days c treatment. However, intracellular yeasts and hyphae in the sul mucosal layers are not eradicated and, therefore, serve as a reservoi of infection. Persistence of this occult infection may be manifested a cyclic vaginal relapse.

Cyclic, premenstrual reappearances of vaginal symptoms (11, 1 and yeast organisms in the vagina (13-15) may be related to th emergence of yeasts from their intracellular location within VEC as function of the maturation of vaginal epithelium. During the mer strual cycle, VEC mature and migrate up to the mucosal surfac where they desquamate and lyse. Candida cells liberated in this fasl ion could be responsible for recurrences of symptomatic CVV tha many women experience in the late luteal phase just before menstru ation. Also, during this phase of the monthly cycle, the cellular in mune response to Candida is reduced (16).

Signs and Symptoms

According to Gardner (11), the main symptom of CVV is vulvar pr ritus. The intensity of itching and the degree of vulvar erythema a closely parallel. Other indications of vulvovaginal yeast infections i clude a burning sensation or irritation, dysuria, edema and a whit cheesy vaginal discharge. This exudate is pathognomonic by its a pearance, and consists of masses of necrotic VEC with some adhere Candida organisms. Leukorrhea is not a sign of vulvovaginal candic asis (11), and where present, probably indicates mixed infection wi bacteria.

Itching from CVV may fulminate overnight and become inc pacitating. It is often exacerbated by intercourse. Dyspareunia m be severe, particularly in nulliparas, and may progress to a total i tolerance of coitus (11).

Hurley (17) described the crippling effects of inveterate vagin thrush in case reports, noting that many women with RVC are di mayed by the apparently summary manner with which their co plaints are often received, and by the disbelief that greets recital

length of their illnesses and the failure of all medication to ieve permanent cure.

The relapsing patient is the focus of this paper. It is proposed that ginal allergy is a predisposing factor in RVC. Indeed, the signs and nptoms of vulvovaginal candidiasis are also hallmark indicators of ergic inflammation. Vaginal allergic reactions can be triggered by ndida, chemicals, and foreign allergens. Each of these risk factors l now be discussed in turn.

ginal Allergy to Candida

some infectious diseases, immunological reactions to the causative anism produce symptoms characteristic of that particular infection). Accordingly, the infectious agent is viewed as an allergen. Aller- reactions to microbial pathogens fall into two clinically important sses. Immediate (Type I) hypersensitivity is mediated by IgE anti- lies. Delayed (Type IV) hypersensitivity is mediated by primed ells. Although T-cell mediated reactions provide immunity against ection, they often produce extensive tissue destruction (18).

Oriel (19) suggested that allergy may contribute to the symptoms of V. His suggestion was based on the observation made by Catterall) that some culture-negative men develop allergic symptoms and ns very soon after unprotected vaginal intercourse with a woman o has yeast vulvovaginitis. Since this represented a transient pen- hypersensitivity reaction, Oriel (19) proposed that vaginal allergy Candida could also be responsible for symptoms and signs in some es of vulvovaginitis. Odds (21) cited numerous papers showing t *C. albicans* is an allergen capable of provoking a variety of aller- responses in different target organs.

The first group of scientists to measure anti-Candida IgE levels in men with RVC was Mathur and associates (22,23). They found that al IgE levels were elevated, and 50% to 74% of these IgE anti- lies were against Candida. Anti-Candida IgE levels were about ice as high in cervicovaginal washings as in sera, indicating a lo- vaginal synthesis. The correlation of elevated levels of both IgA d anti-Candida IgE indicated a synergistic effect in the vaginal im- ne system (22,23).

Hyper-immunoglobulin E syndrome is found in patients with recur- t Candida and staphylococcal infections, and is associated with

manifestations of atopy as well as with the presence of IgE antibodies that cross-react with common allergens (24). Tomsikova and associates (25) found higher antibody levels and stronger allergic skin test reactions to Candida antigens in women with RVC.

The work of Mathur and associates (22,23) was confirmed and extended by Witkin and coworkers (26,27). Specific anti-Candida IgE was found in vaginal washes, but not in sera of women with RVC, indicating a localized vaginal allergic response (26). Vaginal eosinophils were associated with the presence of IgE antibodies to *C. albicans* (27). Hence, these investigators postulated that eosinophils might contribute to vaginal tissue damage by elaborating components that cause inflammation and increase histamine release.

Crandall and associates (28) detected specific IgE antibodies against the extracellular, acidic proteinase produced by *C. albicans* in vaginal swabs from CVV patients. In an enzyme immunoassay, values for anti-proteinase IgE ranged from 1 to 24% of total antiproteinase immunoglobulins (G+A+M+E) in different vaginal specimens. Higher IgE concentrations were correlated with higher proteinase antigen concentration in vaginal swab assays ($r=0.84$) (29). IgE responses have also been reported in experimental models of candidiasis (30,31).

Increased production of IgE in patients with recurrent candidiasis may reflect a defect in cell-mediated immunity, specifically a reduction in a suppressor T-cell population that normally down-regulates IgE levels (22,23,32). When this normal IgE damping mechanism has been disturbed, "allergic breakthrough" may occur where there is coincidental sensitization to environmental allergens (32).

In addition to specific, anti-Candida, IgE-mediated allergic inflammation, another mechanism for histamine release induced by Candida has been described. A cell wall mannanprotein from *C. albicans* was reported to induce erythema, edema, and endotoxin-like reactions in experimental animals, and histamine release from isolated rat peritoneal mast cells (33,34). A direct effect of Candida extracellular glycoproteins on mast cells in vaginal epithelium causing histamine release is a possibility. Histamine, released from mast cells, induced either immunologically or chemically, would be expected to inhibit neutrophil chemotaxis and T-cell mediated immunity, to be discussed below.

While corroborative reports from several laboratories suggest that anti-Candida IgE-mediated, immediate hypersensitivity reactions play a role in RVC, virtually nothing is known about T-lymphocyte-

mediated, delayed-type hypersensitivity (DTH) reactions to Candida antigens in the vagina.

Ganguly and Waldman (35) proposed that localized DTH reactions could be responsible for some forms of allergic vaginitis. Evidence for the existence of resident, or compartmentalized, lymphocytes fixed in mucosal immune systems was proposed by Allardyce and Bienenstock (36), and Strober and Jacobs (37). Hence, results from skin tests or studies of peripheral blood lymphocyte responses to Candida antigen may not be relevant to vaginal immunity.

Evidence for localized, but not systemic, DTH reactions was reported by Marinoff and Turner (38) for the minor vestibular gland syndrome. This enigmatic disease occurs in women with a previous history of vaginal candidiasis, and is characterized as vulvar erythema and pain associated with a lymphocytic infiltrate of the subepithelium. Lack of positive DTH skin tests to Candida in 8 out of 10 of these patients agrees with numerous reports that T-cell mediated immunity is suppressed in RVC patients.

Vaginal Allergy to Chemicals

The vagina is a sensitive secretory immune system which reacts to environmental chemicals, and virtually any substance that contacts the vulvar or vaginal epithelia is capable of causing inflammation in susceptible women. Contact vulvovaginitis was discussed in detail by Gardner (39), who considered primary irritants and allergens as separate entities.

Primary irritants are corrosive substances that produce an irritative response and tissue damage in most people on first exposure. Examples cited (39) include alkali or potassium permanganate which were inserted vaginally by women to induce abortion during the early part of this century. Other chemicals produce cumulative primary irritation only after repeated exposure as, for example, the prolonged use of intravaginal medicaments for vulvovaginitis. Allergens also require previous sensitization, and often clinical changes do not appear until several days or weeks after contact.

The clinical features of both primary irritation and allergic contact vulvovaginitis are the same (39), and include erythema, edema, exudate, and sometimes vesicles or bullae. Symptoms of both types of contact vulvovaginitis include tenderness, pain, a burning sensation, and most commonly, pruritus which can be temporarily disabling.

Contact vulvovaginitis causes dilation of blood vessels in tl epithelium resulting in microscopic and macroscopic erythema a edema (39). The edema can be both intercellular and intracellula the latter resulting in bursting of VEC.

Lysis of VEC would release intracellular contents, including late yeasts. The liberated Candida cells would be expected to overgrow the increased amounts of glucose, proteins and other nutrients ma available as a consequence of vaginal inflammation.

In the normal human vagina, few lymphocytes penetrate the bas layer of the epithelium (40). However, in allergic contact vu vovaginitis, a monocytic infiltrate is observed (39).

In experiments with guinea pigs, Macher and Dorner (41) show that DTH occurs in the epithelia of the vagina, uterus and colon. Hi tological examination revealed lymphocytic infiltration within tl vaginal epithelium and around dilated blood vessels in the vagin wall, but gross reactions on the exposed vaginal mucosa of sensitiz guinea pigs could not be seen (41).

Unsensitized control guinea pigs challenged vaginally with a no irritating concentration of hapten developed edema of the vagin epithelium and lymphocytic infiltrates (42). Sensitized test anima challenged with the hapten two weeks after the initial exposure d veloped perivascular lymphocytic cuffing, congested vessels, su mucosal edema, and epithelial erosion. These histological changes a hallmark manifestations of the DTH response. Yet when observ macroscopically, the vaginas of sensitized animals appeared norm after challenge.

Localized DTH reactions from prolonged use of vaginal prepa tions may be highly significant, especially in the presence of late Candida colonization. Vaginal symptoms are often experienced CVV patients while using topical antifungals. Vaginal suppositori and creams could cause direct irritation, or act as contact allerge after repeated exposure in chemically sensitive women. For this re son, dry vaginal tablets are better.

Some RVC patients may eventually become locally sensitized to vaginal antifungal preparations, and systemic antifungals such oral ketoconazole or fluconazole would be the best treatment to av vaginal allergic reactions. Systemic antifungals have another adva tage in RVC patients. They exhibit good tissue penetration, a therefore should kill latent yeasts inside VEC if administered fo long enough period of time. Oral therapy for CVV is also strong preferred by patients (43).

Even antifungal agents might exacerbate the symptoms they were
esigned to cure. Robertson (44) suggested that symptoms interpreted
s allergy to antifungal agents are really due to "id" reactions to anti-
ens released by lysis of the yeasts. Therefore, antihistamines and
opical steroids should be employed in conjunction with antifungal
herapy for CVV.

Enigmatic syndromes involving focal vulvitis and localized dyspa-
unia (38,45) may be the clinical sequelae of DTH reactions. Tissue
mage caused by DTH develops several days after exposure to the
ntactant, allergen or infection, and persists long after the exposure
removed (39). It is often difficult to identify the offending substance
4), and any chemical may act as a primary irritant or allergen, de-
nding upon the idiotypic reaction of the host (39).

Vaginal contraceptives have long been known as irritants. Sper-
icides may damage VEC by their surfactant action. Holzaepfel and
ssociates (46) found that spermicidal jellies caused inflammation in
he rabbit vagina within 24 hours, and inflammatory reactions of the
ulva and vagina in women. In mild cases there may be no objective
gns, in spite of symptoms, although these may be obvious in more
vere cases (47). Nonoxynol-9, the active ingredient of many contra-
ptives, caused dermatitis, conjunctivitis and corneal injury in rab-
ts, and acute ulcerative vaginitis in dogs (48), but has been ap-
oved for human use because of lack of evidence for significant
dverse effects.

Allergic vaginitis with vaginal discharge containing eosinophils
as been reported after use of spermicidal agents (49), and vaginal
uid IgE antibodies to spermicide preparations were correlated with
aginal symptoms after intercourse (26). Increased adhesion of Can-
da species to epithelial cells after application of nonoxynol-9 may be
he explanation for yeast vaginitis observed in women who use it
0).

Allergic vulvitis can result from use of various commercial agents
1), including douches which may also cause chemical vaginitis (52).
aginal inflammation becomes more severe as douche pH decreases,
s demonstrated by experiments in rabbits (53). However, vulvovagi-
al symptoms caused by contact with chemicals are sometimes ig-
ored by physicians because of lack of objective signs (54). Douching
ith chemical solutions may result in a vicious cycle of symptomatol-
gy and, by altering normal vaginal microflora, create susceptibility
infection. In agreement with this idea, it was found that patients
ho douched regularly had a higher vaginal incidence of *C. albicans*

(55), and CVV patients used vinegar-and-water douches four times more often than unaffected women (56). Incidence of CVV was reported to be more prevalent among women in the medium socioeconomic stratum (57), and was ascribed to automedication, poor hygiene, or stress. But, over-zealous personal hygiene practices may be the real culprit. Use of chemical douches, deodorants, and other feminine products should be discouraged (58). However, in one study, douching with water had no harmful effects (59).

Chlorine in swimming pools may also cause vulvovaginitis. The vaginal mucosa is highly susceptible to chlorinated disinfectants (39), and inflammation of vaginal epithelium has been observed from experimental contact with a gel containing sodium chlorite (60). Specific IgE antibodies to chlorine-based disinfectants can be induced in sensitive individuals by repeated contact (51).

Soap (61), shampoo (62), and bubble bath (63) can irritate and cytological changes may be detected in urinary sediment (63). Evidence of inflammation may be detectable by staining cells obtained from vaginal smears (27,49). Since Candida infection may appear many days after vulvovaginal exposure to a chemical irritant, the primary cause may not be recognized. Hence, atopic patients should be identified and counseled to wash the genital area with water only (61), and avoid urogenital contact with all chemicals (64). Increased patient involvement in health care is likely to produce better results (65) than just offering medication for each new episode of CVV.

Vaginal Allergy to Exoantigens

Allergic reactions can be triggered by exogenous allergens introduced into the vagina by sexual transmission, or transmitted to the vagina via the circulation after inhalation, ingestion or by injection. After sexual intercourse, vaginitis symptoms may develop as a consequence of physical abrasion or as a result of chemical hypersensitivity to lubricating jellies, spermicides or condoms. The differential diagnosis of coitus-induced vaginitis should include examination of the sexual partners of women with RVC for Candida prostatitis by culturing semen collected in a condom during intercourse (66). Local and systemic symptoms have been reported to occur in women due to hypersensitivity to seminal plasma (26,67-69), and IgE antibodies in semen can elicit allergic reactions in the vagina (70). Antibiotics (71,72) and other medications (73) may be present in semen, and cause vaginal

allergic reactions or even anaphylactic shock in susceptible women. Antibiotics or immunosuppressive drugs in semen could also predispose women to RVC.

Exoallergens inhaled (74), ingested (75,76) or injected (75) may target the vagina. Berman (74) reported 16 cases of coryza with concomitant vulvovaginitis induced by pollen; both responded to allergy therapy. Witkin and associates (26) detected IgE antibodies to ryegrass in vaginal fluids. Siegel (75) reported exacerbation of vaginal symptoms with a single food challenge in some patients with vaginitis, and others had exacerbation after injection of candidal antigen. Heckerling (76) reported that enalapril caused vulvovaginal pruritus and urethral pain, possibly by induced elevations of bradykinin and prostaglandin E2. Witkin and coauthors (26) detected PGE2 in vaginal wash fluids, and suggested that vaginal allergic reaction can predispose to recurrent Candida infection as a consequence of PGE2 suppression of T-cell mediated immunity.

Allergy Supresses Cellular Defenses

Histamine inhibits neutrophil chemotaxis and T-cell proliferation. Hence, allergy must be considered a predisposing cause of Candida infections. Chemotaxis of neutrophils is inhibited by histamine (24,77-79) and restored by blocking H2 receptors with antihistamines (77). This predicts that neutrophil chemotaxis would be inhibited in CVV since the signs and symptoms are the same as in allergic inflammation. In agreement, neutrophils are rarely observed in wet mounts of vaginal fluid from CVV (11,39,44,56,80-84). Since phagocytosis is the principal defense mechanism against candidiasis (21,85), and since RVC patients are not reported to develop disseminated candidiasis, it may be concluded that RVC patients have functional polymorphonuclear leukocytes with normal candidacidal activity, but that these neutrophils do not migrate to vaginal sites of Candida infection.

Since T-cell mediated immunity is also critically important in fighting Candida infections (85,86), and since histamine also suppresses this function (87), allergy to Candida and other antigens is considered a predisposing factor in candidiasis (87). Recent reports support this (88-90). Histamine causes immunosuppression by inducing monocytes to produce PGE2, and can be blocked by cimetidine and other H2 receptor blocking agents (91). Vaginal tissue reacts to

allergens (26), drugs (76), and irritants (92) by producing PGE2 Thus, it can be concluded that vaginal allergic responses suppres localized cell-mediated immunity, leading to recurrences of CVV. O this basis, antihistamines and antiinflammatory agents would b helpful adjuncts in breaking the vicious cycle (Fig. 1) in addition t antifungal therapy, avoidance of risk factors, and hyposensitizatio (64).

Immunotherapy for RVC

Although fungal antigen vaccines have long been known to be effec tive therapy for chronic mycoses (93), immunotherapy for RVC wa first reported only relatively recently (94-98). Kudelko (94) found tha vaginal and other allergic symptoms improved after hyposensitiza tion with Candida antigens. Hosen (95) suggested that Candida pene trated into the deeper layers of vaginal tissue where the fungus wa unaffected by local antifungal therapy. He reported (96) excellen clinical response of RVC patients to injections of a pyridine alum pre cipitated extract of *C. albicans*. Palacios (97) agreed that desensitiza tion with Candida antigen was useful in treating resistant vagina candidiasis, and recommended concomitant injection of other alle gens. He suggested (98) booster doses of Candida antigen to prevei recurrences of yeast infections when antibiotics are necessary. Be mer and associates (93) treated many mycoses patients with injectior of the etiological fungal antigen, including cases of RVC. Besides su cessful treatment of the infection, allergic symptoms improved a well.

The first clinical study of hyposensitization for RVC was publishe in 1979 (99). Average time to relapse in patients treated with Ca dida antigen increased significantly from 5.1 to 15.7 months. Sever patients noted less severe symptoms during their less frequent r lapses, and a faster response to antifungals.

Truss (100) proposed anti-Candida immunization as part of tl treatment for RVC, in adddition to antifungals and correction of co ditions such as hypothyroidism, that impair the immune response. H also recommended avoiding risk factors such as dietary sugars, foo containing yeasts or molds, environments with mold spores, oral ant biotics, contraceptive hormones, and immunosuppressive drugs.

For Candida allergy testing, Truss (100) urged careful clinical o servation of immediate hypersensitivity, Arthus, and 24- and 48-ho

elayed immune responses after injecting 0.1 ml of the 1:1000 dilu-
on of the 1:10 concentrate intradermally. If these reactions are neg-
tive, then intradermal testing is repeated using the 1:100 dilution of
ıe 1:10 concentrate. Truss cautioned against using more concen-
ated antigen solution since it can cause severe local and systemic
eactions. For immunotherapy, he advised dilutions of Candida ex-
act from 10^{-6} to 10^{-15} solution, and injection of 0.1 ml subcutaneously
iven twice weekly. Truss cautioned that patients vary in their sensi-
vity to Candida, and commercially available extracts vary in po-
ncy, so there is no standardized protocol. The dose must be adjusted
cording to the clinical response. Emphasis was placed upon the im-
ortance of rekindling the immune response to an organism that per-
etuates its presence in tissues by neutralizing host defenses (100).

Other workers have confirmed the efficacy of Candida antigen im-
unotherapy in this condition (101-103). Following a single intrader-
al inoculation with whole heat-killed *C. albicans* cells, a patient
ith chronic mucocutaneous candidiasis showed clinical improvement
hich coincided with the return to normal of the T_H/T_S cell ratio and
artial restoration of immune functions (101). A Candida ribosomal
accine protected animals against systemic candidiasis by stimulat-
g cell-mediated immunity (102). Rigg and associates (103) reported
significant reduction in the number of relapses in RVC patients
eated with *C. albicans* allergen immunotherapy. An oral vaccine
ntaining *C. albicans* ribosomes also showed statistically significant
duction in recurrence rate (104).

Immunotherapy functions by stimulating synthesis of IgG_1 block-
g antibodies (105), and inducing suppressor T-cells (106). In addi-
on, this form of therapy may boost nonspecific resistance by stimu-
ting natural killer cells (107). Although randomized, double-blind,
acebo-controlled studies of Candida immunotherapy in RVC should
e performed, it is possible, on the basis of present knowledge to help
omen who suffer frequent relapses of CVV (64).

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