Efficient Diagnosis of Vulvovaginal Candidiasis by Use of a New Rapid Immunochromatography Test[∇]

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The clinical symptoms of vulvovaginal candidiasis (VVC) are nonspecific, and misdiagnosis is common, leading to a delay in the initiation of antifungal treatment. We evaluated a new immunochromatography test (ICT), the CandiVagi assay (SR2B, Avrille, France), for the rapid diagnosis of VVC. This test, which employs an immunoglobulin M antibody directed against the β-1,2-mannopyranosyl epitopes found in the yeast cell wall, was compared with direct microscopic examination and culture of vaginal swabs. Two-hundred five women were investigated, including 130 women with symptomatic vaginitis and 75 asymptomatic controls. Two vaginal swabs were obtained from each woman: one was used to prepare a wet mount and Gram-stained preparations for direct microscopic examination and was also cultured on Sabouraud dextrose agar for the isolation of *Candida* spp., and the second swab was used for ICT. The sensitivities of microscopic examination, culture, and ICT for the diagnosis of VVC were 61%, 100%, and 96.6%, respectively, while the specificities of the three methods were 100%, 82%, and 98.6%, respectively. ICT had a negative predictive value of 98.6%, a positive predictive value of 96.6%, and an efficiency of 98%. ICT provided a rapid result and a better compromise between sensitivity and specificity than conventional microscopy and culture for the diagnosis of VVC. This easy-to-perform diagnostic test will be useful to practitioners treating women with symptoms of vaginitis.

Vaginitis is the commonest reason for gynecological consultation in women of childbearing age. Anaerobic bacteria are the most prevalent cause of vaginal infection in the United States and Europe, followed closely by *Candida* spp. (34, 37). It is estimated that at least 75% of healthy adult women will suffer one episode of *Candida* vulvovaginitis during their reproductive lives and that 5% will have recurrent infectious episodes (20, 30). *Candida albicans* is responsible for infection in 80 to 90% of cases, although the incidence of vulvovaginal candidiasis (VVC) due to non-*C. albicans* species such as *C. glabrata* has increased steadily over the past few decades (21, 36).

The main symptoms of VVC have been widely described and include vulvar and vaginal pruritus, pain or a burning sensation, and external dysuria (8). Physical examination may reveal perineal edema, vulvar and vaginal erythema, fissures, and a thick curdy discharge (8). However, these symptoms are nonspecific and do not enable clinicians to distinguish confidently between VVC, bacterial vaginosis, and *Trichomonas vaginalis* infection (2, 22, 23, 31), leading to subsequent suboptimal care. The accurate diagnosis of VVC currently depends on the demonstration of a *Candida* sp. in vaginal swabs by direct microscopic examination and/or culture. A positive Gram stain, the absence of a watery discharge, and patient self-diagnosis of "another yeast infection" have been identified as the best predictors of a positive culture for patients with VVC (1).

Several rapid diagnostic tests have been developed over the past 25 years in an attempt to speed up the diagnosis of VVC (17, 29). Latex particle agglutination (LPA) was found to be more sensitive than KOH microscopy (19, 28, 29) and was more specific than other diagnostic criteria (10). However, a few studies reported false-positive reactions with this test (39) or a sensitivity that was lower than that of KOH microscopic examination carried out by experienced clinical practitioners (38).

We have developed a sensitive immunochromatography test (ICT), the CandiVagi assay (SR2B, Avrille, France), for the rapid diagnosis of VVC using an immunoglobulin M (IgM) monoclonal antibody (MAb) directed against the *Candida* mannan (18, 40). Here, we present the results of a preliminary evaluation of this test and a comparison of the results obtained by ICT with those obtained by conventional microscopy and culture. Specific attention was focused on the ability of ICT to discriminate between *Candida* carriage and *Candida* infection and its specificity for women with bacterial/trichomonal vaginitis.

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MATERIALS AND METHODS

Patients and vaginal specimens. The study population included 130 women referred to one of two clinical laboratories with signs and symptoms of vaginosis

or vaginitis and 75 asymptomatic women presenting for routine obstetric or gynecological care.

Isolation and identification of pathogenic microorganisms. Two high vaginal swabs were obtained from each patient. One swab was placed in 1 ml of sterile physiological saline and shaken vigorously until the saline turned cloudy. This suspension was then used to prepare wet-mount and Gram-stain preparations for direct microscopic examination, in order to identify *Candida* yeast cells, mycelium, and/or pseudomycelium and to rule out other diagnoses, such as bacterial vaginosis, aerobic vaginitis, and trichomoniasis. One hundred microliters of the suspension was also plated onto petri dishes containing 5% sheep blood agar, chocolate agar (heated sheep blood agar), and Sabouraud dextrose agar (SDA) containing chloramphenicol (bioMérieux SA, Marcy l'Etoile, France). The plates were incubated at 37°C for 48 h, and the number of yeast colonies was then recorded as the number of CFU/ml saline. All yeasts were identified by using the Bichro-Latex albicans system, the Glabrata RTT (rapid trehalose test) system (Fumouze Diagnostics, Levallois Perret, France), and the API 32C system (bioMérieux SA).

Diagnosis of vaginal infection. The final diagnosis for each patient was based on symptoms, clinical findings during examination, and laboratory test results, as follows. VVC was diagnosed if one of the following criteria was fulfilled: (i) a positive wet-mount and/or Gram-stain preparation with budding yeasts, pseudohyphae, and/or hyphal forms; (ii) positive culture (>100 CFU/ml suspension) and negative microscopic examination results associated with one sign or symptom (thick, white vaginal discharge with no odor, vulvar and vaginal pruritus, burning, or dyspareunia); and (iii) a positive culture result (>100 CFU/ml suspension) and a negative microscopic examination associated with one of the following clinical findings during the physical examination: vulvar and vaginal erythema, edema, fissures, or a thick, white vaginal discharge adhering to the vaginal walls. A negative microscopy result together with a small number of yeasts (<100 CFU/ml suspension) was considered to indicate *Candida* colonization rather than infection.

Bacterial vaginosis was based on a positive Nugent's Gram score of ≥7. The Nugent Gram score evaluates the number of lactobacilli (gram-positive rods), *Gardnerella* (gram-negative coccobacilli), and *Mobiluncus* (gram-variable rods) per microscopic field (25, 33).

Aerobic vaginitis was diagnosed according to the criteria defined by Donder et al., namely, the absence of lactobacilli, the presence of cocci or coarse bacilli, and the presence of parabasal epithelial cells and/or vaginal leukocytes (7).

A positive diagnosis of *T. vaginalis* was defined as the presence of characteristic motile trichomonads in wet saline preparations.

The second vaginal swab was used for the detection of mannan antigens by ICT, performed in accordance with the manufacturer's instructions.

ICT. ICT (CandiVagi; SR2B) is based on the capture of *Candida* mannan from vaginal secretions by the use of an IgM mouse MAb (MAb 5B2; INSERM license 03297A10). This MAb recognizes mannan epitopes in a wide range of *Candida* spp., including *C. albicans* and *C. glabrata*, which are commonly implicated in VVC. The MAb is conjugated to gold particles in a mobile phase and is also applied to a nitrocellulose strip as a capture antibody (CandiVagi strip).

The ICT stick (Fig. 1) is placed in the vaginal swab suspension, and the sample moves by capillary action through the pad containing the MAb-gold conjugate. The MAb-gold binds specifically to the mannan in the sample and moves with the sample into the test membrane. Moving up the test membrane, the sample passes through a test line, where immobilized MAb captures the mannan-MAb-gold complex, forming a MAb-mannan-MAb sandwich. The test line then turns pink or purple in color. In the absence of mannan, no MAb-mannan-MAb sandwich is formed and the test line does not turn pink or purple. Rabbit anti-mouse antibody immobilized on the control line captures any excess gold passing through the test line. This causes the control line to develop a pink or purple color, which indicates that the liquid sample has correctly flowed up the stick. Therefore, when the test is read, a single line (control) on the membrane indicates a negative result, whereas two lines (test and control) indicate a positive result. The result is invalid if no pink or purple control line appears or the background coloration makes reading of the result impossible.

Immunochromatography procedure with vaginal specimens. The ICT kit is composed of a dipstick and a dissociating medium containing glucanase. This enzyme releases mannan from the constituents of the vaginal discharge on the swab. The vaginal swab is agitated in a test tube containing 300 μl of dissociating solution and is allowed to stand at room temperature for 5 to 10 min to allow antigen extraction. After this time, the swab is pressed against the inside of the tube to extract liquid. The swab is discarded and the end of the dipstick is placed in the solution and allowed to stand at room temperature for 5 to 10 min. The assay results are then recorded.

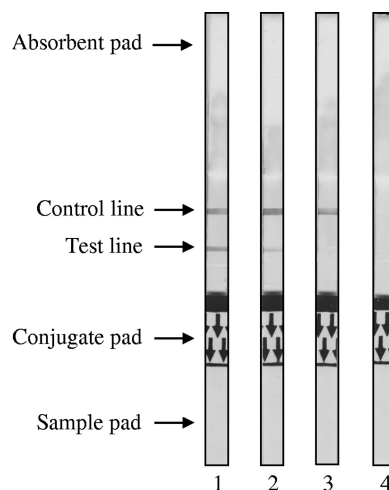One vaginal swab obtained from each woman was treated as described above,

FIG. 1. Comparison of ICT results. The intensity of the test line was graded from ++ to − (++, strongly positive; +, positive; ±, faintly positive; −, negative or noninterpretable). Lane 1, strongly positive (++); lane 2, faintly positive (±); lane 3, negative; lane 4, noninterpretable.

and the results were recorded in a blinded fashion. To evaluate the relationship between the quantity of the mannan detected by ICT and the number of *Candida* CFU/ml or signs, symptoms, and clinical findings during physical examination, the intensities of all positive test lines were recorded. The intensities were graded from ++ to − (++, strongly positive; +, positive; ±, faintly positive; −, negative or noninterpretable) (Fig. 1).

RESULTS

Microbiologic and immunochromatographic findings for asymptomatic women. Fifty-six (74.7%) vaginal specimens from the 75 asymptomatic women were negative for yeasts by microscopic examination, culture on SDA, and ICT. The remaining 19 (25.3%) specimens were microscopy negative but culture positive for *C. albicans* on SDA (10^2 to 10^3 CFU/ml). One swab from the latter group of women was positive by ICT.

Microbiologic and immunochromatographic findings for symptomatic women. The final diagnoses for women with signs and symptoms of vaginitis are listed in Table 1. Fifty-eight (96.6%) of the 60 women with VVC ($n = 53$) or mixed bacterial vaginitis and VVC ($n = 7$) were positive by ICT, whereas all swabs from women with vaginal trichomoniasis ($n = 4$), bacterial vaginosis ($n = 26$), or aerobic vaginosis ($n = 17$) were negative by ICT. Only 1 of 23 specimens from women with noninfectious vaginosis or vaginitis of undetermined cause was positive by ICT.

Comparison of microbiologic and immunochromatographic findings. Table 1 compares the results obtained by ICT with those obtained by direct microscopy and culture. Of the 60 women with a final diagnosis of VVC, 37 (61.6%), 60 (100%), and 58 (96.6%) were positive by direct microscopy, culture, and ICT, respectively. Most infections ($n = 47$) were caused by *C. albicans*, although *C. glabrata* was responsible for the infections in 7 women and *C. tropicalis* was responsible for the infection in 1 woman. Of the 145 specimens from women without VVC (75 swabs from asymptomatic women and 70 swabs from patients with bacterial vaginosis), 143 (98.6%) and 145 (100%) were negative by ICT and microscopic examina-

TABLE 1. Evaluation of ICT, direct microscopy, and culture on SDA for the diagnosis of VVC in asymptomatic women and women with signs and symptoms of vaginosis or vaginitis

Patient group	No. of specimens tested	No. of specimens positive by:		
		ICT	Microscopy	Culture
Symptomatic women	130			
VVC	53	51	30	53[a]
Mixed VVC-bacterial vaginosis	7	7	7	7[b]
Bacterial vaginosis	26	0	0	5[c]
Aerobic vaginosis	17	0	0	2[c]
Vaginal trichomoniasis	4	0	0	0
Noninfectious or nondetermined cause of vaginitis	23	1	0	0
Asymptomatic women	75	1	0	19[c]

[a] Infections caused by *C. albicans* (*n* = 45), *C. glabrata* (*n* = 7), or *C. tropicalis* (*n* = 1).
[b] Infections caused by *C. albicans* (*n* = 7).
[c] Vaginal colonization by *C. albicans* (*n* = 26).

tion, respectively. For 119 (82%) of these women, no yeasts were isolated in culture, while for 26 vaginal cultures were positive for low numbers of *C. albicans*.

The sensitivities of ICT, direct microscopy, and culture on SDA were 96.6%, 61.6%, and 100%, respectively, while the specificities were 98.6%, 100%, and 82%, respectively. The positive predictive values for ICT, microscopy, and culture were 96.6%, 100%, and 69.7%, respectively; the negative predictive values were 98.6%, 86.3%, and 100%, respectively; and the overall efficiencies were 98%, 88.7%, and 87.3%, respectively.

Interpretation of ICT. Sixty samples were positive by ICT (Table 2), and the results were generally easy to interpret. The majority of specimens from women with VVC (53/58; 91.4%) gave test line intensities between + (positive) and ++ (strongly positive). Five swabs were faintly positive by ICT, including one from a woman with noninfectious vaginosis or vaginosis of an undetermined cause and one from an asymptomatic woman.

The relationship between the quantity of mannan detected by ICT (in terms of the test line intensity), the number of yeasts isolated, and the absence or presence of signs or symptoms (vaginal pruritus and/or burning, thick white vaginal discharge, vaginal erythema and/or vaginal edema) was investigated. The intensity of the test line ranged from + to ++ when both microscopy and culture ($>10^3$ CFU/ml) were positive (*n* = 37) and when major signs or symptoms were observed (vaginal pruritus and/or burning associated with a thick, white vaginal discharge, vaginal erythema, and/or vaginal edema) (Table 2). For microscopy-negative, culture-positive specimens (*n* = 21), irrespective of the number of CFU/ml (10^2 to 10^3), the intensity of the ICT line ranged from + to ++ when characteristic signs or symptoms were present, but it was only + when one major sign or a symptom such as vaginal pruritus and/or burning or a thick white vaginal discharge was observed, irrespective of the presence or the absence of vaginal erythema and/or vaginal edema. The intensity of the test line was ± (faintly positive) when vaginal erythema and/or vaginal edema was the single sign observed. Finally, negative ICT results were observed when culture-positive specimens (10^2 to 10^3 CFU/ml) from women without VVC (7 patients with bacterial vaginosis and 19 asymptomatic women) were tested.

DISCUSSION

The accurate diagnosis of VVC is important so that patients do not have to rely on empirical treatment, which may be inappropriate (35). In 2006, Schwiertz et al. reported a rate of misjudgment of VVC by physicians of 77% on the basis of clinical evidence alone (32). Microbiologic testing for episodic VVC is recommended for patients with mild to moderate symptoms and no history of persistent or recurrent infection (41), and women are generally considered to have VVC when vaginal specimens are positive for yeasts by both microscopy and culture. The signs and symptoms of VVC have been reported to be more severe in women with yeast counts of $>10^3$ CFU/ml, whereas lower counts of $<10^2$ CFU/ml are taken to indicate colonization (16), although this relationship has been questioned by some authors (3, 9, 26, 27). Interpretation is

TABLE 2. Numbers of CFU of *C. albicans*/ml in relation to signs and symptoms of VVC and ICT results

Group and no. of CFU/ml by culture	Direct microscopy	Signs and symptoms[a]	ICT intensity[b]
Patients with VVC and positive culture (*n* = 60)			
≥10^3 (*n* = 37)	Positive (*n* = 37)	A + B + C (*n* = 29)	+ to ++
		A + B (*n* = 8)	+ to ++
10^2 to 10^3 (*n* = 21)	Negative (*n* = 21)	A + B + C (*n* = 5)	+ to ++
		A or B, or A + B, or A + C, or B + C (*n* = 11)	+
		C (*n* = 5)	±
10^2 to 10^3 (*n* = 2)	Negative (*n* = 2)	C (*n* = 2)	−
Patients without VVC but with positive culture (*n* = 26), 10^2 to 10^3 (*n* = 26)	Negative (*n* = 26)	NS (*n* = 26)	−

[a] A, vaginal pruritus and/or burning; B, thick white vaginal discharge; C, vaginal erythema and/or edema; NS, no signs or symptoms.
[b] The test line intensity was graded from ++ to − (++, strongly positive; +, positive; ±, faintly positive; −, negative or noninterpretable).

complicated further when microscopic examination is negative and the number of yeasts in culture is between 10^2 and 10^3 CFU/ml (16). In contrast to the findings of Hopwood et al. (16) but like other authors (3, 9, 26, 27), we did not find any positive correlation between yeast counts and the symptoms and signs of VVC in this study (data not shown).

Recently, a polyclonal antibody-based ICT was developed for the rapid detection of VVC (SavvyCheck vaginal yeast test; Savyon Diagnostics Ltd., St. Ashdod, Israel) and was reported to have a specificity of 86% and a sensitivity of 90% compared to the results of culture for yeasts (Savvy-Check).

Our ICT, which uses an MAb to *Candida* mannan, had a significantly higher sensitivity (96.6%) than microscopic examination (61.6%) ($P > 0.001$) and a higher specificity (98.6%) than fungal culture (82%) ($P > 0.001$), and it gave better results than the SavvyCheck system. Furthermore, our ICT had greater sensitivity (96.6% versus 66 to 80%) than the LPA tests previously used for the detection of *Candida* antigens in vaginal secretions, without any loss of specificity (17, 29). Hopwood et al. (17) suggested that some of the false-negative reactions by their LPA test could have been due to infections caused by *C. albicans* serotype B or *Candida* spp. other than *C. albicans* since the polyclonal antibodies used to sensitize the latex particles were raised against *C. albicans* serotype A and differences between the cell wall antigens of the two serotypes, as well as between different *Candida* spp., have been demonstrated. The use of an IgM MAb, which recognizes mannan from a wide range of *Candida* spp. and serotypes, probably contributed to the improved sensitivity of the ICT. Furthermore, the negative ICT results obtained with vaginal specimens from patients with bacterial vaginosis, aerobic vaginosis, or trichomoniasis demonstrate that there is no cross-reactivity with human molecules or other microorganisms. Indeed, in contrast to α-linked mannose residues that can be synthesized by mammals as well as by a large variety of microorganisms, β-1,2-linked mannose residues, which were first identified as prominent epitopes in *C. albicans*, have a much more restricted distribution in yeasts. This restricted distribution was recently confirmed at the genetic level following the identification of the gene family encoding the β-mannosyltransferases responsible for their synthesis (24). These residues are important in the biology of *C. albicans*, *C. tropicalis*, and *C. glabrata* since these yeast species display nine, eight, and seven members of this gene family, respectively.

Previously, Hopwood et al. reported that the likelihood of a positive LPA test result increased in direct proportion to the number of yeasts isolated (17). With our ICT, no clear correlation was found between the number of CFU and the intensity of the test line. All specimens from asymptomatic women that yielded positive cultures containing 10^2 to 10^3 CFU/ml were negative by the ICT. However, specimens from symptomatic women with a fungal load of 10^2 to 10^4 CFU/ml were positive by the ICT, with the test line intensities ranging from ± (faintly positive) to ++ (strongly positive). Thus, a direct correlation between the severity of infection and the results of ICT was observed. When the main clinical signs and symptoms were present (vaginal pruritus and/or burning, a thick white vaginal discharge), ICT had an intensity of + to ++, irrespective of the number of yeasts isolated (10^2 to 10^4 CFU/ml). Conversely,

when only minor symptoms, such as vaginal erythema and/or edema, were present, the antigen level was low, as indicated by a faintly positive ICT result (Table 2). These observations confirm the results of Pike et al., who used an enzyme-linked immunosorbent assay to detect *Candida* mannan in vaginal washings from women with VVC and found a significant association between the mannan levels and the clinical signs (27).

The reason why a positive ICT reaction is associated with infection rather than colonization is unknown but may relate to the characteristics of the antigens detected by MAb 5B2. This MAb was generated following a *C. albicans* experimental infection (18). The early characterization of MAb 5B2 revealed its ability to react more strongly with *Candida* strains isolated under pathogenic conditions than with commensal strains (12). Furthermore, characterization of the MAb 5B2 epitope(s) revealed its ability to recognize all β-1,2-linked mannosides, irrespective of their degree of polymerization, starting with mannobiose as a minimal epitope (5). This class of epitope, shared by *C. glabrata* and *C. tropicalis* (4), has been shown to induce MAbs that protect against experimental *C. albicans* vaginal infection and disseminated infection in rats and mice (6, 13–15). The presence of repetitive epitopes recognized by MAb 5B2 in the majority of *C. albicans* cell wall mannoglycoconjugates (i.e., phosphopeptidomannan, phospholipomannan, non-covalently bound proteins, or proteins covalently associated with β-1,6- or β-1,3-glucans [11]) could explain the sensitivity of the ICT, whereas modulation of the expression of the β-mannoside epitopes and the host reaction during infection could explain why this test is preferentially positive during *Candida* vaginitis rather than during vaginal colonization.

In conclusion, the detection of *Candida* mannan in vaginal secretions by ICT is a sensitive and specific approach to the rapid diagnosis of VVC. This test is easy to perform, and the results are simple to interpret. The test is convenient for use by physicians during patient consultations, enabling the timely initiation of appropriate antimicrobial therapy.

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