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Original Article

Boric Acid for Recurrent Vulvovaginal Candidiasis: The Clinical Evidence

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Abstract

Background: Recurrent vulvovaginal candidiasis (VVC) remains a challenge to manage in clinical practice. Recent epidemiologic studies indicate that non-*albicans Candida* spp. are more resistant to conventional antifungal treatment with azoles and are considered as causative pathogens of vulvovaginal candidiasis.
Methods: We searched PubMed and Scopus for studies that reported clinical evidence on the intravaginal use of boric acid for vulvovaginal candidiasis.
Results: We identified 14 studies (2 randomized clinical trials [RCTs], 9 case series, and 4 case reports) as eligible for inclusion in this review. Boric acid was compared with nystatin, terconazole, flucytosine, itraconazole, clotrimazole, ketoconazole, fluconazole, buconazole, and miconazole; as monotherapy, boric acid was studied in 7 studies. The mycologic cure rates varied from 40% to 100% in patients treated with boric acid; 4 of the 9 included case series reported statistically significant outcomes regarding cure (both mycologic and clinical) rates. None of the included studies reported statistically significant differences in recurrence rates. Regarding the adverse effects caused by boric acid use, vaginal burning sensation (<10% of cases), water discharge during treatment, and vaginal erythema were identified in 7 studies.
Conclusions: Our findings suggest that boric acid is a safe, alternative, economic option for women with recurrent and chronic symptoms of vaginitis when conventional treatment fails because of the involvement of non-*albicans Candida* spp. or azole-resistant strains.

Introduction

Worldwide, one of the most common infections of the lower female genital tract is vulvovaginal candidiasis (VVC). VVC is a mucocutaneous infection caused by yeasts, mainly of the genus *Candida*.[1] Uncomplicated VVC affects 75% of women at least once in their lifetime,[2–4] and recurrent VVC affects up to 5% of premenopausal women.[4,5] Recurrent VVC is defined as four or more episodes of the specific infection during a 12-month period.[6] It is known that non-*albicans* species, most commonly *Candida glabrata*, are responsible for up to 33% of women with recurrent VVC.[5] Different antifungal agents have been used in the treatment of recurrent VVC, among them azoles, flucytosine, and boric acid, although azole resistance was mentioned. Furthermore, it is known that non-*albicans* species are less susceptible to azole antifungals than is *Candida albicans*.[7] For this reason, boric acid suppositories are proposed as an alternative treatment in the literature.

Boric acid is also called boracic acid or orthoboric acid. It is an inorganic acid with the chemical formula H_3BO_3 and is available as a white, odorless powder, in crystalline or in granular form.[8] Lister used boric acid, for the first time, as a topical antiseptic in 1872.[8] It has also been used in various solutions for skin disinfection and cavitary irrigation.[9] To date, boric acid vaginal suppositories are not commercially available and, consequently, must be compounded.[10]

The aim of this study is to review the clinical evidence related to the use of boric acid in the treatment of recurrent VVC or yeast infections caused by non-*albicans* strains of *Candida*.

Materials and Methods

Data sources

We retrieved the results of our study through a systematic search in PubMed (December 16, 2010) and Scopus (December 16, 2010). Both the PubMed and Scopus search strategy

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included a combination of the search term, infection, or of terms referring to specific infectious syndromes (such as vaginitis or vulvovaginitis or candidiasis) with the term, boric acid, by performing a broad, sensitive search on studies referring to the prognosis of infection or of the specific infectious syndromes mentioned. The references cited in the included studies also were hand-searched.

Study selection criteria

Studies reporting data on the outcomes of patients of all ages with *Candida* spp. vaginitis treated with boric acid were included in this review. Abstracts from scientific conferences and studies published in languages other than English, German, French, Italian, and Spanish were excluded from this review.

Data extracted from each of the included studies referred to the study design, the characteristics of the included population, the number of patients included in each study, and the outcomes of patients with vaginitis according to the treatment they received. We also defined the Jadad score of the included randomized clinical trials (RCT).[11] $p < 0.05$ was considered statistical significance. The p values regarding cure, which were not provided by the included studies, were calculated with the use of OpenEpi Software.[12] Outcomes related to the clinical course of the infection, such as clinical cure, mycologic cure, recurrence, posttreatment adverse events, and the duration of follow up, were included in this review.

Mycologic cure was defined as the absence of *Candida* growth on the high vaginal swab (HVS) culture on the last day of treatment; clinical cure was defined as the absence of any subjective signs and symptoms.[13] Recurrence of VVC is defined according to the author of each study, commonly as at least three episodes of VVC unrelated to antimycotic cover that occur within 1 year.[2, 4] Azole resistance is defined by high minimum inhibitory concentration (MIC) (e.g., fluconazole: $> 20\ \mu g/mL$) levels and correlates simultaneously with clinical resistance (absence of mycologic cure).[14,15] Intention to treat (ITT) was defined as the patients initially included in the treatment intent who did not complete the entire treatment administered in the clinical trial. Per protocol (PP) was defined as the patients who completed the entire trial.

Results

Selected studies

The search performed in PubMed and Scopus retrieved a total of 36 and 158 search results, respectively, among which

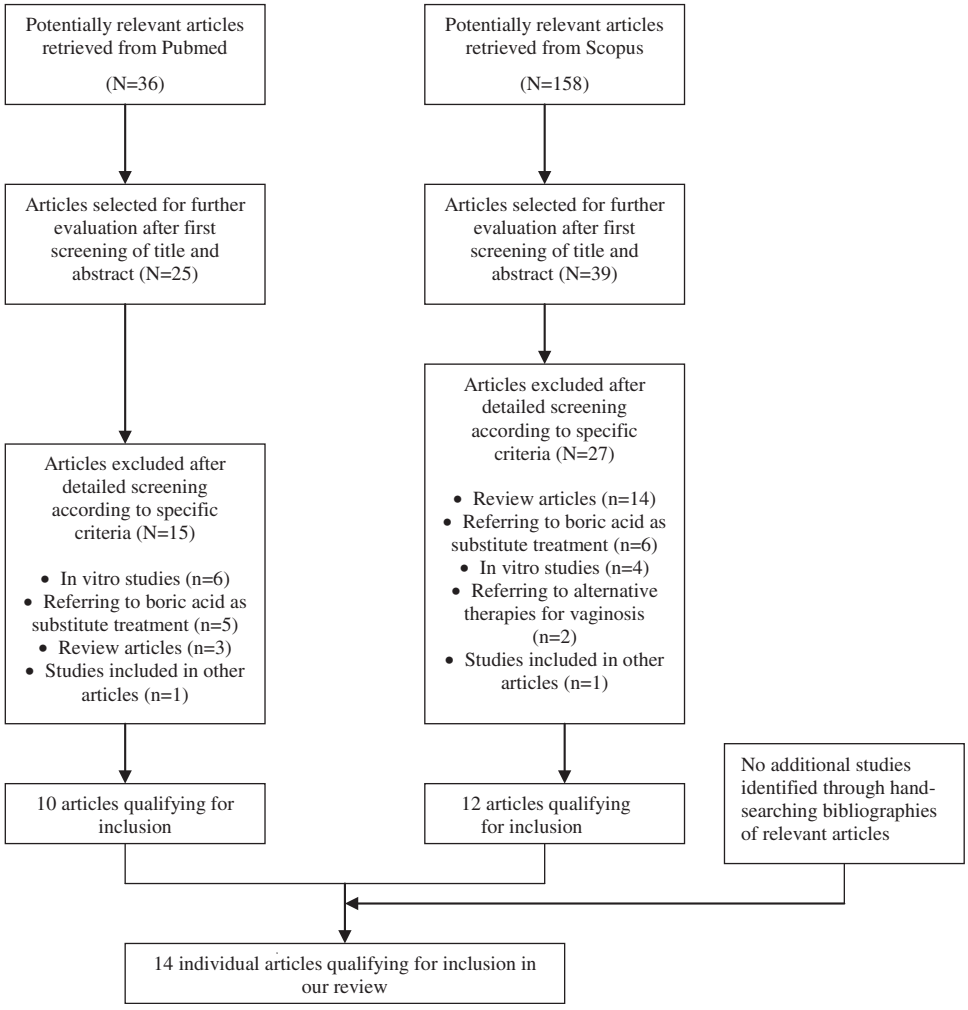

FIG. 1. Flow diagram of the detailed process of selection of articles for inclusion in the review.

14 studies (2 RCTs, 8 case series, and 4 case reports) were identified as eligible for inclusion in this review.[13,16–28] No additional studies were identified through hand-searching of references. The selection of studies to be included in this review is depicted graphically in Figure 1.

The main characteristics of the studies included in our review (study design, study population/comorbidities, compared treatments, isolated pathogens and duration of follow-up) are presented in Table 1. Regarding the comorbidity, we identified 126 women with diabetes mellitus and 1 with HIV. The age of the patients ranged between 16 and 70 years. In 13 of 14 studies, there were available data about dosage and duration of treatment.[13,16–26,28] Boric acid was used as vaginal suppositories at a dose of 600 mg either once or twice per day for 14 days. Different pathogens were identified, including *C. albicans*, *C. glabrata*, *Candida tropicalis*, and *Candida parapsilosis*. The compared regimens in the RCTs included boric acid vs. nystatin, flucytosine, or azoles (such as fluconazole, buconazole, miconazole, itraconazole, clotrimazole, or ketoconazole). The follow-up period of the patients ranged between 14 days and 1 year.

Mycologic cure and clinical cure were evaluated. The mycologic cure rates varied from 40% to 100% in patients treated by boric acid, whereas 50%, 70%, 90%, 90.9%, 36%, 50%, 28.6%–92.3%, 100%, and 100% were the cure rates in the studies for nystatin, terconazole, flucytosine, itraconazole, clotrimazole, ketoconazole, fluconazole, buconazole, and miconazole, respectively. Both clinical and mycologic outcomes were identical in 5 of the 9 case series examined.[23–27] Four of the 9 included case series reported statistically significant outcomes in cure rates.[13,22,23,25] The recurrence rates ranged from 0% to 45.5% in patients using boric acid. None of the included studies found statistically significant recurrence rates. Regarding the adverse effects caused by boric acid use, vaginal burning sensation (<10% of the cases), water discharge during treatment, and vaginal erythema were identified in 7 studies.[13,20–23,25,26] The results of our study are presented in Tables 2 and 3.

Discussion

VVC is one of the most frequent gynecologic infections among women.[29] Almost 8 of 10 of all women will experience at least one episode of VVC in their lifetime.[1] It should be noted that asymptomatic vulvovaginal colonization by yeasts varies from 10% to 20% of the healthy population[30, 31] *C. albicans* is known to be the most frequently involved yeast in VVC (80%–90% of all infections), followed by *C. glabrata* (5%–10%), *C. tropicalis* (5%), and *Candida krusei* (1%).[32,33] Moreover, an increase in the prevalence of VVC caused by *Candida non-albicans* spp. is probably recorded because of inadequate use of over the counter (OTC) antifungal drugs.[34,35] During our review, we tried to analyze the reasons for recurrent VVC.

The reduction of the protective vaginal flora caused by frequent use of antibiotics allows colonization of vaginal epithelium by *Candida* spp., and long duration of antibiotic use seems to increase the risk of recurrent VVC.[36] Recurrence may also be a consequence of patient's noncompliance with a treatment regimen or of an inadequately treated infection. In an *in vitro* study, 15%–20% of women with initially negative vaginal cultures had positive cultures within a period of 3 months after treatment.[37] Another reason for recurrent VVC is the resistance of non-*albicans Candida* species to antifungal agents, such as azoles. Immunodeficiency seems to be another predisposing factor for recurrent VVC.[38] More specifically, we identified 126 patients with diabetes mellitus in our search. This could be explained by the fact that hyperglycemia enhances the capability of *C. albicans* to bind to the vaginal epithelium.[39] Patients with acquired immunodeficiency syndrome (AIDS) are susceptible to systemic candidal infections,[40,41] Although in our review, we identified only 1 HIV-positive patient. It has been shown that 40%–70% of women with recurrent VVC have some specific immunologic anergy resulting in a subnormal T lymphocyte response to *Candida*.[38]

Some methods of contraception can be predisposing factors for recurrent VVC. For example, the use of intravaginal spermicidal creams could increase infection susceptibility as a result of vaginal flora alterations or by increasing the adhesive capability of the different microorganisms.[41] Additionally, there is a higher rate of VVC among women who take oral contraceptives.[7] However, this could be also explained by the fact that these women may use condoms less often or may have more sexual partners because of the safety provided by oral contraceptives. Mechanical factors, such as poorly ventilated underwear or tightly fitted clothes, are associated with increased moisture and local temperature,[41] and finally, irritation of the vulvovaginal area by frequent sexual intercourse or tight clothes can cause infection of already colonized areas.[42]

Resistance to azoles is a common finding in cases of recurrent VVC. Mardh et al. noted that resistance to one or more of the most frequently used azoles can reach up to 7.5% of vulvovaginal candida isolates.[1,6] In particular, resistance to fluconazole may result from blocking of the channels located at the membrane of *Candida* cells.[6] For this reason, the use of alternative treatment options seems to be essential.

Boric acid has a bacteriostatic and a fungistatic action, yet its precise mechanism of action is unclear.[10] A hypothesis about the fungistatic activity is that it could be caused by vaginal acidification, leading to fungal cell wall penetration and disruption of the fungal cell membrane.[20] The MIC of boric acid indicates that it works at a pH similar to that of a noninfected vaginal tract, and as a result, its action may not be explained as a consequence of acidity increase.[10,25] It is known that boric acid is rapidly absorbed in oral ingestion. Denuded skin and severely damaged vaginal epithelium both present good absorption of boric acid in solution or as a powder.[43] Boric acid is accumulated in the liver, brain, and kidneys,[43] although it is primarily excreted without being metabolized by the kidneys. Fifty percent is excreted within 12 hours of administration, and minimal amounts are also excreted in saliva, sweat, and feces.[10,44] It has been shown that intravaginal administration of one to two 600-mg boric acid capsules per day for a period of 1–2 weeks leads to daily blood boron concentrations of $<1\ \mu g/mL$ during use (mean level, $42\ \mu g/mL$).[45] Boron blood levels $<200\ \mu g/mL$ (normal blood boron levels range from 0.1 to $80\ \mu g$ /mL) and considered safe.

In our study, we tried to identify the role of boric acid in the ordinary treatment of VVC, including cure rates, recurrence rate, and possible adverse effects presented in the different studies. From the review of the literature, we found that boric acid (600 mg) in vaginal suppositories twice per day for 14 days is an effective treatment option, as it has optimal out-

Table 1. Main Characteristics of Included Studies

Study	*Study design*	*Number of patients (comorbidities)*	*Age (years)*	*Pathogens isolated*	*Compared treatments (Boric acid group vs. control group)*	*Follow-up (median)*
Ray et al. 2007[13] India	RCT[a]	ITT: 111 (diabetes melitus)	Fluconazole Mean age: 40.2 ± 10.7 Boric acid Mean age: 41.2 ± 11.3	*C. albicans* (28.8%) *C. glabrata* (61.3%) *C. tropicalis* (3.6%)	Boric acid (600 mg once daily × 14 days supp) vs. fluconazole (150 mg one single oral dose)	15 days
		PP: 99	Fluconazole Mean age: 40.2 ± 9.8 Boric acid	*C. albicans* (29.3%) *C. glabrata* (59.6%) *C. tropicalis*		
Van Slyke et al. 1981[25] USA	RCT[a]	ITT: 119 (diabetic 2/119)	Mean age: 22 Nystatin Mean age: 21	*C. albicans*	Boric acid (600 mg once daily × 14 days supp) vs. nystatin (100,000 U once daily × 14 days supp)	1 month
Kennedy and Sobel, 2010[28b] USA	Retrospective study	ITT: 47 PP: 37 (pregnancy 1/80, diabetic 7/80, oral steroid use 2/80, nonsteroid immunosuppresion 3/80)	44.2	*C. glabrata*	Boric acid (600 mg once daily × 14–21 days)	NR
Nyirjesi et al. 2005[18] USA	Retrospective cohort study[f]	ITT: 33	46	*C. parapsilosis*	Boric acid (600 mg twice daily × 14 days supp) vs. fluconazole (200 mg twice weekly for 1 month *per os*) Boric acid vs. buconazole (2 vaginal applications, 1 week apart) Boric acid vs. miconazole (1 vaginal application once daily × 7 days)	4 months
Sobel et al. Israel, 2003[23] USA Israel	Retrospective cohort study	ITT: 102 (estrogen hormone replacement 20/102, diabetes mellitus 5/102)	Median 41 range 16–70	*C. glabrata*	Boric acid (600 mg once daily × 14 days supp) vs. flucytosine (5 g intravaginal cream × 14 days)	21 days
		ITT: 38 diabetes mellitus 1/39, pregnancy 8/39)	Median 31	*C. glabrata*	Boric acid (600 mg once daily × 14 days supp)	NR

(*continued*)

Table 1. (Continued)

Study	Study design	Number of patients (comorbidities)	Age (years)	Pathogens isolated	Compared treatments (Boric acid group vs. control group)	Follow-up (median)
Guaschino et al. 2001[17] Italy	Prospective cohort study	ITT: 22 PP: 22	Boric acid Mean±SD: 30.5±5.8 Itraconazole Mean±SD: 29.4±5.1	*C. albicans* (91%), *Torulopsis glabrata*[c] (9%)	Boric acid (300 mg once daily×14 days supp)[d] vs. itraconazole (200 mg once daily×3 days per os)[e]	1 year
Sood et al. 2000[27] USA	Retrospective study	ITT: 28 PP: 25	Median age: 45	*C. glabrata* (71.4%)	Boric acid vs. treconazole (0.4% intravaginal cream for 7 days)	NR
Sobel and Chaim 1997[22] USA	Retrospective cohort study	ITT: 60	NR	*Torulopsis glabrata* (66.7%)	Boric acid (600 mg once daily×14 days supp—maintenance dose: 600 mg×2/week) vs. clotrimazole (100 mg once daily×7 days supp—maintenance dose: 500 mg/week)	14 days
				Mixed infection including *T.glabrata* (33%)	Boric acid vs. ketoconazole (200 mg twice daily×5 days *per os*—maintenance dose: 100 mg/day)	
Jovanovic et al. 1991[26] USA	Prospective cohort study	ITT: 92 PP: 90	Mean age: 35	*Candida* spp.	Boric acid (600 mg twice daily for 14 days) vs. usual antifungal treatment[g]	6 months
Swate and Weed 1974[24] USA	Prospective cohort study	ITT: 40 PP: 40	NR	*C. albicans* (92.5%)	Boric acid (600 mg twice daily×14 days supp)	14 days

[a]Jadad score: 4.
[b]Insufficient data regarding the outcomes of the treatments used for the rest of the isolated pathogens.
[c]*Torulopsis glabrata* and *Candida glabrata* refer to the same microorganism.
[d]In some cases, initial treatment was followed by 300 mg once daily×5 days for 5 subsequent menstrual cycles.
[e]In some cases, initial treatment was followed by 200 mg as a single dose the first day of the 5 subsequent menstrual cycles.
[f]In some cases, repeated treatment for 2 more weeks and prophylactic use for 4 more months was needed.
[g]Usual treatment included miconazol nitrate cream, 1% clotrimazole cream, 2% butoconazole nitrate cream, oral nystatin.
ITT, intention to treat; NR, not referred; PP, per protocol; RCT, randomized clinical trial; SD, standard deviation; supp, vaginal suppositories.

Table 2. Detailed Data About Outcomes Derived from Included Studies

Study	Cure n/n %					Recurrence	Adverse events
	Mycologic				*Clinical*		
Ray et al.[13] 2007 India	ITT	Boric acid21/	Fluconazole	*p* value	NR	No	Boric acid: 2/56 (3.57%) vaginal burning sensation
	C. glabrata	33 (63.6)	10/35 (28.6)	0.005			
	C. albicans	61.1%	85.7%	0.13			
	Overall	37/56 (66.1)	25/55 (45.4)	0.07			
	PP	Boric acid	Fluconazole	*p* value			
	C. glabrata	21/29 (72.4)	10/33 (33.3)	0.003			
	C. albicans	68.8%	92.3%	0.14			
	Overall	37/50 (74)	25/49 (51)	0.06			
Van Slyke et al. 1981[25] USA	Mycologic and clinical cure (7–10 days after treatment):					NR	Boric acid: slight water discharge during treatment
		Boric acid vs. nystatin 48/52 (92.3) vs. 36/56 (64.3), $p=0.001$[a]					
Kennedy and Sobel 2010[28b] USA	Boric acid 26/47 (55.3)				28/47 (59.6)	21/47 (44.7)	NR
Nyirjesi et al. 2005[18] USA	Boric acid vs. fluconazole 6/6 (100) vs. 17/19 (90), p=NS				NR	NR	NR
	Boric acid vs. buconazole 6/6 (100) vs. 7/7 (100)						
	Boric acid vs. miconazole 6/6 (100) vs. 1/1 (100)						
Sobel et al. 2003[23] USA Israel	Mycologic and clinical cure:					NR	Boric acid: vaginal burning sensation (<10%)
	Boric acid vs. flucytosine 47/73 (64.4) vs. 27/30 (90), $p=0.012$[a]						
	Mycologic and clinical cure:					No	NR
	Boric acid 27/38 (71)						

(*continued*)

Table 2. (Continued)

Study	Cure n/n %		Recurrence	Adverse events
	Mycologic	*Clinical*		
Guaschino et al. 2001[17] Italy	At 6th month Boric acid vs. itraconazole 10/11 (90.9) vs. 10/11 (90.9), p=NS[a]	Boric acid vs. itraconazole 8/11 (72.7) vs. 7/11 (63.6), p=NS[a]	At 12th month: Boric acid vs. itraconazole 5/11 (45.5) vs. 5/11 (45.5), p=0.66[c]	NR
Sood et al. USA, 2000[27]	Boric acid vs. terconazole 4/10 (40) vs. 14/20 (70), p=0.23[a]		NR	NR
Sobel 2000[27] USA and Chaim 1997[22] USA	Boric acid (episodes) vs. clotrimazole (episodes) 20/26 (77) vs. 4/11 (36), p=0.049[a] Ketoconazole (episodes) (mycologic and clinical cure): 3/6 (50)	Boric acid vs. clotrimazole 21/26 (80.7) vs. 5/11 (45.5), p=0.079[c]	NR	Boric acid: 1/26 (3.8%) mild erosive changes, 1/26 (3.8%) vaginal erythema, 1/26 (3.8%) vaginal burning
Jovanovic et al. 1991[26] USA	Boric acid vs. usual therapy 90/92 vs. 0/92, p<0.01[a]	Boric acid vs. usual therapy 90/92 vs. 48/92, p<0.01[a]	Usual antifungal therapy: 48/92	Boric acid: Burning of introitus 4/92 (4.3%)
Swate and Weed 1974[24] USA	Mycologic and clinical cure: Boric acid: 40/40 (100)		2/40 (5) in 30 days	NR

[a]p values were calculated by Fisher exact test (2-tail).
[b]Insufficient data regarding the outcomes of the treatments used for the rest of the isolated pathogens.
[c]p values, Yates corrected chi square, p-value (2-tail), were calculated with the use of OpenEpi software.
NS, nonsignificant; NR, not referred.

Table 3. Details of Included Case Reports

Study	Number of patients (comorbidities)	Age (years)	Pathogens isolated	Previous treatments	Treatment	Cure		Recurrence	Adverse effects	Follow-up (median)
						Mycologic	Clinical			
Savini et al. 2009[19] Italy	NR	27	Azole-resistant *C. glabrata*	Fluconazole (150 mg/day × 1 day) Itraconazole (200 mg/day × 3 days)	Boric acid (600 mg/day × 14 days supp)	Yes	Yes	No	NR	14 days
Dhingra and Roseblade 2006[16] UK	NR	45	*C. glabrata*	Fluconazole (200 mg/day × 2 weeks) Topical flucytosine (1g × 2 weeks) + amphotericin (100 mg/day × 2 weeks)	Boric acid (600 mg/day × 14 days supp)	Yes	Yes	No	NR	8 weeks
Silverman et al. 2001[21] USA	NR	55	*C. lusitaniae*	Fluconazole (200 mg/day × 3 × every 4 days) Ketoconazole (100 mg/day × 5 days)	Boric acid (600 mg/day × 14 days supp)	Yes	Yes	No	Redness	14 days
Shinohara and Tasker 1997[20] USA	HIV (+), CD4 count 10/mm^3	32	*C. krusei, Torulopsis glabrata* (azole-refractory)	Fluconazole (100 mg/day × 9 months) Itraconazole Topical nystatin Topical gentian violet	Boric acid (600 mg × 2 times/day × 10 days supp)	No (azole-sensitive *C. albicans*)	Yes	3 relapses in 5 months	Limited	5 months

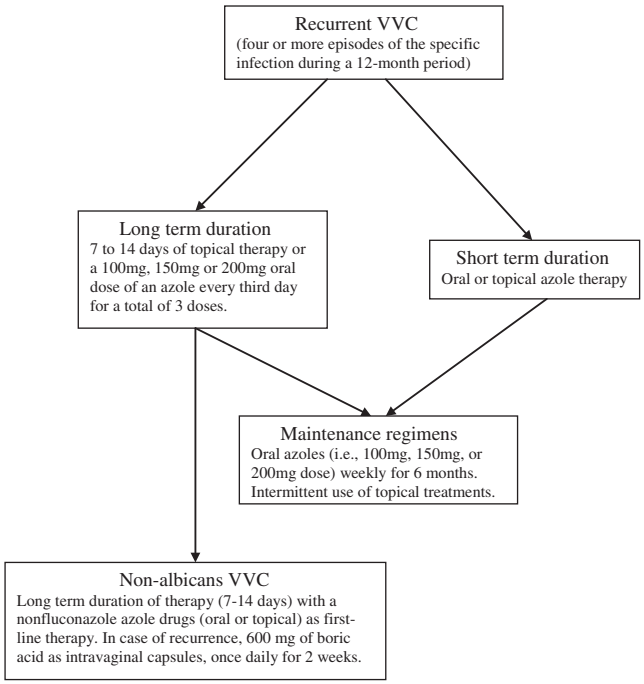

FIG. 2. Flow diagram of the management of recurrent vulvovaginal candidiasis (VVC), according to Centers for Disease Control and Prevention guidelines, 2010.[46]

come (55.3%–100%) use rates compared to nystatin, flucytosine, and azoles, and the recurrence rates are rather small in most of the studies. The proposed management of recurrent VVC based on Centers for Disease Control and Prevention (CDC) guidelines is shown graphically in Figure 2.[46] It is a safe alternative regimen for treatment of recurrent VVC, as vaginal burning or erythema is rarely described in the studies we included in this review.

Our review shows that intravaginal boric acid is usually well tolerated, especially in short-term treatment. A local burning sensation, watery discharge, erythema, as well as male dyspareunia, are the most frequentlly reported adverse events.[20,22,25] The clinical experience also shows that a very small percentage of women with recurrent VVC develop vestibulitis. In those patients, the pain from using boric acid would exceed that observed in patients without this problem, and it may, in fact, exacerbate the vestibulitis. Long-term safety is controversial because of the lack of data. It is believed that boric acid could not be used on a long-term basis because of the danger of systematic absorption of the boric acid and intoxication. Gastrointestinal disturbances, anemia, weakness, confusion, alopecia, anorexia, menstrual disorders, seizures, and dermatitis might be symptoms after chronic intoxication.[43,47] Three cases of acute poisoning were reported in 1888 after topical intravaginal use.[47] For a small percentage of women who have a chronic problem, it is tempting for both clinician and patient to use the treatment twice weekly for quite some time and at the late luteal phase to avoid any systemic complications. Van Slyke et al.[25] noted the absence of both local and systemic toxicity in >2000 patients and stated that the probability of systemic toxicity after intravaginal administration of boric acid is minimum. Moreover, it is known that 20 g (or 0.1–0.5 mg/kg in case of oral administration) is the adult fatal dose.[43] In pregnancy, topical exposure to boric acid is not likely to cause abnormalities of the fetus because boric acid absorption is limited,[48] although a weak teratogenic effect of intravaginal boric acid during pregnancy cannot be excluded.[49] For this reason, its use should be avoided during the first trimester until organogenesis is completed. Finally, interaction of boric acid with other drugs has not been reported.[10]

Boric acid is an economic treatment for VVC. According to the literature, the cost per patient for compounded vaginal gelatin capsules or specifically prepared suppositories may range approximately from $5.60 to $14 for a 7-day course of treatment, depending on brand or product particularities and the pharmacy. Treatment with boric acid may be considered inexpensive if we compare the cost of the treatment with that of miconazole ($17–$20.65 for 7 days).[1,50] In Greece, the price of boric acid suppositories is 1 € per vaginal suppository. In Table 4, we present the prices of different antifungal agents in

Table 4. Cost Comparison in Treatment of Vulvovaginal Candidiasis

Pharmaceutical substance	*Available formulation*	*Cost*[a,50]
Econazole nitrate	vag cr 1% w/w	2.3–5.4€/tube, 16–50$US/tube
Isoconazole nitrate	vag cr 1% w/w	5.7€/tube, not available in USA
	vag supp 600 mg/supp	4.4€/vag supp, not available in USA
Clotrimazole	vag tab 0.5–0.1 g/tab	2.1–3.6€/box, not available in USA
	vag cr 2%, 10%	3.6€/tube, 11$US/tube
Itraconazole	cap 100 mg/cap	6–31.7€/box, 246–415$US/30 cap
Ketoconazole	tab 200 mg/tab	3.5–11.5€/box, not available in USA
Miconazole nitrate	vag supp 200 mg, 400 mg/supp	4.6–4.5€/box, not available in USA
	vag cr 2% w/w	4.5€/tube, 13–15$US/ tube
Terbinafine hydrochloride	tab 125 mg, 250 mg/tab	17.3–51.9€/box, not available in USA
Fluconazole	cap 50 mg, 100 mg, 150 mg/cap	10.5–40.2€/box, 50–435$US/20 tab
Fenticonazole nitrate	vag supp 200 mg, 600 mg/supp	3.8–4.8€/box, not available in USA
	vag cr 2%	22.4€/tube, not available in USA
Voriconazole	tab 50 mg, 200 mg/tab	186–766€/box, 368–1446$US/30 tab
Boric acid	vag supp 600 mg/supp[b]	1€/vag supp, 5.60–14$US[c]

[a]Prices obtained from Greek National Organization for Medicines. The price ranges depend on brand or product formulation.
[b]Prepared on request by compounding pharmacies.
[c]Treatment for 7 days.
cap, capsule; tab, tablet; vag cr, vaginal cream; vag supp, vaginal suppository; w/w, weight for weight.

Greece and the United States in order to show the obvious advantage of cost of boric acid.

Although boric acid seems to be a safe and effective agent in the treatment of VVC, several limitations should be taken into consideration. First, the variability observed in the groups of women compared in the studies and the characteristics of the patients evaluated are among the limits of our study. Another limitation is represented by the absence, in the included studies, of a common definition of disease recurrence. Finally, the limited number of RCTs and the low methodologic quality of the rest of the examined studies are limitations of our review.

In conclusion, the increase in clinically resistant *Candida* strains and the more frequent presence of non-*albicans Candida* in VVC necessitate revaluation of alternative therapeutic treatments. The present clinical evidence suggests that boric acid may be proposed as an effective, safe, and economic treatment of recurrent VVC.

Disclosure Statement

The authors have no conflicts of interest to report.

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