



VERMONT

Department of Vermont Health Access

Therapeutic Class Review Vaginal Antifungals

Overview/Summary

A vaginal infection, characterized by discharge, itching or odor, will occur in most women during their lifetime. The three diseases most commonly associated with vaginal discharge are bacterial vaginosis, trichomoniasis and candidiasis.¹ Specifically, vulvovaginal candidiasis accounts for approximately one third of vaginitis cases. In contrast to oropharyngeal candidiasis, it is generally not considered an opportunistic infection. Furthermore, unlike trichomoniasis, vulvovaginal candidiasis is not considered a sexually transmitted disease because it may occur in women who are not sexually active and because *Candida* is considered part of the normal vaginal flora. *Candida albicans* is responsible for 80 to 92% of cases of vulvovaginal candidiasis. Self diagnosis is often inaccurate leading to a delay in correct diagnosis and treatment, wasted monetary expenditure and precipitation of vulvar dermatitis.² A clinical diagnosis should be confirmed by a wet mount preparation with the use of saline and 10% potassium hydroxide to demonstrate the presence of yeasts, hyphae or pseudohyphae. On the basis of clinical presentation, microbiology, host factors and response to treatment, vulvovaginal candidiasis can be classified as either uncomplicated or complicated. Characteristics of uncomplicated vulvovaginal candidiasis include sporadic or infrequent infection, mild to moderate infection, infection likely to be *C. albicans* or infection in non-immunocompromised women. In contrast, complicated vulvovaginal candidiasis consists of recurrent infection, severe infection, non-*albicans* candidiasis and infection in women with uncontrolled diabetes, debilitation or immunosuppression.^{3,4}

While sporadic attacks of vulvovaginal candidiasis can occur in some women, identified risk factors include diabetes mellitus, antibiotic use, increased estrogen levels, immunosuppression, contraceptive devices, genetic susceptibility and behavioral factors (e.g., sexual behavior). Evidence does not demonstrate a strong link between infection and hygienic habits. The predominant clinical feature of vulvovaginal candidiasis is pruritis, but dysuria, soreness, irritation and dyspareunia can also occur. In contrast to bacterial vaginosis, there is little to no discharge with vulvovaginal candidiasis and the pH of the vagina remains normal.²

Guidelines recommend a variety of treatment options for the management of uncomplicated vulvovaginal candidiasis. Specifically, over-the-counter (OTC) intravaginal antifungal products, prescription intravaginal antifungal products and prescription oral antifungals are recommended. Of the agents included in this review, nystatin, miconazole and terconazole are recognized as potential treatment options; sulfanilamide is not addressed within the guidelines. While the Center for Disease Control and Prevention states that topically applied azole antifungals are more effective than nystatin; overall, there is no available evidence to demonstrate the “superiority” of any intravaginal formulation or regimen, and oral and intravaginal therapies are considered equivalent.^{3,4} Currently, butoconazole, clotrimazole, miconazole and tioconazole intravaginal products are available OTC. As mentioned previously, vulvovaginal candidiasis is not usually acquired through sexual intercourse; therefore, no data supports the treatment of sex partners. In addition, only intravaginal products are recommended in pregnant women infected with vulvovaginal candidiasis.³ The treatments for uncomplicated vulvovaginal candidiasis are also recommended for complicated infections; however suppressive maintenance antifungal therapy is also recommended to reduce recurrent infection in these patients. After treating for the individual episode, a maintenance regimen of oral fluconazole weekly for six months should be initiated. In cases where this is not feasible, intravaginal treatments used intermittently can be considered.^{3,4} Optimal treatments for non-*albicans* vulvovaginal candidiasis remains unknown.³

Included in this review are the prescription vaginal antifungals miconazole, nystatin, sulfanilamide (AVC[®]) and terconazole (Terazol 3[®], Terazol 7[®] and Zazole[®]). All of the agents are specifically Food and Drug

Administration (FDA) approved for the treatment of vulvovaginal candidiasis, with the exception of nystatin which is FDA approved for the treatment of vaginal infections. In addition, all of the agents are available for intravaginal administration.⁴⁻⁹ Terconazole is available generically, with nystatin and sulfanilamide available as branded products only. Miconazole is also available generically in at least one dosage form and/or strength; however, it is important to note that miconazole intravaginal products are also available OTC.

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Miconazole*	Vaginal antifungals	✓
Nystatin	Vaginal antifungals	-
Sulfanilamide (AVC [®])	Vaginal antifungals	-
Terconazole (Terazol 3 [®] , Terazol 7 [®] , Zazole [®])	Vaginal antifungals	✓

*Generic available in at least one dosage form or strength.

Indications

Table 2. Food and Drug Administration Approved Indications⁵⁻¹⁰

Generic Name	Treatment of Vulvovaginal Candidiasis	Vaginal Infections
Miconazole	✓	
Nystatin		✓
Sulfanilamide	✓	
Terconazole	✓	

Pharmacokinetics

Table 3. Pharmacokinetics¹¹

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Miconazole	1.4	<1	Not reported	24
Nystatin	Not reported	Not reported	Not reported	Not reported
Sulfanilamide	Not reported	Not reported	Not reported	Not reported
Terconazole	5 to 16	32 to 56	None	6.9

Clinical Trials

Clinical trials evaluating the safety and efficacy of the vaginal antifungal products in Food and Drug Administration approved indications are outlined in Table 4.¹²⁻²² Overall, treatment is “superior” to placebo, and in line with current treatment guidelines. Head-to-head trials do not consistently demonstrate one vaginal antifungal product or regimen to be consistently “superior” to another.^{3,4,12-22} Clinical trial data also demonstrates that vaginal antifungal products are generally well tolerated.¹²⁻²²

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Thomason et al¹²</p> <p>Miconazole 100 mg vaginal suppository intravaginally once daily for 7 days</p> <p>vs</p> <p>terconazole 80 mg vaginal suppository intravaginally once daily for 3 days, followed by placebo for 7 days</p> <p>vs</p> <p>placebo</p>	<p>DB, PC, RCT</p> <p>Nonpregnant patients with ≥1 clinical vulvovaginal sign or symptom and culture-confirmed VVC</p>	<p>N=29</p> <p>7 days</p>	<p>Primary: Microbiologic cure, clinical cure, therapeutic cure</p> <p>Secondary: Adverse events</p>	<p>Primary: At eight to 10 days, 100% of patients receiving terconazole achieved clinical, microbiologic and therapeutic cure. At that time, 100, 89 and 89% of patients receiving with miconazole achieved clinical, microbiologic, and therapeutic cure, respectively. At that time, 44, 33 and 33% of patients receiving placebo achieved clinical, microbiologic, and therapeutic cure, respectively.</p> <p>Terconazole and miconazole achieved significant improvements in clinical, microbiologic and therapeutic cure compared to placebo ($P<0.05$). There was no difference in cure rates between miconazole and terconazole (P value not reported).</p> <p>Secondary: No adverse events were reported.</p>
<p>Brown et al¹³</p> <p>Butoconazole 1% vaginal cream intravaginally for 3 days, followed by placebo for 3 days</p> <p>vs</p> <p>butoconazole 1% vaginal cream intravaginally for 6 days</p> <p>vs</p> <p>butoconazole 2% vaginal cream intravaginally for 3 days, followed by placebo for 3 days</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients 17 to 67 years of age with confirmed VVC</p>	<p>N=580</p> <p>3 to 6 days</p>	<p>Primary: Microbiological cure, clinical cure, therapeutic cure</p> <p>Secondary: Adverse events</p>	<p>Primary: Clinical and microbiological cure rates were greater with all butoconazole- and miconazole-containing regimens compared to the placebo regimen ($P<0.003$ for each comparison). There was no difference in microbiologic and clinical cure rates between the various butoconazole regimens and butoconazole compared to miconazole (P values not reported).</p> <p>There was no difference in therapeutic cure rates with butoconazole 1% for six days compared to placebo. All other treatments demonstrated significance in this parameter ($P<0.001$).</p> <p>Secondary: Systemic adverse events were not observed. The most common adverse events associated with all treatments were local side effects.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs butoconazole 2% vaginal cream intravaginally for 6 days vs miconazole 2% vaginal cream intravaginally for 6 days vs placebo				
Davis et al ¹⁴ Miconazole 2% vaginal cream 5 g intravaginally once daily for 14 days vs nystatin 100,000 units vaginal tablet intravaginally BID for 15 days	PG, RCT Patients with mycologically confirmed VVC	N=116 14 to 15 days	Primary: Overall cure, cure in sub-groups Secondary: Adverse events	Primary: Cure rates were higher with miconazole compared to nystatin (91.1 vs 76.6%, respectively; $P=0.05$). In pregnant patients, 100 and 82.6% of patients receiving miconazole and nystatin achieved cure, respectively. In nonpregnant patients, 84.8 and 73.0% of patients receiving miconazole and nystatin achieved cure, respectively. In nonpregnant patients taking oral contraceptives, 82.4 and 63.2% of patients receiving miconazole and nystatin achieved cure, respectively (P values not reported). Secondary: Adverse events associated with nystatin included condyloma acuminata of the labia, severe burning and vulvar edema and pelvic pain. Adverse events associated with miconazole included mild headache, vaginal burning and moderate irritation.
Corson et al ¹⁵ Miconazole 2% vaginal cream 5 g intravaginally once daily vs	DB, MC, RCT Nonpregnant patients 17 to 61 years of age with signs and symptoms of	N=574 7 days	Primary: Clinical response, microbiological response, therapeutic cure, relapse	Primary: Relative to demographics, the use of contraceptives appears to have a negative effect on cure rate across all treatments; patients not on contraceptives achieved a higher cure rate ($P=0.01$). Between eight to 10 days, microbiologic cure rates with terconazole 0.4%, terconazole 0.8% and miconazole 2% were 91.1, 86.9 and 83.6%,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
terconazole 0.4% vaginal cream 5 g intravaginally once daily vs terconazole 0.8% vaginal cream 5 g intravaginally once daily	VVC, microbiologically-confirmed VVC and either history of being postmenopausal for 2 years or using an effective means of contraception		Secondary: Adverse events	<p>respectively; clinical cure rates were 95.5, 93.4 and 91.6%, respectively; and therapeutic cure rates were 87.9, 83.8 and 81.3%, respectively. The microbiologic cure rates were higher with terconazole 0.4% compared to miconazole 2% (91.1 vs 83.6%; $P=0.02$). There was no difference for other comparisons.</p> <p>After seven days, patients receiving terconazole 0.4%, terconazole 0.8% and miconazole 2% had complete symptom relief rates of 83.3, 77.0 and 79.5%, respectively (P values not significant).</p> <p>After seven days, combined clinical and microbiological cure rates with terconazole 0.4%, terconazole 0.8% and miconazole 2% were 87.9, 83.8, and 81.3%, respectively (P values not significant).</p> <p>Between 30 to 35 days, there were no differences in microbiologic, clinical or therapeutic cure rates between the three treatments (P values not reported).</p> <p>Secondary: There was no difference in the incidence of adverse effects with terconazole 0.4%, terconazole 0.8% and miconazole 2% (61.1, 62.2 and 57.2%), respectively. Adverse reactions most commonly reported involved the central nervous system or genital-reproductive system. Patients receiving terconazole 0.4% had significantly less side effects associated with the genital-reproductive system compared to patients receiving other treatments, that patients receiving the lower strength of terconazole had significantly lower rates of pruritus and metrorrhagia, that patients receiving miconazole experienced more vulvovaginal symptoms and rhinorrhea compared to both terconazole doses and that patients receiving terconazole 0.4% experienced more pyrexia compared to the other groups (P values not reported).</p>
Brown et al ¹⁶ Miconazole 2% vaginal cream 5 g intravaginally once daily for 7 days vs	MC, PG, RCT Nonpregnant patients with confirmed VVC	N=205 1 to 7 days	Primary Clinical cure, microbiological cure Secondary: Adverse events	Primary: With miconazole, symptoms declined after treatment from 23 to 19% after the first dose. At eight to 10 days, 92 and 87% of patients improved clinically and had negative cultures, respectively. At 30 days, 86 and 77% of patients improved clinically and had negative cultures, respectively. With butoconazole, symptoms declined after treatment from 20 to 1% from

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
butoconazole 2% vaginal cream 5 g intravaginally once daily for 1 day				<p>day one to seven. At eight to 10 days, 92 and 87% of patients improved clinically and had negative cultures, respectively. At 30 days, 88 and 74% of patients improved clinically and had negative cultures, respectively.</p> <p>All parameters between miconazole and butoconazole were not different, with the exception of the significant difference in the rapidity of severe symptom relief after the first dose of butoconazole compared to miconazole ($P=0.01$).</p> <p>Secondary: No systemic events were reported. Vulvovaginal irritation (e.g., burning, itching) was reported.</p>
<p>Kaufman et al¹⁷</p> <p>Miconazole 2% vaginal cream 5 g intravaginally once daily for 7 days</p> <p>vs</p> <p>butoconazole 2% vaginal cream 5 g intravaginally once daily for 3 days</p>	<p>MC, PG, RCT</p> <p>Nonpregnant patients 18 to 61 years of age with confirmed VVC</p>	<p>N=225</p> <p>3 to 7 days</p>	<p>Primary: Microbiological cure, clinical cure</p> <p>Secondary: Adverse events</p>	<p>Primary: At eight to 10 days, 91 and 88% of patients receiving miconazole and butoconazole, respectively, were <i>Candida</i> free ($P=0.888$); 82 and 80% of patients were clinically cured, respectively ($P=0.541$).</p> <p>At 30 days, 69 and 73% of patients receiving miconazole and butoconazole were <i>Candida</i> free, respectively ($P=2.14$); 80 and 78% of patients were clinically cured, respectively ($P=0.996$); 52 and 59% of patients experienced therapeutic cure (P value not reported).</p> <p>All parameters between miconazole and butoconazole were not different (P values not reported).</p> <p>Secondary: Minimal side effects were reported with both treatments, including vaginal irritation.</p>
<p>Jacobson et al¹⁸</p> <p>Miconazole 2% vaginal cream 5 g intravaginally once daily</p> <p>vs</p> <p>butoconazole 1% vaginal cream 5 g intravaginally once</p>	<p>DB, MC, PG, RCT</p> <p>Patients 13 to 39 years of age with confirmed VVC by clinical signs and symptoms of vaginal yeast</p>	<p>N=130</p> <p>6 days</p>	<p>Primary: Microbiological cure, clinical cure, relapse</p> <p>Secondary: Adverse effects</p>	<p>Primary: On day eight, 83, 91 and 98% of patients receiving miconazole, butoconazole 1% and butoconazole 2% achieved negative fungal cultures, respectively. Likewise, 68, 75 and 78% of patients achieved clinical cure, respectively (P values not reported).</p> <p>At 30 days, 68, 80 and 82% of patients receiving miconazole, butoconazole 1% and butoconazole 2% maintained negative fungal cultures, respectively; therefore, relapse rates were low. Likewise, 66, 67 and 73% of patients</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
daily vs butoconazole 2% vaginal cream 5 g intravaginally once daily	infection or presence of <i>C albicans</i> confirmed by potassium hydroxide test and culture			maintained clinical cure at this visit, respectively. The differences between cure rates of the three treatments were not different (<i>P</i> values not reported). Secondary: Two patients in each treatment group reported side effects, including headache, vaginal burning, leakage of cream and bleeding.
Higton ¹⁹ Clotrimazole 100 mg vaginal tablet intravaginally once daily vs nystatin 100,000 unit vaginal tablet 2 intravaginally once daily	PG, RCT Obstetrical and gynecological patients with mycologically confirmed VVC	N=50 6 days	Primary: Relapse, overall cure Secondary: Adverse event	Primary: After six days, initial cure rates were 96 and 76% with clotrimazole and nystatin, respectively (<i>P</i> value not reported). At four weeks post treatment, infection relapse rates were 12.5 and 42.0% with clotrimazole and nystatin, respectively. At this time, overall cure rates were higher with clotrimazole compared to nystatin (84 vs 58%; <i>P</i> value not reported). Both clotrimazole and nystatin reduced symptoms five days post treatment (<i>P</i> <0.05) and at four weeks post treatment (<i>P</i> <0.05), and complaints of discharge at six days (<i>P</i> <0.05). There was no difference between treatments; though trends favored clotrimazole over nystatin. Secondary: No local or general adverse event was reported with either treatment.
Thomason ²⁰ Miconazole 2% vaginal cream intravaginally for 7 days vs miconazole 100 mg vaginal suppository intravaginally for 7 days	MA (AC, DB, PC, PG, RCT) Nonpregnant patients >18 years of age with signs and symptoms of VVC and confirmed VVC	N=1,259 3 to 7 days	Primary: Clinical cure, mycological cure, relapse Secondary: Adverse events	Primary: Terconazole vaginal cream and suppository were more efficacious compared to placebo (<i>P</i> <0.001 and <i>P</i> <0.001, respectively). At 35 days, trials with terconazole vaginal cream demonstrated 87.3 to 95.5%, 76.9 to 91.1% and 10.4 to 22.2% in terms of clinical cure, microbiologic cure and relapse rates, respectively. After 10 days, mycological cure rates were similar between terconazole 0.4% vaginal cream and miconazole 2% vaginal cream; however, in trials with a large number of patients, microbiologic cure rates were higher with terconazole (<i>P</i> values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs terconazole 0.4% vaginal cream intravaginally for 7 days vs terconazole 80 mg vaginal suppository intravaginally for 3 days vs terconazole 80 mg vaginal suppository intravaginally for 3 days, followed by placebo for 4 days vs placebo (cream) vs placebo (suppository)				At 35 days, trials with terconazole 80 mg vaginal suppository demonstrated 90.0 to 92.2%, 80.4 to 85.0% and 20.0 to 28.1% for clinical cure, microbiological cure and relapse rates. After 10 days, mycological cure rates were similar between terconazole 80 mg vaginal suppository and miconazole 100 mg vaginal suppository for seven days (<i>P</i> values not reported). Secondary: The adverse effects associated with terconazole were minimal. Frequency of common adverse effects was similar between terconazole and miconazole vaginal suppositories. Relative to vaginal cream formulations, skin rash was associated with terconazole and rhinorrhea, pain and burning was associated with miconazole.
Hirsch ²¹ Clotrimazole 200 mg vaginal tablet* for 3 days vs clotrimazole 1% vaginal cream 5 g intravaginally once daily for 7 days	MA (16 trials) Patients with confirmed VVC	N=1,800 1 to 7 days	Primary: Clinical cure Secondary: Adverse effects	Primary: The most effective regimens of terconazole were the 80 mg vaginal suppository for three days, 240 mg vaginal suppository for one day and the 0.4% vaginal cream for seven days. The 240 mg vaginal suppository for one day was more effective than the 80 mg vaginal suppository for three days, which may have been due to better compliance. The clinical efficacies of the 0.4 and 0.8% vaginal cream for seven days were comparable. After four weeks, 92% of patients receiving terconazole 80 mg vaginal suppository achieved clinical cure; 88% with terconazole 240 mg vaginal suppository for one day, 94% with terconazole 0.8% vaginal cream for five

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>vs</p> <p>econazole 150 mg vaginal suppository* for 3 days</p> <p>vs</p> <p>miconazole 2% vaginal cream 5 g intravaginally once daily for 7 days</p> <p>vs</p> <p>terconazole 40, 80 and 240 mg vaginal suppository; 0.2, 0.4 and 0.8% vaginal cream or other formulations for 1 to 7 days</p>				<p>days and 90% with terconazole 0.4% vaginal cream for seven days.</p> <p>After four weeks, mycological cure rates with terconazole 0.2% vaginal cream were similar to miconazole 2% vaginal cream, but less compared to terconazole 0.4% vaginal cream.</p> <p>After four weeks, mycological cure rates were 100 and 80% with terconazole 0.4% vaginal cream and clotrimazole 1% vaginal cream, respectively, for nonpregnant patients. After four weeks, mycological cure rates were 92 and 89% with terconazole 0.4% vaginal cream and clotrimazole 1% vaginal cream, respectively, for pregnant patients.</p> <p>After four weeks, mycological cure rates were similar between terconazole 80 mg vaginal suppository and econazole 150 mg vaginal suppository for pregnant and nonpregnant patients.</p> <p>After four weeks, mycological cure rates were similar between terconazole 80 and 240 mg vaginal suppository and clotrimazole vaginal tablets.</p> <p>Secondary: Vaginal burning was reported by two, two and one percent of patients receiving terconazole 80 mg vaginal suppository, terconazole 0.4% vaginal cream and terconazole 0.8% vaginal cream, respectively. Regimens comprised of terconazole 240 mg vaginal suppository were well tolerated.</p>
<p>Young et al²²</p> <p>Clotrimazole</p> <p>vs</p> <p>econazole</p> <p>vs</p> <p>hydrargaphen*</p>	<p>SR (10 RCTs)</p> <p>Pregnant patients receiving any topical treatment for VVC</p>	<p>N=not reported</p> <p>Duration varied</p>	<p>Primary: Cure or symptom relief</p> <p>Secondary: Not reported</p>	<p>Primary: According to data from five trials, topical azoles achieved greater cure rates compared to nystatin (OR, 0.21; 95% CI, 0.06 to 0.29).</p> <p>According to data from one trial, there was no difference between nystatin compared to hydrargaphen (OR, 0.14; 95% CI, 0.05 to 1.84).</p> <p>According to data from trials with clotrimazole, the following results were reported: clotrimazole is more effective compared to placebo (OR, 0.14; 95% CI, 0.06 to 0.31), clotrimazole was similar regardless of single or multiple (i.e., three to four days) dosing, clotrimazole for seven days was more effective compared to four days (OR, 11.70; 95% CI, 4.21 to 29.15), clotrimazole was</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs miconazole vs nystatin vs terconazole vs placebo				similar regardless of seven or 14 days of treatment (OR, 0.41; 95% CI, 0.16 to 1.05) and clotrimazole and terconazole had similar efficacy (OR, 1.41; 95% CI, 0.28 to 7.10). Secondary: Not reported

*Not available in the United States.

Drug regimen abbreviations: BID=twice daily

Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, MA=meta analysis, MC=multicenter, OR=odds ratio, PC=placebo-controlled, PG=parallel-group,

RCT=randomized controlled trial, SR=systematic review

Miscellaneous abbreviations: VVC=vulvovaginitis candidiasis

Special Populations**Table 5. Special Populations**^{5-10,23,24}

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Miconazole	No dosage adjustment required in the elderly. Safety and efficacy in children <12 years of age have not been established.	No dosage adjustment required.	No dosage adjustment required.	C	Yes; use with caution.
Nystatin	No dosage adjustment required in the elderly. Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required.	A	Unknown; not recommended.
Sulfanilamide	No dosage adjustment required in the elderly. Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required.	C	Yes; avoid use.
Terconazole	No dosage adjustment required in the elderly. Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required.	C	Unknown; use with caution.

Adverse Drug Events**Table 6. Adverse Drug Events (%)**⁵⁻¹⁰

Adverse Events	Miconazole	Nystatin	Sulfanilamide	Terconazole (0.4% Cream/0.8% Cream/Suppository)
Abdominal pain/cramps	✓	-	-	- / 3.4 / -
Body pain	-	-	-	2.1 / - / 3.9
Chills	-	-	-	0.4 / - / 1.8
Discomfort	-	-	✓	-
Dysmenorrhea	-	-	-	- / 6 / -
Fever	-	-	-	1.7 / 1.0 / 2.8
Genital complaints	-	-	-	- / 5 / -
Headache	-	-	-	26.0 / 21.0 / 30.3
Hypersensitivity reactions	-	✓	-	-
Irritation	✓	-	-	3.1 / - / -
Itching	✓	-	-	2.3 / - / -
Local sensitivity reactions	-	-	0.2	-
Pain of the female genitalia	-	-	-	- / - / 4.2
Vulvovaginal burning	✓	-	✓	5.2 / - / 15.2

✓ Percent not specified.

- Event not reported.

Contraindications/Precautions

Miconazole vaginal products are contraindicated with hypersensitivity to any of the components of the vaginal cream and suppository.⁵ Nystatin vaginal tablet is contraindicated with hypersensitivity to any of the components of the vaginal tablet.⁶ Sulfanilamide vaginal cream is contraindicated with hypersensitivity to any of the components of the vaginal cream or to sulfonamides.⁷ Terconazole vaginal products are contraindicated with hypersensitivity to terconazole or to any of the components of the various products.⁸⁻¹⁰

Miconazole vaginal products should be discontinued if sensitivity or irritation occurs. A health care professional should be consulted before using an over-the-counter miconazole product if there is vaginal itching/discomfort, lower abdominal pain, back or shoulder pain, chills, nausea, vomiting, foul-smelling discharge or if it is the first vaginal infection or if the patient has been exposed to human immunodeficiency virus. A health care professional should be contacted if symptoms do not begin to improve after three days or last longer than seven days. Use of a miconazole vaginal product may damage condoms or diaphragms.⁵

Because sulfonamides are absorbed from the vaginal mucosa, the usual precautions for oral sulfonamides apply in patients receiving sulfanilamide vaginal cream. Patients should be observed for skin rash or evidence of systemic toxicity, and if these develop, the medications should be discontinued. Deaths associated with administration of oral sulfonamides have reportedly occurred from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias. In addition, goiter production, diuresis and hypoglycemia have reportedly occurred rarely in patients receiving oral sulfonamides. Cross-sensitivity may exist with these agents. Vaginal applicators or inserters should be used with caution after the seventh month of pregnancy.⁷

Terconazole vaginal products should be discontinued if sensitization, irritation, fever, chills or flu-like symptoms are reported during use.⁸⁻¹⁰ The base contained in the terconazole suppository may interact with certain rubber or latex products; therefore, concurrent use is not recommended.^{8,10} If there is a lack of response to any of the terconazole vaginal products, appropriate microbiologic studies should be repeated to confirm the diagnosis and rule out other pathogens.⁸⁻¹⁰

Drug Interactions

No clinically significant drug interactions have been documented with miconazole, nystatin and sulfanilamide vaginal products.⁵⁻⁷ The therapeutic effect of terconazole vaginal products is not affected by oral contraceptive usage.⁸⁻¹⁰

Dosage and Administration**Table 7. Dosing and Administration**⁵⁻¹⁰

Generic Name	Adult Dose	Pediatric Dose	Availability
Miconazole	<u>Treatment of vulvovaginal candidiasis:</u> Vaginal kit (vaginal suppository/vaginal cream): one vaginal suppository intravaginally once daily for three days/apply onto itchy, irritated skin outside the vagina BID for up to seven days Vaginal suppository: one intravaginally once daily for three days	Safety and efficacy in children <12 years of age have not been established.	Vaginal kit: 200 mg vaginal suppository/2% vaginal cream (9 g) Vaginal suppository: 200 mg
Nystatin	<u>Vaginal infections:</u> Vaginal tablet: one tablet intravaginally once daily for 14 days	Safety and efficacy in children have not been established.	Vaginal tablet: 100,000 units*
Sulfanilamide	<u>Treatment of vulvovaginal candidiasis:</u> Vaginal cream: one applicator full (6 g)	Safety and efficacy in children have not	Vaginal cream: 15% (4 oz/tube with

Generic Name	Adult Dose	Pediatric Dose	Availability
	intravaginally once daily or BID for 30 days	been established.	applicator)
Terconazole	<p><u>Treatment of vulvovaginal candidiasis:</u> Vaginal cream (0.4%): one applicator full (5 g of cream containing 20 mg of terconazole) intravaginally once daily for seven days</p> <p>Vaginal cream (0.8%): one applicator full (5 g of cream containing 40 mg of terconazole) intravaginally once daily for three days</p> <p>Vaginal suppository: one (2.5 g containing 80 mg of terconazole) intravaginally once daily for three days</p>	Safety and efficacy in children have not been established.	<p>Vaginal cream: 0.4% (45 g/tube with applicator) (Terazol 7[®], Zazole[®]) 0.8% (20 g/tube with applicator) (Terazol 3[®])</p> <p>Vaginal suppository: 80 mg (carton of 3 with applicator) (Terazol 7[®], Zazole[®])</p>

*May also be given orally.

Drug regimen abbreviations: BID=twice daily

Clinical Guidelines

Treatment guidelines for the vaginal antifungal products included in Table 8 are regarding the management of the Food and Drug Administration approved indication of vulvovaginal candidiasis. Of note, guidelines are summarized globally for the treatment of vulvovaginal candidiasis and are not limited to the role of the vaginal antifungals contained in this review.

Table 8. Clinical Guidelines

Clinical Guideline	Recommendations
Centers for Disease Control and Prevention: Sexually Transmitted Diseases Treatment Guidelines (2010) ³	<p>Uncomplicated vulvovaginal candidiasis (VVC)</p> <ul style="list-style-type: none"> • Short course topical formulations (i.e., single dose and regimens of one to three days) effectively treat uncomplicated VVC. • Topically applied azole drugs are more effective than nystatin. • Treatment with azoles results in relief of symptoms and negative cultures in 80 to 90% of patients who complete therapy. • Recommended regimens include over-the-counter (OTC) intravaginal agents, prescription intravaginal agents and oral agents. • Recommended OTC intravaginal agents include the following: <ul style="list-style-type: none"> ○ Butoconazole 2% vaginal cream 5 g intravaginally for three days. ○ Clotrimazole 1% vaginal cream 5 g intravaginally for seven to 14 days. ○ Clotrimazole 2% vaginal cream 5 g intravaginally for three days. ○ Miconazole 2% vaginal cream 5 g intravaginally for seven days. ○ Miconazole 4% vaginal cream 5 g intravaginally for three days. ○ Miconazole 100 mg vaginal suppository, one suppository for seven days. ○ Miconazole 200 mg vaginal suppository, one suppository for three days. ○ Miconazole 1,200 mg vaginal suppository, one suppository for one day. ○ Tioconazole 6.5% vaginal ointment 5 g intravaginally in a single application. • Recommended prescription intravaginal agents include the following: <ul style="list-style-type: none"> ○ Butoconazole 2% vaginal cream (single dose bioadhesive

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	<p>product) 5 g intravaginally for one day.</p> <ul style="list-style-type: none"> ○ Nystatin 100,000 unit vaginal tablet, one tablet for 14 days. ○ Terconazole 0.4% vaginal cream 5 g intravaginally for seven days. ○ Terconazole 0.8% vaginal cream 5 g intravaginally for three days. ○ Terconazole 80 mg vaginal suppository, one suppository for three days. <ul style="list-style-type: none"> ● Recommended oral agents include the following: <ul style="list-style-type: none"> ○ Fluconazole 150 mg tablet, one tablet in a single dose. ● The vaginal creams and vaginal suppositories are oil based and might weaken latex condoms and diaphragms. ● Intravaginal preparations of butoconazole, clotrimazole, miconazole and tioconazole are available OTC. ● Women previously diagnosed with VVC are not necessarily more capable of diagnosing themselves; therefore, women whose symptoms persist after using an OTC preparation or who has a recurrence of symptoms within two months should be evaluated with office-based testing. ● Unnecessary or inappropriate use of OTC preparations is common and can lead to a delay in the treatment of other vulvovaginitis etiologies, which can result in adverse clinical outcomes. ● Patients should be instructed to return to follow up visits only if symptoms persist or recur within two months of onset of the initial symptoms. ● VVC is not usually acquired through sexual intercourse; therefore, no data supports the treatment of sex partners. A minority of male sex partners might have balanitis, which is characterized by erythematous areas on the glans of the penis in conjunction with pruritis or irritation. These men benefit from treatment with topical antifungal agents to relieve symptoms. ● Topical agents usually cause no systemic side effects. Local burning or irritation might occur. ● Oral agents are associated with nausea, abdominal pain and headache. <p><u>Complicated VVC</u></p> <ul style="list-style-type: none"> ● Recurrent complicated VVC, defined as four or more episodes of symptomatic VVC in one year, affects a small percentage of women. ● Vaginal cultures should be obtained from patients with recurrent VVC to confirm the clinical diagnosis and to identify unusual species, including non-<i>albicans</i> species. Conventional antimycotic therapies are not as effective against these species as they are against <i>Candida albicans</i>. ● Each individual episode of recurrent VVC caused by <i>C albicans</i> responds well to short duration oral or topical azole therapy; however, longer duration of initial therapy (e.g., seven to 14 days of topical therapy or a 100, 150 or 200 mg dose of oral fluconazole every third day for a total of three doses) may be appropriate. ● A maintenance regimen of oral fluconazole (100, 150 or 200 mg dose) weekly for six months is first line. If not feasible, topical treatments used intermittently as a maintenance regimen can be considered. ● Suppressive maintenance antifungal therapies are effective in reducing recurrent VVC. ● Routine treatment of sex partners is controversial.

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> • Severe vulvovaginitis (i.e., extensive vulvar erythema, edema, excoriation and fissure formation) is associated with lower clinical response rates in patients treated with short courses of topical or oral therapy. • For severe vulvovaginitis, either seven to 14 days of topical azole or 150 mg of fluconazole in two sequential doses (second dose 72 hours after initial dose) is recommended. • The optimal treatment for non-<i>albicans</i> VVC remains unknown. Options include longer duration of therapy (seven to 14 days) with a non-fluconazole azole drug (oral or topical) as first line therapy. If recurrence occurs, 600 mg of boric acid in a gelatin capsule is recommended, administered intravaginally once daily for two weeks. <p><u>Special considerations</u></p> <ul style="list-style-type: none"> • Women with underlying debilitating medical conditions do not respond as well to short term therapies. Efforts to correct modifiable conditions should be made, and more prolonged (i.e., seven to 14 days) conventional antimycotic treatment is necessary. • VVC frequently occurs during pregnancy and only topical azole therapies for seven days are recommended. • Therapy in human immunodeficiency virus (HIV) infected women should not differ from that for seronegative women. Although long term prophylactic fluconazole 200 mg weekly is not recommended for routine primary prophylaxis in HIV infected women in the absence of recurrent VVC.
<p>Infectious Diseases Society of America: Clinical Practice Guidelines for the Management of Candidiasis: 2009 Update by the Infectious Diseases Society of America (2009)⁴</p>	<ul style="list-style-type: none"> • The following intravaginal antifungal agents are effective for the treatment of VVC, and no one agent is clearly “superior”: <ul style="list-style-type: none"> ○ Butoconazole 2% vaginal cream 5 g intravaginally for three days. ○ Butoconazole 2% cream 5 g (sustained-release) single intravaginal application. ○ Clotrimazole 1% vaginal cream 5 intravaginally for seven to 14 days. ○ Clotrimazole 100 mg vaginal tablet for seven days. ○ Clotrimazole 100 mg vaginal tablet, two tablets for three days. ○ Miconazole 2% vaginal cream 5 intravaginally for seven days. ○ Miconazole 100 mg vaginal suppository, one suppository for seven days. ○ Miconazole 200 mg vaginal suppository, one suppository for three days. ○ Miconazole 1,200 mg vaginal suppository, one suppository for one day. ○ Nystatin 100,000 unit vaginal tablet, one tablet for 14 days. ○ Tioconazole 6.5% vaginal ointment 5 g intravaginally in a single application. ○ Terconazole 0.4% vaginal cream 5 intravaginally for seven days. ○ Terconazole 0.4% vaginal cream 5 intravaginally for three days. ○ Terconazole 80 mg vaginal suppository, one suppository for three days. • A single 150 mg dose of fluconazole is recommended for the treatment of uncomplicated Candida VVC. • For recurring Candida VVC, 10 to 14 days of induction therapy with a topical or oral azole, followed by fluconazole at a dosage of 150 mg once per week for six months, is recommended.

Clinical Guideline	Recommendations
<p>Centers for Disease Control and Prevention: Guidelines for the Prevention and Treatment of Opportunistic Infections in Human Immunodeficiency Virus-Infected Adults and Adolescents (2009)²⁵</p>	<p><u>Microsporidiosis</u></p> <ul style="list-style-type: none"> Itraconazole may be effective in disseminated disease when combined with albendazole. <p><u>Mucocutaneous Candidiasis</u></p> <ul style="list-style-type: none"> Routine primary prophylaxis is not recommended. Oral fluconazole is as effective and (in certain studies) “superior” to topical therapy for oropharyngeal candidiasis. It is also more convenient and better tolerated. Fluconazole is the drug of choice for oropharyngeal candidiasis. Initial episodes of oropharyngeal candidiasis can be treated with topical therapy including clotrimazole troches, nystatin suspension or pastilles or once daily miconazole mucoadhesive tablets. Itraconazole oral solution is as effective but less well tolerated compared to fluconazole for oropharyngeal candidiasis. Posaconazole is as effective as fluconazole and generally better tolerated than itraconazole. Itraconazole and posaconazole are alternatives to fluconazole but few circumstances would require them to be used in preference to fluconazole for the treatment of mucocutaneous candidiasis. Ketoconazole and itraconazole capsules are not recommended if other alternatives are available. Systemic antifungals are required for esophageal candidiasis. Fluconazole and itraconazole solution are highly effective. Oral ketoconazole and itraconazole capsules are less effective due to variable absorption. Oral or intravenous fluconazole is the treatment of choice for esophageal candidiasis. The echinocandins appear to have a higher relapse rate compared to fluconazole. Uncomplicated vulvovaginal candidiasis may be treated with oral fluconazole, topical azoles, or itraconazole oral solution. Severe or recurrent episodes of vulvovaginal candidiasis require oral fluconazole or topical therapy for at least seven days. Itraconazole solution is effective in about two thirds of patients with fluconazole-refractory mucosal candidiasis. Posaconazole immediate-release oral suspension is effective in 75% of patients with azole-refractory oropharyngeal and/or esophageal candidiasis. Amphotericin B intravenous is usually effective and can be used in refractory disease. Amphotericin B oral suspension is sometimes effective in patients who do not respond to itraconazole. This is not available in the United States. Azole-refractory esophageal candidiasis can be treated with posaconazole, anidulafungin, caspofungin, micafungin or voriconazole. In general, secondary prophylaxis is not recommended. It may be considered in patients with frequent severe recurrences. Oral fluconazole may be used for oropharyngeal or vulvovaginal candidiasis. For recurrent esophageal candidiasis, daily fluconazole can be used. Oral posaconazole is also effective, but potential azole resistance should be considered when choosing an agent. Secondary prophylaxis should be initiated in patients with fluconazole-

Clinical Guideline	Recommendations
	<p>refractory oropharyngeal or esophageal candidiasis who have responded to echinocandins, voriconazole or posaconazole.</p> <ul style="list-style-type: none"> • Topical therapy is preferred in pregnancy. • Amphotericin B should be substituted for high-dose fluconazole in the first trimester of pregnancy for invasive or refractory esophageal candidal infections. <p><u>Cryptococcosis</u></p> <ul style="list-style-type: none"> • The majority of experts do not recommend routine primary prophylaxis. • Recommended initial treatment is amphotericin B deoxycholate plus flucytosine. • Lipid formulation amphotericin B may be considered in patients with renal dysfunction or at risk for renal dysfunction. • Fluconazole plus flucytosine is an alternative but is inferior to amphotericin B and should be reserved for patients who are unable to tolerate or unresponsive to standard treatment. • After successful induction therapy, step-down therapy to fluconazole is recommended. Itraconazole is an acceptable but less effective alternative. Limited data are available for voriconazole and posaconazole. • In the event of treatment failure, those initially treated with fluconazole may be treated with amphotericin B with or without flucytosine. Liposomal amphotericin B may have improved efficacy over the deoxycholate. Higher doses of fluconazole plus flucytosine may be useful. Posaconazole and voriconazole may have a role in therapy. • Maintenance treatment with fluconazole is recommended, either life-long or until immune reconstitution. Itraconazole is inferior to fluconazole for prevention. <p><u>Histoplasmosis</u></p> <ul style="list-style-type: none"> • Primary prophylaxis with itraconazole can be considered in patients with advanced HIV infections living in areas where histoplasmosis is highly endemic. • Patients with moderately severe to severe disease should be treated with lipid formulation amphotericin B followed by oral itraconazole. • In patients with less severe disease, oral itraconazole is appropriate as initial therapy. The liquid formulation is preferred due to better absorption and fewer food interactions. • Patients with confirmed meningitis should be treated with liposomal amphotericin B followed by maintenance therapy with itraconazole. • Posaconazole has been reported as salvage therapy in some studies. • Limited data suggests posaconazole or voriconazole may be effective in the case of treatment failure. • Long-term suppressive therapy with itraconazole is recommended in patients with severe disseminated or central nervous system infection and in those who relapse despite appropriate therapy. Fluconazole is less effective than itraconazole. The role of voriconazole and posaconazole is unclear. • Azoles should be avoided during the first trimester of pregnancy. <p><u>Coccidioidomycosis</u></p> <ul style="list-style-type: none"> • Primary prophylaxis with oral fluconazole or itraconazole may be considered in patients living in areas where the disease is endemic and

Clinical Guideline	Recommendations
	<p>who have a positive IgM or IgG serologic test.</p> <ul style="list-style-type: none"> • Clinically mild infection may be treated with fluconazole or itraconazole. Data is limited for posaconazole and voriconazole but they may be useful in patients who do not respond to fluconazole or itraconazole. • Severely ill patients and those with diffuse pulmonary involvement should be treated with amphotericin B. • Treatment failure on an azole should be treated with amphotericin B. • Life-long or suppressive therapy may be considered with fluconazole or itraconazole. • Avoid azoles during the first trimester of pregnancy. <p><u>Aspergillosis</u></p> <ul style="list-style-type: none"> • No data on primary prophylaxis of HIV infected patients exists. • Voriconazole is the drug of choice for treatment but should be used cautiously in patients taking HIV protease inhibitors and efavirenz. • Amphotericin B, caspofungin and posaconazole are alternatives. • Other echinocandins are also alternatives. • In the event of treatment failure, if voriconazole was used initially, amphotericin B, an echinocandin or posaconazole may be considered. • No data are available to recommend for or against chronic maintenance or suppressive therapy after successful initial course of treatment.

Conclusions

The prescription vaginal antifungals, metronidazole, sulfanilamide (AVC[®]) and terconazole (Terazol 3[®], Terazol 7[®], Zazole[®]) are Food and Drug Administration (FDA) approved for the treatment of vulvovaginitis candidiasis. Nystatin is also included in this review and is FDA approved for the treatment of vaginal infections. All agents are available for intravaginal administration. Nystatin is available as a vaginal tablet, sulfanilamide is available as a vaginal cream and terconazole is available as a vaginal cream and vaginal suppository. Also included in this review is the miconazole vaginal kit (contains vaginal suppositories and vaginal cream) and vaginal suppository. Of note, there are a variety of miconazole vaginal products that are also available over-the-counter (OTC).⁵⁻¹⁰ Currently, miconazole and terconazole are available generically.

Guidelines recommend OTC intravaginal antifungal products, prescription intravaginal antifungal products and prescription oral antifungals for the treatment of uncomplicated vulvovaginitis candidiasis. Of the agents included in this review, nystatin, miconazole and terconazole are recognized as potential treatment options. While the Center for Disease Control and Prevention states that topically applied azole antifungals are more effective than nystatin, overall there is no available evidence to demonstrate the “superiority” of any intravaginal formulation or regimen. Additionally, oral and intravaginal therapies are considered equivalent.^{3,4} Currently, butoconazole, clotrimazole, miconazole and tioconazole intravaginal products are available OTC. No data supports the treatment of sex partners of patients infected with vulvovaginitis candidiasis and only intravaginal antifungal products are recommended for the treatment of pregnant patients with vulvovaginitis candidiasis.³ The treatments for uncomplicated vulvovaginitis candidiasis are also recommended for complicated infections; however, suppressive maintenance antifungal therapy is also recommended in these patients to reduce recurrent infection. After treating for the individual episode, a maintenance regimen of oral fluconazole weekly for six months should be initiated. In cases where this is not feasible, intravaginal treatments used intermittently can be considered.^{3,4} Optimal treatments for non-*Candida albicans* vulvovaginitis candidiasis remain unknown.³

Clinical trials consistently demonstrate that the vaginal antifungal products are safe and effective in the management of vulvovaginitis candidiasis. Furthermore, head-to-head trials do not consistently demonstrate the “superiority” of one vaginal antifungal product or regimen over another.¹²⁻²²

Appendix I: Utilization Within Vaginal Antifungals for DVHA: April 1, 2011 to September 30, 2011

Medication	Unique utilizers	# of Rx's	Market Share (%)	Plan Cost \$	Avg \$/Rx
Terconazole	255	253	65.89%	\$7,295.21	\$28.83
Clotrimazole	27	29	7.55%	\$260.10	\$8.97
Miconazole 7	26	26	6.77%	\$245.80	\$9.45
Miconazole Nitrate	24	24	6.25%	\$247.39	\$10.31
Miconazole 3 Combo Pack	16	16	4.17%	\$407.73	\$25.48
Nystatin Vaginal [®]	8	9	2.34%	\$618.56	\$68.73
SM Clotrimazole Vaginal	4	5	1.30%	\$49.60	\$9.92
SM Miconazole 7	3	3	0.78%	\$33.35	\$11.12
Clotrimazole 3 Day	3	3	0.78%	\$39.04	\$13.01
SM Miconazole 3	3	3	0.78%	\$49.12	\$16.37
Monistat 7 [®]	3	3	0.78%	\$34.99	\$11.66
Monistat 7 Combination [®]	3	3	0.78%	\$56.29	\$18.76
Monistat 3 [®]	2	2	0.52%	\$31.22	\$15.61
Gyne-Lotrimin [®]	1	1	0.26%	\$20.19	\$20.19
SM 3 Day Vaginal	1	1	0.26%	\$12.46	\$12.46
Miconazole 3 [®]	1	1	0.26%	\$49.86	\$49.86
Terazol 7 [®]	1	1	0.26%	\$48.04	\$48.04
Miconazole	1	1	0.26%	\$10.50	\$10.50
Class Total:	NA	376	100%	\$9,509.45	\$24.76

Recommendations

At this time, the Department of Vermont Health Access does not have restrictions on generically available over-the-counter vaginal anti-infectives. The recent OTC coding changes implemented in July 2011 only allow generically available products with no opportunity for PA requests for branded products. In recognition of the low utilization of the branded products, no changes are recommended.

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