

# Abnormal vaginal discharge: What does and does not work in treating underlying causes

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### Practice recommendations

- Treat bacterial vaginosis with oral or intravaginal metronidazole or with clindamycin (SOR: **A**); recurrences are common (SOR: **C**).
- Oral and intravaginal imidazoles are equally effective in the treatment of candidiasis (SOR: **A**); alternate therapies for resistant cases have been little studied.
- Oral metronidazole is the standard therapy for trichomoniasis (SOR: **A**). Oral tinidazole, newly available in the US in 2004, should be used in resistant cases (SOR: **B**).

**A**ntifungal medications for intravaginal use have been available in the United States for more than a decade. Women may be inclined to self-diagnose yeast infections with any vaginal discharge or other vulvovaginal symptoms that they deem abnormal. As we saw in the first

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part of this article, “Abnormal vaginal discharge: Using office diagnostic testing more effectively” (*JFP* 2004; 53[10]:805–814), abnormal discharge is more likely to be bacterial vaginosis or no pathogen at all. Potential delay in diagnosis and treatment of a sexually transmitted disease is also a concern. Increasing resistance of *Candida* sp. to imidazoles is associated with indiscriminate use of over-the-counter products.

### ■ BACTERIAL VAGINOSIS

The standard treatment for bacterial vaginosis (BV) has been oral metronidazole (Flagyl) 500 mg twice daily for 5 to 7 days. Intravaginal 0.75% metronidazole gel (MetroGel) has been shown to be as effective as oral metronidazole (SOR: **A**).<sup>1,2</sup>

Oral metronidazole can cause nausea and abdominal pain in some patients; vaginal treatment may be preferable for them. A meta-analysis of 52 studies of regimens of oral metronidazole at a dose of 2 g daily of varying duration showed similar initial cure rates of 85%, 87%, 86%, and 87% for 1, 2, 5, and 7 days, respectively (strength of recommendation [SOR]: **A**).<sup>3</sup> Single-dose therapy may improve adherence (SOR: **C**).

Clindamycin (Cleocin), orally or in vaginal cream, for 5 days is also effective for BV (SOR:

**A).**<sup>4-8</sup> Clindamycin cream is used at a dose of 5 g daily and a concentration of 2%. Lower concentration (1%) has been less effective.<sup>6</sup> Oral regimens range from 300 mg twice daily to 450 mg 3 times daily. Oral and vaginal preparations have shown equal efficacy in direct comparisons (SOR: **A**).<sup>8</sup> A 3-day course of vaginal clindamycin is as effective as a 5-day course (SOR: **B**).<sup>9</sup>

Several studies have compared clindamycin and metronidazole head to head. They have shown similar cure rates that were not statistically different in the 75% to 90% range (SOR: **A**).<sup>4,5,10,11</sup>

Other antibiotics that have shown in vitro efficacy for treating the spectrum of microbes associated with BV are amoxicillin-clavulanate (Augmentin), imipenem (Primaxin), and cefmetazole (Zefazone) (SOR: **C**).<sup>8,12</sup> Some *Mobiluncus* strains show resistance to metronidazole (SOR: **C**).<sup>12</sup>

**Recurrences of BV are common.** The initial regimen or an alternative regimen may be used. A longer, 10- to 14-day, course of antibiotic therapy has been recommended by one expert for treating relapses (SOR: **C**).<sup>13</sup> Recolonizing the vagina with lactobacilli by eating yogurt or using bacteria-containing suppositories is an approach that deserves further study (SOR: **C**).<sup>14</sup> Suppressive therapy such as intravaginal metronidazole twice weekly may also be considered as maintenance therapy to prevent recurrences (SOR: **C**).

### **BV and pregnancy**

A number of studies have been published on screening for BV in pregnancy using Gram stain and on treating positive cases with antibiotics. While studies that used metronidazole for treatment have not shown consistently good results, more recent studies using clindamycin orally or intravaginally have been promising (SOR: **B**).<sup>7,15</sup> Oral dosing at 300 mg twice daily, at 12 to 22 weeks gestation, has reduced preterm delivery for pregnant women with BV diagnosed by Nugent's criteria (number needed to treat [NNT]=10).<sup>7</sup> Likewise, for women with BV treated at 13 to 20 weeks gestation, intravaginal clindamycin therapy for 3 days has reduced the

incidence of preterm births (NNT=17).<sup>15</sup>

Clindamycin appears to be the treatment of choice for BV in pregnancy (SOR: **C**) since it is considered safe (category B) throughout pregnancy, and because use of metronidazole in the first trimester is controversial.

### **■ CANDIDIASIS**

Treating vulvovaginal candidiasis (VVC) with intravaginal imidazoles reduces symptoms with NNT=3 after 1 month (SOR: **A**) (**Table**).<sup>16</sup> No difference has been seen in outcomes with the various imidazoles or with treatment durations of 1 to 14 days. Intravaginal nystatin also decreases symptoms of VVC, with a NNT of 3 after 1 week compared with placebo (SOR: **B**).

Data showing that imidazoles are more effective than nystatin are not strong (SOR: **B**). A *Clinical Evidence* review<sup>16</sup> identified 1 trial comparing intravaginal miconazole, clotrimazole, econazole, and nystatin; symptomatic relapse was lower with intravaginal imidazoles than with nystatin. Another trial comparing clotrimazole and nystatin showed no difference in the proportion of women with persistent symptoms after 4 weeks. An open label study<sup>17</sup> comparing econazole, miconazole, and nystatin showed that the imidazoles had more antifungal activity, but there was no difference in clinical outcome assessment.

Oral treatments are popular, most commonly a single dose of fluconazole. Oral itraconazole and ketoconazole have also been used successfully (SOR: **A**).<sup>18-21</sup> A systematic review of oral vs vaginal azoles showed similar efficacy, but more side effects occurred with oral therapy (SOR: **A**).<sup>22</sup> Gastrointestinal side effects occur in up to 15% of women.<sup>23</sup>

### **Treating complicated VVC**

About 5% of women diagnosed with VVC will have frequent recurrences, 4 or more per year.<sup>24</sup> Current therapies are fungistatic rather than fungicidal, so the yeast are reduced but not eradicated. Hypersensitivity and allergic reactions to topical preparations may be confused with recur-

**TABLE**

**Antifungal medications used to treat vulvovaginal candidiasis**

Generic name	Trade name	Dose	Duration	Cost per course of treatment*
<b>Over the counter</b>				
Butoconazole 2% cream	Femstat-3 Mycelex-3 generic	5 g every night	3 days	\$5–\$34
Clotrimazole 1% cream	Mycelex-7 generic	5 g every night	7–10 days	\$2–\$7
Clotrimazole 200 mg suppository	Gyne-Lotrimin generic	1 every night	3 days	\$2–\$9
Miconazole 100 mg suppository	Monistat generic	1 every night	7 days	\$2–\$14
Miconazole 2% cream	Monistat generic	5 g every night	7–10 days	\$2–\$11
Miconazole 200 mg suppository	Monistat-3	1 every night	3 days	\$3–\$22
Miconazole 100 mg suppository plus 2% external cream	Gyne-Lotrimin generic	1 every night	5 days	\$5–\$12
Tioconazole 6.5% ointment	Vagistat-1 generic	4.6 g	1 day	\$2–\$19
<b>Prescription</b>				
Econazole 1% cream	Spectazole	5 g	3–6 days	\$18 for 15 g \$31 for 30 g
Terconazole 0.4% cream	Terazol-7	5 g	7 days	\$41
Terconazole 0.8% cream	Terazol-3	5 g	3 days	\$41
Terconazole 80 mg suppository	Terazol-3	1 every night	3 days	\$41
Nystatin 100,000 U vaginal tablets	Generic	1 every night	7–14 days	\$14–\$35
Fluconazole 150 mg tablet	Diflucan	1 orally daily	1 day	\$14
Itraconazole 100 mg tablet	Sporonox	2 orally daily 4 orally	3 days 1 day	\$56 \$37 (\$281 for 30 tablets)
Ketoconazole 200 mg tablet	Nizoral generic	2 orally daily	5 days	\$32–\$43 (\$95 for 30 generic tablets)

\*Average wholesale price for entire regimen in US dollars.

rences. Experts recommend that, if wet mount or culture results confirm recurrent vaginitis, topical therapy should be increased from 5 to 7 days up to 10 to 14 days, or that a second oral fluconazole tablet be given 3 days after the first (SOR: C).<sup>24</sup> Women with severe cases of VVC also benefit from 2 sequential doses of fluconazole given 3 days apart (SOR: B).<sup>25</sup>

Suppressive therapy may be used after initial treatment for 6 months or more (SOR: B). Suppressive therapy options include oral fluconazole 150 mg or vaginal clotrimazole 500 mg once a week, oral or intravaginal nystatin twice weekly, and oral itraconazole 200 mg monthly.<sup>24,26</sup>

Non-*albicans* species tend to be more resistant to oral and topical azoles (SOR: B).<sup>27-29</sup> If this species is detected on culture, a long course of suppressive therapy should be attempted (SOR: C).<sup>24</sup> If imidazole therapy fails to control symptoms, suspect resistance.

Resistance to azoles may be demonstrated by in vitro susceptibility testing. Cross-resistance to topical and oral (fluconazole) azoles has been documented.<sup>30</sup> There have been few studies of alternatives to azoles for treatment of resistant yeast vaginitis. One little-studied alternative is intravaginal boric acid, which may be used as a 14-day course of 600 mg daily in gelatin capsules (SOR: C).<sup>31</sup> Nystatin and flucytosine (Ancoban) for 7 to 14 days are other alternatives (SOR: C).<sup>24</sup>

### Candida in pregnancy

Commonly used topical imidazoles are classified as category C in pregnancy and have not been associated with increased risk of birth defects.

### ■ TRICHOMONIASIS

Current treatment for trichomoniasis is oral metronidazole, given as a 2-g single dose, 250 mg 3 times daily for 7 days or 500 mg twice a day for 7 days. Treatment should also be given to the woman's partner (SOR: A).<sup>32</sup> Intravaginal therapy is not effective, probably due to the parasite's presence in inaccessible areas such as the vaginal

**Intravenous high-dose metronidazole has been reported to treat highly resistant trichomonas**

glands and urethra.<sup>33,34</sup> Short-term treatment is comparable with long-term treatment, with similar rates of nausea and vomiting (SOR: A).<sup>32</sup> A 1.5-g single-dose treatment has been shown to be equivalent to 2 g (SOR: B).<sup>35</sup>

The incidence metronidazole-resistant trichomoniasis has been estimated at 5%.<sup>36</sup> In such cases, higher-dose therapy may be still be effective. For low to moderate resistance, 2 to 2.5 g daily for 3 to 10 days has been recommended (SOR: B).<sup>37</sup> Intravenous high-dose metronidazole, 2 g every 8 hours for 3 days, has been reported to successfully treat highly resistant trichomonas (SOR: C).<sup>38</sup> Another case report of 2 women with presumed allergy to metronidazole were successfully treated with incremental dosing of IV metronidazole (SOR: C).<sup>39</sup> A small case series of women with metronidazole allergy or resistance treated with paromomycin cream intravaginally showed cure in 6 of 9 cases (SOR: C).<sup>40</sup> Oral tinidazole has been approved in 2004 for use in the treatment of metronidazole-resistant trichomoniasis (SOR: B).<sup>41</sup>

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