Resistance in Vulvovaginal Candidiasis (VVC) – A Growing Problem

Mark Martens, MD, FACOG

See Quiz on Key Points at end of webinar
# Table of Contents

- About Dr. Martens ................................................................. 3
- *Candida* Species Causing VVC ............................................. 4
- Recurrent and Resistant Yeast Infections ............................... 5
- Yeast Activity in the GI and Genitourinary Tracts .................... 8
- Fluconazole Resistance and the Impact on Dosing Practices ...... 14
- Challenges and Approaches in Treating *Non-albicans* Infections 16
- Concerns with Fluconazole Use in Specific Patient Populations 20
- Recent Study Results on Miconazole .................................... 23
- Summary ............................................................................ 26
- Quiz on Key Points ............................................................... 27
- Appendix ........................................................................... 32
- References ......................................................................... 35
Mark G. Martens, MD

Chairman, Dept. of Obstetrics and Gynecology, Jersey Shore University Medical Center
Clinical Professor and Vice-Chair, Rutgers Robert Wood Johnson School of Medicine

- Published over 150 peer-reviewed articles and book chapters, and is reviewer or editorial board member of various peer-reviewed journals
- Educator, researcher, and clinician in the areas of infectious diseases in women, menopause, osteoporosis, and minimally invasive surgery for over 25 years
- Past president of the International Infectious Disease Society for Obstetrics and Gynecology (I-IDSOG)
**Candida Species Causing VVC**

Although *Candida* is the most common cause of VVC, *non-albicans* species of *Candida*, such as *Candida glabrata*, have increasingly been identified as a cause of VVC.

**Albicans: C. albicans 70.8%**

**Non-albicans:**

- *C. glabrata* 18.9%
- *C. parapsilosis* 5.0%
- *C. krusei* 2.0%
- *C. cerevisiae* 1.5%
- *C. tropicalis* 1.4%
- *C. lusitaniae* 0.2%
- *Trichosporon sp* 0.2%

### Past

- 95% of infections were caused by *Candida albicans*
- 5% of infections were caused by *non-albicans Candida* species

### Present

- ~70% of infections are caused by *Candida albicans*
- 29.2% of infections are caused by *non-albicans Candida* species

Recurrent and Resistant Yeast Infections
Understanding Recurrence and Resistance

To best treat patients with VVC infection, the clinician must differentiate:

**Recurrent** infection occurs when antibiotics and other environmental factors result in reinfection; the *Candida* species remain susceptible to the antifungal agents.

**Resistant** infection is when nonsusceptible *Candida* organisms that are resistant to antifungal agents persist and cause infection.
Recurrent Vulvovaginal Candidiasis (RVVC)

**Definition of RVVC:** According to the CDC guidelines, RVVC is defined as 4 or more yeast infections in 1 year

- Although <5% of women have RVVC, they are among the most difficult to treat
- Diabetic and immunocompromised women are at higher risk for RVVC
- 30–50% of women will have RVVC after maintenance treatment is discontinued
- 10–20% of women with RVVC are infected with *non-albicans Candida*

Source: CDC 2014
Yeast Activity in the GI and Genitourinary Tracts
Recurrent and Resistant Yeast Infection

The gastrointestinal tract flora include many species of *Candida*, as does the vagina.

When microscopic organisms from the GI tract are transferred to the vulvogenital area, these organisms may colonize in the vagina. Some of these are *non-albicans* species, which are less susceptible to commonly prescribed antifungal agents.

Source: Sudbery 2011, Source: Samra-Latif 2014; Mintz 2013
Impact of Antibiotic Use

Exposure to antibiotics may affect the environment of the vagina

- Widespread use of antibiotics may eradicate *lactobacillus* in the GI tract and vagina, changing vaginal pH
- The resulting environment favors recurrence, as *Candida* proliferate and cause infection, primarily by *C. albicans*
- *Candida* become pathogenic as the hyphae of their mycelial form attach to the lining of the vaginal wall, causing infection
- Continued antibiotic use perpetuates recurrent infection in susceptible women

Source: Sudbery 2011
Effect of Fluconazole Use

Routine use of Rx oral fluconazole may create an environment where *non-albicans Candida*, which are less susceptible to azoles, thrive and spread in the vagina

- Oral fluconazole is systemic and achieves minimal tissue concentration at the site of infection, while the rest remains in systemic circulation
- A significant amount of drug remains in the GI tract, reducing *C. albicans* and allowing less susceptible *non-albicans* species to grow
- These *non-albicans* species, such as *C. glabrata*, reach the vagina and are more likely to be fluconazole-resistant
- Renewed systemic antifungal therapy perpetuates drug-resistant species

Source: Mintz 2013; Pfizer Diflucan PI 2014
Susceptibility Trends for *C. albicans* Negatively Impacted by Fluconazole Use

Evolution and selection of vaginal-colonizing *Candida* species with reduced susceptibility could play a critical early role in the development of antifungal resistance among *C. albicans* isolates responsible for refractory candidiasis.

Study looking at MIC\(_{90}\) trends from 1986 to 2007 for 250 *C. albicans* vaginal isolates:

- Miconazole resistance low and unchanged over time (MIC\(_{90}\)=0.06 µ g/mL)
- Fluconazole resistance steadily increased (MIC\(_{90}\): 0.25 µ g/mL → 0.5 µ g/mL)
  - Percent isolates with MIC\(_{90}\) ≥1 µ g/mL and ≥2 µ g/mL both increased from 3% to 9% over this period
  - While not a clinically significant MIC\(_{90}\) increase, the increase in isolates with elevated MIC\(_{90}\) may have clinical relevance, given the achievable concentrations of fluconazole in vaginal fluid (maximum 2 µ g/mL)

Source: Marchaim 2012
Increase in *Non-albicans* Species and Emerging Resistance

Prevalence of *Candida* in patients with recurrent symptoms

In a recent study of 103 patients with confirmed candidiasis infection, 50% (15/30) tested positive for *C. albicans* and 50% (15/30) tested positive for a *non-albicans* species.

*Non-albicans Candida* species frequency (n=21)

Clinically relevant *non-albicans* species seen included *C. glabrata* (CG), *C. parapsilosis* (CP), *C. lusitaniae* (CL), *C. krusei* (CK), and other *non-albicans Candida* species (OC)

Source: Mintz 2013
Fluconazole Resistance and the Impact on Dosing Practices
Fluconazole Use Has Increased Dramatically Over Time

Over 58% of Patients Get >1 Fluconazole Tablet Initially

Number of Fluconazole Tablets Prescribed at Initial Prescription
n=284

- 52% OB/GYN (n=127)
- 37% NP/PA (n=118)
- 8%
- 3%

Call-Backs for Second Tablet
(Percent of times HCP receives a call back when 1 tablet prescribed)
n=213

- 46%
- 23%
- 12%
- 5%
- 6%
- 4%

Average: 20%

Source: IMS 2Q2016, IPSOS Survey August, 2016
Challenges and Approaches in Treating *Non-albicans* Infections
Treatment Implications Associated With Non-\textit{albicans} Species

Management of \textit{non-albicans} Candida is often difficult and optimal treatment is unknown:

- At least 50\% of women positive for \textit{non-albicans} Candida may be minimally symptomatic or asymptomatic
  - \textit{Non-albicans} species have no hyphae; do not cause itching
- First line treatment for \textit{non-albicans} VVC recommended by the 2014 CDC Guidelines is a non-fluconazole azole for a longer duration of therapy (7–14 days), while ISSVD* guidance suggests use of miconazole for suspected \textit{C. glabrata} (the most common \textit{non-albicans} species)
- If recurrence occurs after extended use of topical therapy, then boric acid 600 mg is recommended to treat \textit{non-albicans}

*ISSVD=International Society for the Study of Vulvovaginal Disease
ISSVD App Recommendation for Treatment of *Candida glabrata*, the Most Prevalent *Non-albicans* Species

Use as directed by package labeling. All pharmacies may not carry all products. The creams and suppositories are often oil-based and might weaken latex condoms and diaphragms.

**Topical**
- Miconazole
- Nystatin

**Compounded**
- Boric acid suppositories
- Amphotericin B suppositories
- Flucytosine
- Nystatin suppositories
Miconazole, the active ingredient in MONISTAT®, is the only antifungal azole treatment for *C. glabrata*, the most prevalent *non-albicans* yeast species.

Use this chart to determine the appropriate non-compounded treatment for your patients with yeast infections.

<table>
<thead>
<tr>
<th>Yeast Species</th>
<th>% of Cases</th>
<th>Miconazole</th>
<th>Fluconazole</th>
<th>Terconazole</th>
<th>Clotrimazole</th>
<th>Butoconazole</th>
<th>Ticlozanole</th>
<th>Itraconazole</th>
<th>Nystatin</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>C. albicans</em></td>
<td>70.8%</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>C. glabrata</em></td>
<td>18.9%</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td><em>C. parapsilosis</em></td>
<td>5.0%</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>C. krusei</em></td>
<td>2.0%</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>C. cerevisiae</em></td>
<td>1.5%</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**98.2%** MONISTAT® treats more than **98.2%** of yeast infections.

MONISTAT® provides the broadest treatment of yeast infection occurrences, more than Diffucan®, Gynazole®, and Terazol®.

*Of all non-compounded drug products.*

"Diffucan®" is a registered trademark of Pfizer Inc. "Gynazole®" is a registered trademark of Pfizer Pharma International (P.A.C.), and "Terazol®" is a registered trademark of Johnson & Johnson.

ISSVD app, April 2016
Concerns With Fluconazole Use in Specific Patient Populations

- Drug-to-drug interactions
- Pregnancy
Patients at Increased Risk for Drug-to-drug Interactions

_CDC Vaginitis Guidelines highlight that clinically important drug interactions may occur when fluconazole is administered with other agents._

<table>
<thead>
<tr>
<th>Patient Type</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic Women</td>
<td>• Oral antimycotics such as fluconazole may potentiate hypoglycemic response to oral hypoglycemics (ex., sulfonylureas) by increasing plasma levels of the drugs</td>
</tr>
<tr>
<td>Women on Oral Contraceptives</td>
<td>• A potential for a clinically significant interaction between coadministration of fluconazole and ethinyl estradiol</td>
</tr>
</tbody>
</table>
| Women on drugs metabolized by the CYP450/CYP3A4 system| • Fluconazole is a potent inhibitor of cytochrome P450 and a moderate inhibitor of CYP3A4  
• Moderate inhibitors of CYP3A4 reduce clearance of other drugs by 50%-80% and increase AUC by 2–5 fold  
• Other Drugs: statins, warfarin, phenytoin, cyclosporine and more                                                                                       |

Systemic exposure after one dose of fluconazole can remain 4–5 days after discontinuation of treatment because of a long half-life; approximately 30 hours (range 20–50 hours).

Source: Pfizer Diflucan PI 2014; Sinofsky 1998

Difference in AUC 29% ± 23%
FDA evaluating results of a Danish study that concludes there is a possible risk of miscarriage with use of low dose fluconazole for yeast infections (JAMA; January, 2016)

- Nationwide register-based cohort study in Denmark, 1997–2013, with a cohort of 1,405,663 pregnancies, compared oral fluconazole-exposed pregnancies to unexposed pregnancies and intra-vaginal azole-exposed pregnancies
- Use of oral fluconazole in pregnancy was associated with a possible increased risk of spontaneous abortion compared with risk among unexposed women and women with intra-vaginal azole exposure in pregnancy; risk of stillbirth not significantly increased

Recommendation in FDA’s MedWatch Safety Communication April 26, 2016:

- “Until FDA’s review is complete and more is understood about this study and other available data, FDA advises cautious prescribing of oral fluconazole in pregnancy.”
- “Healthcare professionals should be aware that the CDC guidelines recommend ONLY using topical antifungal products to treat pregnant women with vulvovaginal yeast infections, including for longer periods than usual if these infections persist or recur.”

Healthcare professionals and patients are encouraged to report adverse events or side effects related to the use of these products to the FDA’s Medwatch Safety Information and Adverse Event Reporting Program
Recent Study Results on Miconazole

- Speed of relief vs oral fluconazole
- Efficacy
- Patient satisfaction
ACCELERATE Study Data Presented at ACOG 2015

- In a randomized, double-parallel group study, 300 women were treated with either MONISTAT® 1 Combination Pack or Diflucan® 150 mg.
- There was a statistically significant difference in time to onset of relief of itching, irritation, and overall symptoms between treatment groups.

<table>
<thead>
<tr>
<th>SYMPTOM</th>
<th>MONISTAT® 1 HOURS (N=122)</th>
<th>DIFLUCAN® HOURS (n=135)</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itching</td>
<td>1.0</td>
<td>4.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>Burning</td>
<td>1.0</td>
<td>4.0</td>
<td>0.0894</td>
</tr>
<tr>
<td>Irritation</td>
<td>1.0</td>
<td>4.0</td>
<td>0.0071</td>
</tr>
<tr>
<td>Combined symptoms</td>
<td>4.0</td>
<td>16.0</td>
<td>0.0010</td>
</tr>
</tbody>
</table>

For the individual symptoms, MONISTAT® 1 Combination Pack provided statistically significant faster onset of relief of itching and irritation than systemic Diflucan® oral therapy.

For the combined symptoms, MONISTAT® 1 Combination Pack delivered 4X faster onset of relief of symptoms when compared to systemic Diflucan® oral therapy (4 hours vs 16 hours).

*Kaplan–Meier analysis based on overall time to event curves*

Source: Bachmann 2015
Patient Satisfaction and Symptom Relief with MONISTAT®

94% MONISTAT® relieved my symptoms quickly (n=298)

6%: MONISTAT® did not relieve my symptoms quickly (n=19)

100% I would use MONISTAT® again (n=95)

100% of first-time yeast infection sufferers reported that they would use MONISTAT® again (n=95)
Summary

1. *Candida* resistance to miconazole is low despite widespread use of the drug

2. *Non-albicans* species are becoming more prevalent and are more difficult to treat

3. Miconazole treats more of the most common yeast species than the leading Rx and OTC VVC treatments, including oral fluconazole and topical terconazole, making miconazole a good first-line choice for many patient types

4. Topical agents have been shown to have fewer adverse effects and drug interactions than systemic agents

5. The increasing trend toward resistance is concerning, yet options exist to reduce the impact

*Up next: Quiz on Key Points*
Quiz on Key Points
Question

Use of oral fluconazole is believed to result in:

1. Rapid symptom relief by users
2. Fluctuations in vaginal pH
3. Insignificant change in estrogen and progesterone levels
4. More VVC infections caused by resistant *non-albicans Candida*
Question

Use of oral fluconazole is believed to result in:

1. Rapid symptom relief by users
2. Fluctuations in vaginal pH
3. Insignificant change in estrogen and progesterone levels
4. More VVC infections caused by resistant non-albicans Candida
Question

Which statement(s) about first-line treatment of recurrent and resistant *Candida* infections is/are true?

1. These are difficult to treat
2. They can be treated best with systemic antifungal therapy
3. They can be treated best with topical antifungal therapy
4. Both a and c
Question

Which statement(s) about first-line treatment of recurrent and resistant *Candida* infections is/are true?

1. These are difficult to treat
2. They can be treated best with systemic antifungal therapy
3. They can be treated best with topical antifungal therapy
4. **Both a and c**
Appendix

- Facts about VVC
- Demographics and incidence of VVC
Facts About VVC

$3B

Diagnosis and treatment of VVC is estimated to cost the US $3 billion

VVC

VVC is one of the most common causes of vaginal infection

75% of women have experienced a yeast infection at least once in their lifetime

2 out of 3 women 18 – 49 years old have had a yeast infection

Source: Mintz 2013; Data on file
Demographics and Incidence of VVC

Past Year Incidence
Overall demographics and incidence of yeast infection is primarily in women 18–34 years old

Age Suffered 1st VYI
Most VVC sufferers experience their first infection before the age of 25 years old

VVC infection is highly treatable but a small yet growing number of women have recurrent or resistant *Candida* infections, which are more difficult to manage

Patients at risk for VVC include diabetic, immunocompromised and pregnant women

Source: Data on file
References


ISSVD app; accessed April 26, 2016


MedWatch Safety Communication 4/26/2106


