Incidence of Vulvovaginal Candidiasis (VVC)

Epidemiology
Recurrent Vulvovaginal Candidiasis (RVVC)

• Definition
  – ≥4 episodes of proven VVC/yr

• Occurs in 5% to 8% of premenopausal women in the United States (estimated 3 million to 6 million women)
VVC: Incidence by Age, History

Proportion with VVC (past year)

No history of VVC
VVC in past
VVC ≥4 times in 1 yr

Age in years

18-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65+
### Microbiology of RVVC

<table>
<thead>
<tr>
<th>Yeast Species</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>C. albicans</em></td>
<td>89%</td>
</tr>
<tr>
<td><em>C. glabrata</em></td>
<td>40%</td>
</tr>
<tr>
<td><em>C. guilliermondii</em></td>
<td>1</td>
</tr>
<tr>
<td><em>C. krusei</em></td>
<td>1</td>
</tr>
<tr>
<td><em>C. parapsilosis</em></td>
<td>1</td>
</tr>
<tr>
<td><em>C. tropicalis</em></td>
<td>1</td>
</tr>
<tr>
<td><em>C. lipolytica</em></td>
<td>1</td>
</tr>
<tr>
<td><em>C. zeylananaides</em></td>
<td>1</td>
</tr>
<tr>
<td><em>S. cerevisial</em></td>
<td>1</td>
</tr>
</tbody>
</table>

Sobel JD AAC 47:34, 2003
Several series show ↑ non-\textit{albicans} \textit{Candida} species > 20-30%

General principles:
- Majority due to fluconazole susceptible \textit{C. albicans}
- Culture, speciation mandatory before treatment of RVVC
Pathogenesis of RVVC

- Multifactorial etiology
Pathogenesis of RVVC

Host Factors
- HIV
- Uncontrolled diabetes
- Steroids
- Antibiotics
- Hormone replacement therapy (HRT)

Genetic
- Lewis Nonsecretor Status
- Black
- Familial Polymorphism

Behavioral
- Oral contraceptive
- Sponge/IUD
- Intercourse (frequency/periodicity)
- Orogenital sex

Vulvar Dermatosis

↑ Vaginal Colonization

Microbial (Non-albicans Candida NAC)

Host Factor
- Antibiotics
- Diabetes
- HIV
- Dietary
- Atopy

Idiopathic

Behavioral
- Intercourse
- Orogenital sex

Recurrent Candida Vaginitis

Dietary
- Atopy
Vaginal Yeast Colonization

- Point-prevalence 10-50% - depends upon population
  - 10-15% USA medical students

- Cumulative colonization
  - 1 year study (4 samples) Beigi et al 2004
    - 70% at sometime positive
    - 4% positive at all visits
  - 7 year [HERS] – 14 samples
    - 90% at sometime positive

- Risk factors - recent sexual intercourse
  - Depomedroxyprogesterone
  - Colonization with lactobacilli
  - Not use of antifungals

Beigi et al, AJOG, 104:926, 2004
Host Immune-Reactivity in RVVC

- Innate immunity – TLR, MBL, down-regulatory → preventing microbial proliferation
- Loss of “protective” immune-response i.e. local T-cell hypo-reactivity at mucosal level
  Versus
- Loss of local tolerance i.e. ↑ host hyper-reactivity
Gene Polymorphism in RVVC

- Epithelial cell receptor genes → colonization susceptibility
- Immunoregulation genes → altered immune response
Mannose-Binding Lectin (MBL) and MBL Gene Polymorphism in Recurrent VVC

- MBL functions as an antimicrobial factor
- Reduced ↓ MBL levels in vaginal secretions in RVVC (also serum)
- ↑ polymorphism in MBL genes – in women with RVVC
  - mbl2
  - polymorphism in codon 54
  - ↑ carriage of variant mbl2 codon 54 allele B

Diet, Glucose Tolerance and Diabetes and RVVC

• Anecdotal data that Diet important
• Donders et al. demonstrated that with normal GTT blood sugars significantly ↑ in RVVC
The graph illustrates the plasma glucose levels (mg/dl) over time (minutes) after the intake of 75 g of glucose. The data is divided into two groups:

- **Recurrent vaginal candidiasis (n = 62)**
- **Control (n = 32)**

The time points are 0, 30, 60, and 120 minutes. The significance levels for the differences between the groups are indicated as follows:

- At 30 minutes: $P = 0.05$
- At 60 minutes: $P = 0.009$

The graph shows a significant increase in plasma glucose levels in the recurrent vaginal candidiasis group compared to the control group, particularly at 60 minutes.
RVVC in HIV

- History
- ↑ colonization correlate with ↓ CD4
  - ↑ viral load
- ↑ NAC
- Modest ↑ symptomatic VVC
  - Oral >>>> VVC
  - Why??
- Clinically identical to HIV-negative
- Response to therapy identical
Vaginal Candidiasis + HIV Transmission

In VVC (both asymptomatic colonization and symptomatic infections)

• ↑ numbers of copies of cell-associated, cell-free HIV-1 RNA in cervicovaginal secretions in HIV infected women

• HIV-1 RNA in plasma correlation with HIV-1 DNA

Mostad S 1997; Rasheed S 1998; Iversen A 1998; Debioggi M 1999; Spinillo A 2005
Vaginal Candidiasis + HIV Transmission

Symptomatic VVC

• Clinical pathology – erosive fissures etc facilitate transmission of HIV-1

• Shedding and replication of HIV ↑

Spinillo A 2005
HIV Transmission in VVC

- VVC may facilitate HIV transmission
- ?? justification for treating asymptomatic VVC/recurrent VVC?

Wang CC, JID, 2001
Pathogenesis of RVVC

• Forget the Host!!

What about the yeast?
Fungal Factors in RVVC

- Vaginopathic yeast??
  - Species?
  - Strains?
Fungal Contribution in RVVC

Early studies – No vaginopathic yeast!!
(species, strains)

-- Exp. vaginitis

? Misleading
Are all *Candida* species equally virulent?

1. *Candida parapsilosis*?

2. *Candida glabrata*?

- Animal models?
- Clinical studies
What About Azole Resistance?

- Rare cases of fluconazole resistance in *C. albicans*
  - clinical presentation
  - management
- *C. krusei* – Problem
- *C. parapsilosis* – No problem
- *C. tropicalis* – No problem
- *C. glabrata* - Problem
## Comparative Susceptibility of Vaginal

*C albicans* and *C glabrata* (MIC$_{90}$)

<table>
<thead>
<tr>
<th></th>
<th><em>C albicans</em></th>
<th><em>C glabrata</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampho B</td>
<td>0.25</td>
<td>1.0</td>
</tr>
<tr>
<td>5 FC</td>
<td>1.00</td>
<td>0.125</td>
</tr>
<tr>
<td>Clotrimazole</td>
<td>0.03</td>
<td>2.00</td>
</tr>
<tr>
<td>Miconazole</td>
<td>0.03</td>
<td>0.25</td>
</tr>
<tr>
<td>Butoconazole</td>
<td>0.03</td>
<td>0.50</td>
</tr>
<tr>
<td>Terconazole</td>
<td>0.03</td>
<td>4.00</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>0.03</td>
<td>1.00</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>0.03</td>
<td>2.00</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>0.50</td>
<td>&gt;64.00</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>0.03</td>
<td>1.00</td>
</tr>
</tbody>
</table>
C. glabrata Azole Resistance

- **Frequency**
  - Response ~50%
- **Alternatives**
  - Nystatin
  - Boric acid
  - Flucytosine (topical)
  - Amphotericin B
  - AmB + flucytosine
- **Maintenance therapy?**
C. albicans Azole Resistance

- What have we learned from RVVC studies?
- Baseline MIC’s rare resistance
- Post fluconazole i.e.
  - Rare resistance
  - Rare $\Delta$ in MIC$_{90}$
C. albicans Azole Resistance

However…
# Fluconazole MIC’s + Resistance

<table>
<thead>
<tr>
<th>Resistance</th>
<th>MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistance</td>
<td>( \geq 64 , \mu g/ml )</td>
</tr>
<tr>
<td>S-DD</td>
<td>16-32 ( \mu g/ml )</td>
</tr>
<tr>
<td>Sensitive</td>
<td>( \leq 8 , \mu g/ml )</td>
</tr>
</tbody>
</table>

- Should we apply these MIC’s to vagina??

Rex et al 2001, CLSI
Peak Concentration of Fluconazole in Vaginal Secretions

- After 150 mg dose
  - $4 \mu g/ml$
- MIC$_{90}$ fluconazole 0.5 $\mu g/ml$
- Suggested breakpoint for *C. albicans* in vagina = $1 \mu g/ml$
C albicans: Correlation Between MIC and Outcome of Therapy

- Baseline: 28/393 (7.1%) MIC >1 µg/mL
  - Follow-up data=24
- Comparison of 24 (MIC >1 µg/mL) vs 350 (MIC ≤1 µg/mL)
  - Clinical improvement/cure
    - Day 14: no statistically significant difference (NSD)
    - Day 35: NSD
  - Mycological eradication
    - Day 14
    - Day 35
      \[ P \leq 0.01 \]
- Conclusion
  - Clinical response same
  - Mycological responses ↓ with ↑ MIC

Sobel JD et al, AAC 47:34, 2003
**C albicans**: Correlation Between MIC and Outcome of Therapy (cont’d)

- Majority of patients with clinical failure or relapse did so with a **sensitive** organism.
- Having a less-sensitive *C albicans* increased the likelihood of mycological failure and, hence, persistent colonization.
- Majority of patients with baseline resistance to fluconazole did well clinically but not mycologically—explanation?

Sobel JD et al, AAC 47:34, 2003
On the other hand…
In vivo fluconazole fungicidal not fungistatic
### VAGINAL SIMULANT (VS) MEDIA MIMICS

#### VAGINAL MICROENVIRONMENT

- 3.5 g/l NaCl
- 1.4 g/l KOH
- 0.22 g/l Ca(OH)$_2$
- 18 mg/l bovine serum albumin
- 2.2 g/l 90% lactic acid
- 1 g/l glacial acetic acid (20 mM)
- 0.32 g/l 50% glycerol
- 0.4 g/l urea
- 5 g/l glucose
- pH 4.2
FLZ IS FUNGICIDAL IN VS

1. At pH 4.2, FLZ alone is not fungicidal
2. FLZ is fungicidal at pH 4.2 in VS
3. VS derivatives leaving out acetate are not fungicidal
CONCLUSIONS

• FLZ is fungicidal for *C. albicans* in VS but not other media at pH 4.2

• In VS, FLZ fungicidal at concentrations ≥ 8 µg/ml + reduced viability by 99.9%

• Other Candida species also killed except *C. krusei* and *C. glabrata*
Role of Acetic Acid

• In vitro conditions support the view that FLZ is fungicidal in vaginal candidiasis treatments

• Acetate alone is fungicidal for *S. cerevisiae*, and causes an apoptotic-like death that involves cytochrome c release from mitochondria

• FLZ-induced membrane changes may increase intracellular acetate in *C. albicans*
Summary of MIC Data

- *C. albicans* azole resistance rare
- Breakpoint for resistance in vagina 1µg/ml
- MIC’s do ↑ with prolonged therapy
- MIC’s should not be evaluable according to NCCLS standards
- Optimal method for determining MIC NOT ESTABLISHED.

- CLINICAL IMPLICATIONS
Diagnosis of Symptomatic VVC

• Culture remains Gold Standard

• PCR offers little advantage in symptomatic women (Tabrizi SN 2006)

• Are these false negative cultures?? – Uncommon!

• Under study – several rapid ELISA assays…??

• PCR does pick up *Candida* colonization in culture negative women
Treatment of Acute *Candida* Vaginitis

- Signs/symptoms
- Vaginal culture +
- Therapy

Weeks
Treatment of Acute *Candida* Vaginitis

- **Signs/symptoms**
- **Vaginal culture +**
- **Therapy**

Asymptomatic Mycological Relapse = Colonization
Recurrent *Candida* Vaginitis

Symptomatic Recurrence = Relapse

- **Rx**
  - Signs/symptoms
  - Vaginal culture +
  - Therapy

Weeks

0 1 2 4 8 12
RVVC: Induction and Maintenance Therapy

Signs/symptoms
Vaginal culture +
Therapy

Rx
Fluconazole for the Maintenance/Prophylactic Therapy of Vaginal Candidiasis, Protocols R-0507/R-0508: Time to Clinical Failure (Carried-Forward Analysis) Efficacy (Evaluable Subjects)

Survival distribution function (%)

Time to failure (mo)

Sobel JD NEJM 2003
Fluconazole for the Maintenance/Prophylactic Therapy of Vaginal Candidiasis, Protocols R-0507/R-0508: Time to Mycological Failure (Carried-Forward Analysis) Modified Intent-to-Treat Subjects

Sobel JD NEJM 2003
RVVC – Why Do Some Women Remain in Remission?

- After cessation of the fluconazole ~50% remain in clinical remission
  - culture negative
  - culture positive
- ~50% recur with symptomatic VVC
  - usually identical strains
  - sensitive MIC
Fluconazole Adaptive Strains of *C. albicans*

- Low conventional MIC’s
- Genetically separate
- Resistant to cidal-activity of fluconazole + acetic acid
What To Do With Multiple Recurrences of Fluconazole?

- Long term maintenance fluconazole, ? voriconazole
  
  or

- Intensive daily antifungal therapy
  
  or

- Probiotics (↑ acetic acid in vivo)
  
  or

- Desensitize
What To Do With Breakthrough Symptoms While on Fluconazole Maintenance?

- Confirm symptoms due to breakthrough infection
- Twice weekly fluconazole 100 mg