Chronic Vulvovaginal Candidiasis

Definition
Management
Long Term Outcomes
Learning objectives:

1. Diagnose chronic vulvovaginal candidiasis
2. Manage in short and long term

No conflict of interests to declare
Off-label medication usage
Virtually every patient I have seen with a vulvar complaint was either self-diagnosed or diagnosed by a pharmacist or primary care physician with “thrush” initially, no matter what was wrong with them.
Vulvovaginal Candidiasis (VVC)

- Common vulvovaginitis causally associated with *Candida* species in vagina
  - 95% azole-sensitive *C. albicans*, 5% *C. glabrata* and others
- Two currently recognized types of vulvovaginal candidiasis (VVC)
  1. **Acute (AVVC)**: Intermittent/ 70% lifetime prevalence
  2. **Recurrent (RVVC)**: Defined 3-4 proven attacks/year 5% prevalence
- The definition of RVVC was by consensus about 20 years ago and was not based on any data or study.
- Prevalence is an estimate: meaningful epidemiology impossible
What I do not see in my clinic

› I don’t see AVVC => pharmacist, primary care

› I rarely see RVVC => pharmacist, primary care
What I do see in my clinic

› Patients with a **chronic unremitting** vulvovaginitis with a pre-menstrual exacerbation
› Otherwise completely healthy young women with normal immunity
› Itch, pain, discharge, dysuria, dyspareunia
› Huge effect on quality of life (Mean DLQI 15)
› Many do **NOT** have +ve culture at the time I meet them, despite severe symptoms
› Even though the vulva is involved, the organism, when isolated, is in the vagina
› Excellent response to oral anti-fungal treatment
› Cessation of treatment => relapse

› Let’s call this **Chronic Vulvovaginal Candidiasis (CVVC)**
The course of the disease

This has never been documented in any study but anecdotally...

› Does not occur in childhood
› May appear for the first time around menarche
› Emerges as a problem with first sexual activity
› Most severe in 20’s
› Often remits with pregnancy
› Can sometimes appear for the first time after a pregnancy
› Always remits during lactation
› Improves in mid-life
› Flares pre-menopause
› Remits at menopause
› Re-appears with HRT
Case 1: 21 year old university student

- Itch, soreness, swelling, splitting, discharge, dysuria
- Started after first sexual activity at 19
- Dyspareunia is ruining her life: miserable
- DLQI 22
- Worse pre-menstrual and after antibiotics
- Swabs sometimes positive for *C. Albicans* but not consistently
- Uses lots of antifungals intermittently
- Symptoms almost better with topical and oral antifungals but rapidly recur
Case 2: 52 year old teacher post-menopause on HRT for last 4 years

- As a young woman recalls many attacks of “thrush”
- Menopause 5 years ago: commenced estrogen HRT and can’t cope without it
- For the last year itch, dyspareunia, erythema
- No discharge
- Vaginal swab +ve for *C. albicans*
- Minimal response to antifungals
- DLQI 18
Candida as a pathogen

- Candida is a commensal of the GIT
- Classically transformation from yeast to hyphal form is associated with pathogenicity
- Systemic pathogen in immune suppression, high mortality
- Local pathogen in diabetes, SGLT2 inhibitors
- Biofilm formation: dentures

**But the majority of patients with CVVC are healthy women**
What does previous research tell us?

- Not related to virulence of organism
- Not related to immune deficiency
- Not related to drug resistance
- Not related to biofilm formation
- Not transmissible
- Not related to pH (normal)
- Mucosal biopsies show spongiosis and inflammation but PAS is –ve: organism is not present
What do healthy women with CVVC have in common?

- **Estrogen**: Not before menarche or after menopause, cyclic symptoms, HRT

- **Vaginal micro-environment**: Exacerbation with antibiotics, oral mucosa not involved

- **Genetics**: family history, rarely seen in Asian women, atopy

- *It is host factors, not the organism that determines this condition*

- **But**

- *We still don’t know the exact pathogenesis*
Intravaginal challenge using *C. albicans* in healthy humans
Exaggerated inflammatory vaginal response to *Candida* => symptoms
Lack of symptoms = lack of inflammatory response
Those with a response had a history of VVC

Vaginal candidiasis is not an immune deficiency
Susceptible persons lack anti-Candida activity and mount an exaggerated immune response

Intolerance of a commensal organism which is tolerated by most
Variable : difference in threshold for response?
How does this work?

Candida

Vaginal epithelium

Inflammatory response
Let’s look at innate immunity

- Toll like receptors (TLR) are critical to innate immunity and implicated in auto-immune disease
- They are pattern recognition receptors
- TLR exist on keratinocytes on the wall of the vagina
Candida

Pro-inflammatory reaction
Cytokines IL 17, 22, 23
Interferon-gamma

Vaginal epithelium

Toll-like receptor

Inflammatory response
Let’s look at why estrogen is important

› Candida has a receptor for Estrogen
› ER-α is the major estrogen receptor in vulva and vagina (but not mouth)
› Toll like receptors are modulated by ER-α
› Deficiency of ER-α in mice protects them from lupus
Candida inflammatory reaction

Cytokines IL 17, 22, 23

Interferon-gamma

Vaginal epithelium

Inflammatory response

Pro-inflammatory reaction
Cytokines IL 17, 22, 23
Interferon-gamma

Toll-like receptor

ER-α

Estrogen
Polymorphisms of TLR result in auto-immune disease

Polymorphisms of TLR 2 have been found in patients with Candidiasis
(Rosentul C et al Frontiers in Microbiology Sept 2014)

TLR2 and 4 polymorphism found in atopy (Candida patients more likely to be atopic)
(Korman MSD et al Allergy 2009 64:636)
Is the site of pathology the TLR, modified by ER-α?

Candida

Vaginal epithelium

Inflammatory response

Pro-inflammatory reaction
Cytokines IL 17, 22, 23
Interferon-gamma

Toll-like receptor

ER-α

Estrogen
Yet they respond to fluconazole: why?

- Simple answer is false -ve from antifungal medications
- BUT
- Could fluconazole be targeting something that is not able to be cultured?
- Could this entity be at the TLR?

- Yes! Azoles modify the TLR (Mihu R, Pattabhi R, Nosanchuck JD Frontiers of Microbiol 2014)
- BUT
- Maybe they just keep the *Candida* levels too low to register with the TLR
Back to the macroscopic world.
How do you diagnose CVVC without a +ve culture?

- Study group n=50 (CVVC) compared to age-matched controls (psoriasis)
- Diagnostic criteria determined statistically (sensitivity, specificity, predictive values)
- Studied forward on 163 women

Hong E, Dixit S, Fidel P, Bradford J, Fischer G. “Vulvovaginal Candidiasis as a Chronic Disease: diagnostic criteria and definition” JLGTD 2013
### Chronic Vulvovaginal Candidiasis Diagnostic Criteria

**Diagnostic**: One major + 5 minor criteria  
**Presumptive**: One major + 3-4 minor criteria

<table>
<thead>
<tr>
<th>Major Criterion</th>
<th>Minor Criteria</th>
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<tbody>
<tr>
<td>Chronic non-erosive, non-specific vulvovaginitis</td>
<td>• Positive vaginal swab either on presentation or in the past when symptomatic</td>
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<tr>
<td></td>
<td>• Soreness</td>
</tr>
<tr>
<td></td>
<td>• Cyclicity</td>
</tr>
<tr>
<td></td>
<td>• Dyspareunia</td>
</tr>
<tr>
<td></td>
<td>• Previous response to antifungal therapy (even if incomplete)</td>
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<td></td>
<td>• Exacerbation with antibiotics</td>
</tr>
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<td></td>
<td>• Swelling</td>
</tr>
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<td></td>
<td>• Discharge</td>
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Letter to the editor of JLGTD:

This doesn’t obey Koch’s postulates!

Our response:

Exactly!!
Many previous studies using fluconazole, 150mg weekly

› Theory: If this is immunologically mediated rather than infective it will respond better to daily Rx

› 91 patients
› 48% of these patients had a negative culture when first seen
› 25% had never had a +ve culture

› 82/91 (90%) completed course of treatment with fluconazole 50mg daily
› Outcome measures: DLQI and Graded Erythema (VAS)
Grade of Erythema Visual Analogue Scale (VAS)

<table>
<thead>
<tr>
<th>Grade 0 Erythema</th>
<th>Grade 1 Erythema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2 Erythema</td>
<td>Grade 3 Erythema</td>
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</tbody>
</table>
## Results: Symptoms Pre- and Post-Treatment

<table>
<thead>
<tr>
<th>Clinical Finding</th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequency</td>
<td>Percentage (%)</td>
<td>Frequency</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>71</td>
<td>86.6</td>
<td>17</td>
</tr>
<tr>
<td>Soreness</td>
<td>64</td>
<td>78.0</td>
<td>3</td>
</tr>
<tr>
<td>Swelling</td>
<td>56</td>
<td>68.3</td>
<td>2</td>
</tr>
<tr>
<td>Discharge</td>
<td>53</td>
<td>64.6</td>
<td>8</td>
</tr>
<tr>
<td>Cyclicity</td>
<td>43</td>
<td>52.4</td>
<td>10</td>
</tr>
</tbody>
</table>

*McNemar’s Test
Change in DLQI and VAS Scores Pre- and Post-Treatment

› Change in DLQI score: Mean 11.6 95% CI [10.1, 13.0]  p<0.001

› Change in objective grades of erythema VAS  p<0.001

**Paired Samples T-Test  ***Wilcoxon Signed Ranks Test
15.9% of patients reported side effects
- 3.7% of these had to cease fluconazole treatment
- Adverse effects requiring cessation of fluconazole therapy
  - Rash
  - Diarrhoea
- No patient had any LFT abnormalities
Fluconazole is highly successful in the short term.

But studies say it’s a “failure” because patients relapse after 6 months.

- This is using an infection paradigm….so the assumption is cure
- This is a chronic, probably genetic condition
  - Immunologically mediated
  - Control => keep *Candida* levels below the threshold for symptoms
  - This means ongoing suppressive therapy
208 patients: previous recovery. Contacted by phone or email.

Maintenance regime

- 98% of patients were still using antifungal treatment up to 8 years later
- Doses variable
- 46.2% of patients required oral fluconazole 50mg twice weekly
- 205 patients continued to require daily oral fluconazole 50mg (29.2%) or 100mg (11.1%)
- 3 remitted: one pregnant, two menopause

Mean duration of follow up – 26.2 months (range, 5 months to 8.5 years)
95% tolerated fluconazole long term
Fluconazole did not cause drug induced hepatitis in any patient

This is an off label use
In Australia cost is $A30 per month

Patients titrated dose to response
Increased to daily if relapse, antibiotics or travel or any other known trigger

Vulva may always look red even when asymptomatic
Available medications

- Topical azoles
- Nystatin
- Boric acid
- Topical amphotericin and flucytosine
- Fluconazole ✅: outstandingly safe, effective and inexpensive.
- Itraconazole
- Ketoconazole ☹️

- Case series of 13 patients with levonorgestrel-containing IUD
- CVVC started after insertion of device
- 6 had device removed
- 5 remitted
- 1 needed ongoing treatment

- ? Biofilm formation
- ?Hormonal effect
What happened to Case 1: Pre-menopausal woman

- Fluconazole 50mg daily for 12 weeks
- DLQI dropped from 25 to 5
- All symptoms resolved but ongoing dyspareunia
- Fluconazole continued while undergoing physiotherapy for pelvic floor spasm
- Returned at 24 weeks, asymptomatic
- Fluconazole reduced to 50mg twice a week
- Increased to daily when on antibiotics
- Continues to take fluconazole 3 years later with no problems
What happened to Case 2: Post-menopausal woman

- HRT ceased
- Fluconazole 50mg daily for 6 weeks
- Returned asymptomatic but now has vaginal dryness and wants to re-start HRT
- HRT re-started under fluconazole cover 50mg twice a week
- Continued for 3 years then ceased HRT
- No further fluconazole required
Questions asked by patients

› Should I be on a special diet?
› Should I take probiotics?
› Does my partner need treatment?
› Can I stay on fluconazole?
› Will this harm my baby?
› Will the fluconazole stop working?
Practical advice to patients

› Titrate your dose to your symptoms
› Take fluconazole daily if you are on antibiotics
› Know your triggers and avoid them (eg long-haul flights, panti-liners, tight jeans)
› Avoid IUD
› Stop oral medications before attempting to get pregnant
› Avoid things that irritate your skin: soap, pads, G-strings
Candida is a normal commensal of gut and vagina
Vulvovaginitis from this commensal organism is host dependent
It is probably a genetic tendency
It behaves like an auto-immune response modulated by estrogen

Safest management => suppress the antigen for as long as the patient remains susceptible
In summary: a paradigm shift

- Patients with CVVC experience significant impact on quality of life
- A continuous low dose oral fluconazole treatment regime results in a significant improvement in quality of life measured by DLQI scoring
- Majority of patients require long-term, on-going oral azole therapy to maintain symptom control at mean 2 years of follow up
- Majority of patients tolerate treatment with minimal adverse effects
- Long term liver toxicity is rarely a problem

- Many patients use the words “life-changing”
Thanks to my co-workers Prof Paul Fidel Jnr, Dr Jennifer Bradford, Dr Esther Hong and Dr Yvonne Nguyen