Vulvovaginal Candidiasis as a Chronic Disease

Definition
Impact of Oral Fluconazole Therapy
Long Term Outcomes
Learning objectives:

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

No conflict of interests to declare and no association with industry
How common is ‘thrush’?

Virtually every patient I have seen with a vulvar complaint either self-diagnosed or was diagnosed by the pharmacist or primary care physician as having “thrush” initially, no matter what was wrong with them.
Vulvovaginal Candidiasis (VVC)

- Common vulvovaginitis
- Causally associated with presence of *Candida* species in the vagina

Two currently recognized types of vulvovaginal candidiasis (VVC)

1. Acute (AVVC): 70% prevalence
2. Recurrent (RVVC): Defined as 4 proven attacks/year 5% prevalence

The definition of RVVC was by consensus about 20 years ago
Who gets VVC?

- Classically this is secondary to something
- Immunosuppressed
- Long term antibiotics
- Mirena
- Diabetic
- NOT children
What I see in my clinic

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

› I rarely see RVVC=> pharmacist, primary care

› Patients with a chronic unremitting usually cyclical vulvovaginitis
› Otherwise completely healthy women with normal immunity
› Itch, pain, discharge, dysuria, dyspareunia
› Huge effect on quality of life (Mean DLQI 15)
› Many do not have +ve culture
› But they get better with anti-fungal treatment
› When the treatment is ceased their symptoms recur

› Let’s call this Chronic Vulvovaginal Candidiasis
Typical case: 21 year old university student

- Itch, soreness, swelling, splitting, discharge, dysuria
- Started after first sexual activity at 19
- Dyspareunia
- Worse before periods and after antibiotics
- Swabs sometimes positive for *C. Albicans* but not consistently
- Symptoms almost better with topical and oral antifungals but rapidly recur
- Uses lots of antifungals
- Miserable and depressed
Another typical scenario: 52 year old teacher post-menopause, on HRT for last 4 years

- For last year itch, dyspareunia, erythema
- No discharge
- Swab +ve for *C. albicans*
- No response to antifungals
- Continues to take HRT (tibolone) and not keen to stop
Candida is a commensal. Commensals are normally opportunistic pathogens in the immunosuppressed.

What is going on with these young healthy women?

- Not related to virulence of organism
- Not related to immune deficiency
- Not related to drug resistance

- Is related to oestrogen => not before menarche or after menopause
- Is related to antibiotics
- Often runs in families
- Is rarely seen in Asian women
Intravaginal challenge using *C. albicans* in healthy humans

Vaginal candidiasis is not an immune deficiency

Exaggerated inflammatory vaginal response to *Candida* => symptoms

Lack of symptoms = lack of inflammatory response

Those with a response had a history of VVC

Susceptible persons lack anti-Candida activity and respond +++

Even in absence of +ve culture there can be ++ symptoms

Intolerance of a commensal organism which is tolerated by most

?Genetic: it can run in families

Variable: difference in threshold for response?
FIG 1 Anatomical defenses and host damage associated with the various manifestations of candidiasis. The illustration shows the diverse and site-specific diseases caused by *C. albicans*, highlighting the disease pathogenesis in each case and site-specific host immune responses.
How do you diagnose something that looks non-specific without a test?

- 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
How do you diagnose when swab is –ve?
CVVC: Diagnosis: MPhil Dr Esther Hong

<table>
<thead>
<tr>
<th>Chronic Vulvovaginal Candidiasis Diagnostic Criteria</th>
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<tbody>
<tr>
<td><strong>Diagnostic:</strong> One major + 5 minor criteria</td>
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<tr>
<td><strong>Presumptive:</strong> One major + 3-4 minor criteria</td>
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<table>
<thead>
<tr>
<th><strong>Major Criterion</strong></th>
<th><strong>Minor Criteria</strong></th>
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<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>
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<td>• Cyclicity</td>
</tr>
<tr>
<td></td>
<td>• Dyspareunia</td>
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<td>• Previous response to antifungal therapy (even if incomplete)</td>
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<td></td>
<td>• Exacerbation with antibiotics</td>
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<td>• Swelling</td>
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<td>• Discharge</td>
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Short term treatment

Many previous studies using fluconazole, 150mg weekly

- Theory: If this is immunologically mediated it will respond better to daily Rx

- Before-After study conducted between January 2014 and September 2015
- 91 patients recruited from vulvar dermatology disease clinic in public and private settings
- 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)

Grade 0 Erythema

Grade 1 Erythema

Grade 2 Erythema

Grade 3 Erythema
## Results: Symptoms Pre- and Post-Treatment

<table>
<thead>
<tr>
<th>Clinical Finding</th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
<th>Significance</th>
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<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>
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*McNemar's Test*
Change in DLQI and VAS Scores Pre- and Post-Treatment

› Initial DLQI score: Mean 15.0 (Range 2-28)

› Follow up DLQI score: Mean 3.4 (Range 0-18)

› Change in DLQI score: Mean 11.6 (95% CI [10.1, 13.0]) (Range 0-25) p<0.001

› Difference between objective grades of erythema VAS score pre- and post-treatment compared

  - Improvement in grade of erythema 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

- Is insulin therefore a failure in managing diabetes?

- This is a chronic, possibly genetic condition
- It is not an infection
- Immunologically mediated
- Best way to control it is to keep *Candida* levels below the threshold for symptoms
- This means ongoing suppressive therapy
How do you keep these patients asymptomatic?

› Long term outcome study

› 208 patients: previous recovery. Contacted by phone or email.

› Maintenance regime
  - 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)

› Nguyen et al Australas J Dermatol 2016
98% still using antifungal treatment, mainly fluconazole, up to 8 years later
Vulva may always look red even when asymptomatic
Doses varied from prn to daily
46.2% 50mg twice a week
Fluconazole did not cause drug induced hepatitis in any patient
95% tolerate fluconazole long term
This is an off label use
In Australia cost is $A30 per month

Patients titrate dose to response
Increase to daily if relapse, antibiotics or travel
Candida is a normal commensal of gut and vagina
Vulvovaginitis from this commensal organism is host dependent
It behaves like a hypersensitivity response to something that is a normal part of the human body
The threshold for that response is genetic
In order to suppress the response you need to suppress the antigen for as long as the patient remains hypersensitive
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
› Many patients use the words “life-changing”
› 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
› Abnormal LFT’s were not seen in short or long term treated patients
Thanks to my co-workers Dr Jennifer Bradford, Dr Esther Hong MPhil and Dr Yvonne Nguyen MPhil