Management of vaginal discharge

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Vaginal infections

- Bacterial vaginosis
- Candida infections
- Trichomonas vaginalis

Prevalence varies from country to country but rank order remains the same
Prevalence of bacterial vaginosis

Commonest cause of abnormal discharge in women of child bearing age

In UK

- General practice: 9%
- Antenatal clinic: 15%
- Pre TOP clinic: 15-30%
- Attending STI clinic: 25-35%

Rates much higher in Africa

- Rural district, Uganda: 51%

Aetiology of Bacterial Vaginosis

- Gardner and Dukes discovered *Gardnerella vaginalis* in 1955. They hypothesised it was the specific sexually transmitted aetiological agent of BV but other bacteria isolated in BV.
- Defined as overgrowth of *G. vaginalis*, genital mycoplasmas and anaerobic bacteria, which replace the lactobacilli of the vagina.
- The bacteria are increased 100 times normal
- Symbiotic relationship between *P. bivia* and *G. vaginalis*
- Bacterial 16S ribosomal DNA amplification identified organisms very specific for BV
- Detection of *Megasphaera*-1 or BVAB 1, 2, 3
  - Sensitivity 96%, specificity 94% compared with Gram stain
    - Fredricks et al. *NEJM* 2005
- *Atopobium vaginae*, BVAB-1, BVAB-3, highly specific for BV - NPV >92%

But no prime aetiological bacteria identified – cause still unknown
Aetiology of Bacterial Vaginosis

Discovery of biofilms on vaginal biopsies
40 women without BV, 20 women with BV
• Loosely dispersed bacteria (*Lactobacilli* and aerobes) in those without BV
• Dense biofilm of *G. vaginalis* in women with BV
• *A. vaginae* also present in 80% of biofilms

Only *G. vaginalis* developed a biofilm specific to BV

*G. vaginalis* is the adherent Gram-negative bacteria on clue cells

Role of *Gardnerella vaginalis* in the pathogenesis of BV: a conceptual model

**BV and sexual transmission**

Women with BV are significantly more likely to:
• Have earlier first sexual intercourse
• Have greater number of lifetime male and female sexual partners
• Have a new sexual partner
• Have chlamydia and gonorrhoea
BV and sexual transmission

Women with BV are significantly more likely to:

- Have earlier first sex and greater number of lifetime male and female sexual partners
- Have a new sexual partner
- Have chlamydia and gonorrhoea

Yet 6 RCTs of oral metronidazole, tinidazole and clindamycin treatment of male sexual partner - no improvement in cure rate, or reduction in recurrence rate

But all 6 had significant flaws

Antibiotic treatment for the male sexual partners of women with bacterial vaginosis does not increase the rate of cure or reduce rate of recurrence


BV and sexual transmission

BUT in WSW significant concordance of vaginal flora in couples

43% Berger 1995
95% Marrazzo 2002
87% Evans 2008

Monogamous WSW couples frequently have identical lactobacilli WGS

77% Marrazzo 2009

Incubation period for incident BV in WSW estimated 4 days – consistent with other bacterial STIs

Muzney 2019

Original experiments by Gardner and Dukes:
11 of 15 women inoculated with vaginal material from infected women developed clinical features of BV

Only 1 of 13 women inoculated with G vaginalis from culture developed clinical features of BV

**BV and sexual transmission**

No prevalent or incident BV in young women without coital or non-coital sexual experience  
*Fethers et al. J Infect Dis 2009 & Sex Transm Dis 2010*

Several BVAB rare or absent in sexually unexposed women  

Recurrence 2-3 fold higher if same regular sex partner after treatment compared with change in partner  
*Bradshaw et al. J Inf Dis 2006*

Male contacts of women who developed BV had significantly more female partners in last 30 days than those without BV  
*Schwebke et al. Sex Transm Dis 2005*

Consistent condom use strongly protective against BV  
Ad OR 0.37 (95% CI 0.20-0.94)  *Hutchinson et al. Epidemiology 2007*

**Symptoms and signs of BV**

About 50% of women are asymptomatic  
Main symptoms:  
- increased vaginal discharge  
- malodour  
Odour worse during menses and after vaginal ejaculation
Diagnosis of BV
Amsel’s clinical diagnosis

Homogenous discharge

Measuring vaginal pH

Amine whiff test

Mix vaginal discharge with 10% KOH to detect fishy-smelling amines

Clue cells

Examine a “wet-prep” slide microscopically

Three of the following should be present:
- thin homogenous discharge
- vaginal pH >4.5
- amine odour with potassium hydroxide
- clue cells on microscopy

Causes of raised vaginal pH

- Premenarche or postmenopausal
- Menses
- Cervical mucus
- Post-coital
- Bacterial vaginosis
- Trichomonas vaginalis
**Diagnosis of BV**

**Gram-stained vaginal smear**

Normal vaginal flora  
Bacterial vaginosis

Gram-stained vaginal smear considered ‘Gold-standard’

**Swab from mid-low lateral walls more sensitive than fornix**

_Azevedo et al J Low Genit Tract Dis 2019_

**Gram-stain smear more sensitive**

Compared with Gram-stained smear:

Amsel’s 3/4 sensitivity 72%  
_Singh et al Sex Transm Infect 2012_

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**Treatment of bacterial vaginosis**

Treatment is recommended in:

- symptomatic women
- women with PID
- those undergoing gynaecological surgery
- those undergoing TOP
**Treatment of bacterial vaginosis in UK**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cure rate at one month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole 400mg bd for 7 days</td>
<td>78-88%</td>
</tr>
<tr>
<td>2gm single dose</td>
<td>72-73%</td>
</tr>
<tr>
<td>Vaginal gel 5gm for 5 days</td>
<td>71-79%</td>
</tr>
<tr>
<td>Clindamycin 300mg bd for 7 days</td>
<td>94%</td>
</tr>
<tr>
<td>Vaginal cream 5gm for 7 days</td>
<td>71-86%</td>
</tr>
<tr>
<td>Tinidazole 2gm single dose</td>
<td>71-84%</td>
</tr>
</tbody>
</table>

Clindamycin and metronidazole same failure rates irrespective of regimen  
*Oduyebo et al. Cochrane Database of Systematic Reviews 2009*

Clindamycin with metronidazole versus metronidazole alone – cure rate and recurrence rates the same 
*Bradshaw et al. PLoS One 2012;7:e34540*

2 week course metronidazole higher cure rate at 7 days but relapse rate the same. Combination with azithromycin gave no improvement  
*Schwebke et al. Clin Inf Dis 2007*

**Frequency and risks of recurrent BV**

121 women successfully treated; Follow up for 12 months

Recurrence rates: 23% 1 month  
43% 3 months  
58% 12 months  
*Bradshaw et al. J Inf Dis 2006*

Recurrent BV associated with:  
- Raised pH (present 65% with recurrence v 25% controls) 
- Abnormal Gram-stain (56% v 11%)  
*Cook et al. J Clin Microbiol 1992*

Biofilm forming *G. vaginalis* more likely to persist after treatment  
*Swidsinski et al. Am J Obstet Gynecol 2008*

WSW Risks for incident BV:  

<table>
<thead>
<tr>
<th>Bacterial Species</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>G. vaginalis</em></td>
<td>3.9</td>
</tr>
<tr>
<td><em>A. vaginae</em></td>
<td>4.2</td>
</tr>
<tr>
<td>BVAB-1</td>
<td>6.3</td>
</tr>
<tr>
<td><em>Megasphaera</em>-1</td>
<td>11.5</td>
</tr>
<tr>
<td>BVAB-2</td>
<td>18.2</td>
</tr>
<tr>
<td><em>L. crispatus</em></td>
<td>0.18</td>
</tr>
<tr>
<td>BVAB-3</td>
<td>12.6</td>
</tr>
</tbody>
</table>

*Marrazzo et al. PLoS One 2010*
Managing recurrent BV

**Contraception and BV**

**IUD Predisposes whereas COCP and condoms protective**

Increase in BV following IUD insertion:

RR 2.8 (95% CI 1.5-5.1) \(\text{Avonts et al. Sex Transm Dis 1990}\)

From 27% baseline, 35% 30 days, 40% 90 days, 49% 180 days

\(P = .005\) \(\text{Bassis et al. Contraception 2017}\)

Consistent condom use strongly protective against BV:

OR 0.37 (95% CI 0.20-0.94) \(\text{Hutchinson et al. Epidemiology 2007}\)

Meta-analysis of hormonal contraception:

Incident BV RR 0.82 (0.72-0.92) \(\text{Vodstrcil et al. PLoS One 2013}\)

Recurrent BV RR 0.69 (0.59-0.91) \(\text{Riggs et al. Sex Transm Dis 2007}\)

Recurrent bacterial vaginosis

The low pH is attributed to lactic acid production by lactobacilli and vaginal epithelial cells

Semen and menses raise the vaginal pH, and both are known predisposing factors for BV

Optimum pH for *Prevotella bivia* and *Gardnerella vaginalis* to grow is pH 6 - 7

Both are susceptible to low pH and die at pH 4.5

At pH 4.5 lactobacilli proliferate but anaerobes and *Gardnerella vaginalis* inhibited 

\(\text{Klebanoff et al. J Infect Dis 1991}\)
Prevention of recurrent BV
Maintain vaginal pH at 4.5

RCT of vaginal lactate gel 3 days after menses for 6 months to BV free at 6 months: 88% versus 10% placebo
High drop out rates - ‘More intensive treatment would probably be better’  
Andersch et al. Gynecol Obstet Invest 1990

Before/after study using vaginal acidifying gel to prevent BV
BV free at 6 months 52.5%
Before acidifying gel 4.4 recurrences per woman/year
After acidifying gel 1.5 recurrences per woman/year
Wilson et al. Int J STD AIDS 2005

Lactic acid gel available as Relactagel, Balance Activ, Canesbalance

Prevention of recurrent BV
Reducing overgrowth of BV organisms

RCT in 112 women, twice weekly metronidazole vaginal gel or placebo for 16 weeks, 28 week follow up
At 16 weeks ITT RR 0.43 (95% CI 0.25-0.73)
At 28 weeks ITT RR 0.68 (95% CI 0.49-0.93)
BV free at 28 weeks 34% and 18%
Candida significantly more common with MTZ gel

RCT in 234 women: vaginal pessaries metronidazole 750mg plus miconazole 200mg or matched placebo for 5 nights per month for 12 months
Evaluated 2-monthly
BV episodes 21.2% v 32.5%; RR 0.65 (95%CI 0.48-0.87)
VVC episodes 10.4% v 11.3%; RR 0.92 (95% CI 0.62-1.37)
Mc Clelland et al. J Infect Dis 2015
Prevention of recurrent BV
Reducing overgrowth of BV organisms

RCT in 310 women, monthly oral metronidazole 2g for 1 year as part of treatment of vaginal infections study
BV Hazard ratio at 12 months 0.55 (95% CI 0.49-0.63)

Mc Clelland et al. J Infect Dis 2008

Sub-analysis of same study; 105 (34%) had BV at enrolment
BV incidence with baseline BV 294/100py in intervention arm
with baseline BV 522/100py in placebo arm
With BV at baseline: BV Hazard ratio 0.55 (95% CI 0.41-0.76)
BV incidence without baseline BV 141/100py in intervention arm
without baseline BV 202/100py in placebo arm
No BV at baseline: BV Hazard ratio 0.71 (95% CI 0.47-1.09)

Mochache et al. Sex Transm Dis 2014

Recurrent BV and psychosexual impact

Semi-structured interviews - telephone or face-to-face
30 women with between 2-35 recurrent BV episodes in past
All were symptomatic with BV recurrences

32% no great impact on lives with recurrent BV
68% moderate or severe impact – associated with frequency of recurrences and severity of symptoms

Malodour the most distressing symptom
Oral sex avoided, or sexual abstinence because of the smell
Most felt embarrassed, self-conscious and uncomfortable
Frustration at lack of control with recurrent BV

Bilardi et al. PLoS One 2013
### BV and acquisition of STIs

**Increased acquisition with BV of:**

<table>
<thead>
<tr>
<th>STI</th>
<th>Fold Change</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>GC and CT</td>
<td>1.5-2.0 fold</td>
<td>Brotman et al. J Infect Dis 2010</td>
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<tr>
<td>TV</td>
<td>9-fold</td>
<td>Rathod et al. Sex Transm Dis 2011</td>
</tr>
<tr>
<td>HPV</td>
<td>1.2 fold</td>
<td>King et al. Infect Dis O&amp;G 2011</td>
</tr>
<tr>
<td>CIN</td>
<td>1.5 fold</td>
<td>Gillet et al. PLoS One 2012</td>
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**TV**

9-fold

Rathod et al. Sex Transm Dis 2011

**HPV**

1.2 fold

King et al. Infect Dis O&G 2011

**CIN**

1.5 fold


**Longitudinal study of risks of HSV-2 acquisition:**

Risk of acquiring HSV-2 with BV:

- Ad HR 2.1 (1.0-4.5)  

**BV risk factor for HSV-2 shedding:**

- Adjusted OR 2.3 (1.3-4.0)  
  Cherpes et al. Clin Inf Dis 2005

**Enhanced acquisition and shedding of HSV-2 may be a major cofactor in BV/HIV increased acquisition**

### BV and acquisition of STIs

**Increased acquisition with BV:**

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<td>Rathod et al. Sex Transm Dis 2011</td>
</tr>
<tr>
<td>HSV-2</td>
<td>2.1 fold</td>
<td>Cherpes et al. Clin Inf Dis 2003</td>
</tr>
<tr>
<td>HSV-2 shedding</td>
<td>2.3 fold</td>
<td>Cherpes et al. Clin Inf Dis 2005</td>
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**Treatment then prophylaxis asymptomatic BV versus observation**

- Prophylaxis: 1.58 (95% CI 1.20-1.87) ppys  
- Observation: 2.29 (95% CI 1.95-2.63) ppys

**Treatment then RCT monthly metronidazole gel or placebo**

Almost 50% reduction of CT/NG/MG over 12 months with monthly presumptive treatment  

Balkus et al. JID 2016
BV and HIV acquisition

Meta-analysis of 23 studies; 30 739 women
HIV incidence with BV RR 1.6 (95% CI 1.2-2.1)
  - low HIV risk RR 2.3 (95% CI 1.7-3.2)
  - high HIV risk RR 1.4 (95% CI 1.5-1.8)
Risk similar to that for non-ulcerative STIs
BV prevalence 30% with RR 1.6; Attributable risk 15%

Atashili et al. AIDS 2008

HIV positive women:
  Prevalence of BV OR 1.29 (1.08-1.55)
  Persistence of BV OR 1.49 (1.18-1.89)
Immunocompromised women had more severe BV on Gram-stain
OR 1.50 (1.12-2.00)


BV and HIV transmission

Heterosexual transmission
Prospective study of 2236 HIV-1+ve women and uninfected male partners (part of large HIV/HSV trial)
50 incident infections (sequencing proven transmissions)
• HIV-1 incidence with BV 2.91/100 person years
• HIV-1 incidence normal flora 0.76/100 person years
• Adjusted Hazard ratio 3.17 (95% CI 1.37-7.33)


Vertical transmission
16S ribosomal DNA amplification of vaginal secretions from 10 transmitters and 54 non-transmitters
MTCT of HIV associated with altered vaginal microbiota
Gardnerella vaginalis significantly associated with HIV MTC transmission - Adjusted OR 1.7; P = 0.004

Frank et al. J Acquir Immune Defic Synr 2012
BV - Vaginosis or Vaginitis?

↑ proinflammatory cytokines, TNFα, IL-1β

↑ IL-8, CD4 T cells, monocytes, dendritic cells

Proinflammatory cytokines and cervical CD4 cells decrease with effective therapy of BV

BV and pregnancy

Cohort studies
Meta-analysis of 18 studies; 20,232 women

Preterm birth
Overall risk 2.19 (1.54-3.12)
BV <16 weeks 7.55 (1.80-31.65)
BV <20 weeks 4.20 (2.11-8.39)

Spontaneous abortion
Overall risk 9.91 (1.99-49.34)
Postnatal infection
Overall risk 2.53 (1.26-5.08)


BV common infection; population attributable risk of PTB due to BV estimated to be 30% in USA at cost $1 billion

Koumans et al. Sex Transm Dis 2001
**Treatment of BV to prevent PTB?**

Antibiotic prophylaxis in all pregnancies no reduction in PTB
In subset of women with previous PTB with BV in current pregnancy:
  - Reduction in PTB \( \text{RR} 0.64 \ (95\% \ CI \ 0.47 \ to \ 0.88) \)
Women with previous PTB and no BV in current pregnancy
  - No reduction in PTB \( \text{RR} 1.08 \ (95\% \ CI \ 0.66-1.77) \)

*Thinkhamrop J et al. Antibiotic prophylaxis during the second and third trimester to reduce adverse pregnancy outcomes and morbidity. Cochrane Database of Systematic Reviews June 2015*

Antibiotic prophylaxis in low risk pregnancies no reduction in PTB - PREMEVA trial of 3105 women given oral clindamycin versus placebo:
  - No reduction in PTB \( \text{RR} 1.10 \ (95\% \ CI \ 0.53-2.32) \)
  - Adverse events more common in clindamycin group

*Subtil D et al. Early clindamycin for BV in pregnancy Lancet 2018*

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**BV and Pelvic Inflammatory Disease**

Cervical and endometrial samples for BVAB from 545 women in PID Evaluation and Clinical Health (PEACH) study (no metronidazole)
* A. vaginae, BVAB1, Sneathia sanguinegens, S. amnionii significantly associated with BV

<table>
<thead>
<tr>
<th>Condition</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometritis at presentation</td>
<td>All BVAB Ad OR 2.0 (1.0-4.0)</td>
</tr>
<tr>
<td>Endometritis 30 days after treatment</td>
<td>All BVAB Ad OR 5.7 (1.4-23.3)</td>
</tr>
<tr>
<td>Excluding women with CT and NG</td>
<td>All BVAB Ad OR 8.5 (1.6-44.6)</td>
</tr>
<tr>
<td>Recurrent PID</td>
<td>All BVAB Ad OR 3.9 (1.9-8.2)</td>
</tr>
<tr>
<td>Infertility</td>
<td>All BVAB Ad OR 3.8 (1.4-10.2)</td>
</tr>
</tbody>
</table>

Antibiotic sensitivities of many of BVAB not known but supports including cover against anaerobes in PID treatment

*Haggerty et al. Sex Transm Infect 2016*
Prevalence of Candida infections

Estimated 75% of women get at least one episode of symptomatic candida and 40-50% of these will get further episodes
About 20% women asymptomatic colonisation
30-40% asymptomatic colonisation in pregnancy and poorly controlled diabetes

Worldwide estimates of RVVC -
Annually affects: 138 (range 103-172) million women
Prevalence: 3871 per 100,000 women
Affect over lifetime: 372 million women
25-34 year age group highest prevalence at 9%

Denning et al. Lancet Infect Dis 2018

Aetiology of candida infections

90% Candida albicans

Others Candida glabrata
Candida parapsilosis
Saccharomyces cerevisiae
Candida tropicalis

Recognised predisposing factors:
pregnancy
diabetes
immunosuppression
broad spectrum antibiotics
local irritation or trauma
Candida and antibiotics

44 women receiving AB; 33 age-matched controls
After 4-6 weeks
10/27 (37%) AB group candida culture +ve
3/27 (11%) control candida culture +ve
  RR 3.33 (95% CI 1.03-10.79); p=0.03
6/27 (22%) AB group symptomatic VVC
0/27 (0%) control symptomatic VVC
  RR Infinity; p=0.02
Short term antibiotics increase asymptomatic colonisation and incidence of symptomatic VVC
  
  Xu et al. J Am Board Fam Med 2008

Epidemiology of candida infections

Sex hormone related
  - rare pre-menarche and post-menopausal
  - onset often prior to menstruation
Oestrogen lowering contraceptives such as Depoprovera and Cerazette/Cerelle may reduce incidence but lack of evidence to support this

Not a sexually transmitted infection – prevalence/incidence identical in sexually active and non-sexually active women
Randomised placebo controlled trials shown no reduction in recurrent infections with treatment of the male partner
Symptoms and signs of candida

Main symptom: - vulval itching
- increased vaginal discharge

Also vulval burning, external dysuria, vaginal soreness and superficial dyspareunia

Diagnosis of Candida

Gram-stained vaginal smear or wet-mount slide examined for yeast cells or pseudo hyphae
- Sensitivity 50%

10% KOH to wet-mount, examined for yeast cells or pseudo hyphae
- Sensitivity 70%

Culture on Sabouraud’s medium should be performed if Candida suspected and above are negative
- Sensitivity ~100%

Asymptomatic carriage usually <10 colonies per plate

Candida albicans distinguished from others by molecular tests
Treatment of candida infections

Topical treatments

- **Clotrimazole**
  - vaginal cream 1-3 nights
  - pessaries 1-6 nights
- **Miconazole**
  - vaginal cream 7 nights
  - pessaries 7 nights
  - ovule 1 night
- **Econazole**
  - pessaries 1-3 nights

Oral treatments

- **Fluconazole**
  - 150mg once
- **Itraconazole**
  - 200mg bd for one day

All give similar cure rates of about 90% at one week
Meta-analysis showed topical as good as oral treatment

*Watson et al. BJOG 2002*

Treatment of acute VVC based on classification of infection:

**Uncomplicated**
Mild-mod severity, and <4 episodes per year and healthy non-pregnant host
Single/short dose course

**Complicated**
Moderate to severe, or ≥4 episodes per year, or adverse factors eg pregnancy, diabetes, immunocompromised
More intensive regimen eg fluconazole 150mg x3 in 7/7 or fluconazole 50mg daily for 5-7 days
Avoid short courses

*Sobel et al. Am J Obstet Gynecol 2001*
Recurrent Candida infections

5-8% of women with candida get recurrent candida

Defined as at least four mycologically proven symptomatic episodes in one year

Vaginal relapse or incomplete eradication
- Swabs initially become negative but become positive again with the same strain of yeast
- PCR studies show the infection never fully clears

Longer courses of treatment may work
Prophylactic or episodic treatment can be used

Managing recurrent candidiasis due to *C. albicans*

Symptoms and signs of candidiasis non-specific so diagnosis cannot be made on basis of history and examination

Must confirm mycologically before diagnosing as recurrent candidiasis

104 women clinical diagnosis RVVC
- 30% culture positive (25 *C. albicans*, 6 *C. glabrata*)
- 42% PCR positive or culture positive
- 58% not due to candida – most vulval dermatoses

*Weissenbacher et al. Arch Gynecol Obstet 2009*
Recurrent Candida infections

Identification of species
Non-albicans species are often resistant to azoles and triazoles.

Use:
- Nystatin pessaries or vaginal cream for 14 days
- Flucytosine + Amphotericin vaginal cream for 14 days
- Flucytosine + Nystatin vaginal cream for 14 days
- Caspofungin vaginal cream for 14 days
  (all produced by Stoke Pharmaceuticals)
- Boric acid intravaginal 600mg for 2-3 weeks
- Voraconazole orally for 2 weeks

Guidance on treatment of non-albicans vaginal yeasts

Davies et al. Sex Transm Infect 2013

Recurrent Candida infections

387 women with proven recurrent candida
- 3 doses fluconazole 150mg in first week
- Randomised to fluconazole 150mg weekly or placebo for 6 months

Disease free at (mths) 6 9 12
- Fluconazole 90.8% 73.2% 42.9%
- Placebo 35.9% 27.8% 21.9%

Median time to clinical recurrence
- Fluconazole 10.2 months
- Placebo 4.0 months

Sobel et al. NEJM 2004
Clinical presentations of Candida

• Why do some women remain entirely asymptomatic despite being heavily colonised with Candida species?
• Why do other women have marked pruritis and inflammation with low levels of Candida present?

Recurrent candidiasis due to *C. albicans*

Asymptomatic despite being heavily colonised

Presenting with candida plaques but minimal symptoms
e.g. in pregnant women or HIV positive women – low proinflammatory response
Recurrent candidiasis due to *C. albicans*
Marked pruritis and inflammation with low amounts of Candida present

Minimal Candida but lots of inflammation

**Recurrent Candida infections**

Candida infections initially recognised by innate immune system through toll-like receptors and lectin-like receptors
These receptors induce proinflammatory and anti-inflammatory cytokines
Candida eliminated through activation of macrophages from the proinflammatory response
Imbalance of these mechanisms in some women producing a defective proinflammatory or an increased anti-inflammatory response.
Some studies have reported polymorphisms in the genes responsible for these innate systems in women with recurrent candidiasis suggesting a genetic predisposition
Recurrent Candida infections

C. albicans is a potent allergen – causes local hypersensitivity

Intravaginal live challenge of *Candida albicans*

- With RVVC: symptomatic VVC developed in 55%
- Without: symptomatic VVC developed in 15%

RVVC in some women not caused by lack of inflammatory response but by aggressive innate response by PMNs

*Fidel et al. Infect Immun 2004*

Vaginal fluid tested for cytokines in RVVC versus controls:
- IgE related cytokines and candida-specific IgE, PgE(2), in vaginal fluid higher in RVVC group

Suggests local allergic response


Recurrent Candida infections

Many women with recurrent disease are atopic and have allergic rhinitis

Treatment with antihistamines, cromoglicate and leukotriene receptor antagonists potentially could reduce recurrences

- 20 women with recurrent VVC and atopy given zafirlukast 20mg bd for 24 weeks
- 6 (30%) complete response
- 14 (70%) reported subjective response

*White et al. Sex Transm Inf 2004*

Successful treatment of refractory recurrent VVC with cetirizine plus fluconazole

*Neves NA. J Lower Gen Tract Dis 2005*
Recurrent Candida infections

In women with proven recurrent *Candida albicans*:

- Start with longer induction course, eg fluconazole 50mg daily or topical treatment for 7-14 days
- Give maintenance treatment such as:
  - Clotrimazole pess 500mg weekly if pregnant
  - Fluconazole 150mg weekly
- Give advice about vulval care, e.g. avoid local irritants, use emollients and soap substitutes
- Regular use of topical Canesten HC or Daktacort
- Add antihistamines or leukotriene receptor antagonists if response to above not adequate

Recurrent Candida infections

- During prophylaxis treatment 90% should be protected from symptomatic recurrences
- 30-40% will get further recurrences on stopping prophylaxis
- A small percentage of women need prophylaxis regimens for several years
Complications of Candida

Candida and pregnancy – initially thought no complications
13914 pregnant; 22% colonisation; 10% significant growth
No adverse pregnancy outcomes

*Cotch et al. Am J Obstet Gynecol 1998*

RCTs of vaginal infection screening and treating to prevent PTB

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Control</th>
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<tbody>
<tr>
<td>PTB</td>
<td>7 (2.7%)</td>
</tr>
<tr>
<td>PTB</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

*Kiss et al. BMJ 2004
Roberts. BMC Pregnancy & Childbirth 2011*

Systematic review and meta-analysis of above studies n=685

PTB reduced with intervention 0.36 (0.17-0.75)

*Roberts at al. Systematic Reviews 2015*

Complications of Candida

Candida and STIs
No associations with STIs – not a STI

**Psychological factors in recurrent Candida**
Women with recurrent Candida more likely to have:
• clinical depression and lower self esteem
• interference with sexual and emotional relationships

*Irvin et al. Sex Transm Inf 1998*

Women with recurrent Candida had significantly lower health related quality of life scores than controls

*Zhu et al. Health Qual Life Outcomes 2016*

Significant improvement in QoF with regular fluconazole treatment in a before/after study

*Nguyen et al. Austras J Dermatol 2016*
Prevalence of Trichomonas

- Marked reduction in TV in developed countries
- ? hormonal contraception
- ? cervical cytology screening
- Worldwide most common STI
- In Africa, Asia TV remains major cause of vaginal discharge
- Study of STIs in Uganda rate of TV 22.4%

Aetiology of Trichomoniasis

*Trichomonas vaginalis* - motile protozoan 10-20µm wide (size of WBC)
Four free flagella with fifth embedded in undulating membrane
Sexually transmitted - asymptomatic infection important
Infects uro-genital tract, i.e. vagina, urethra, Skene’s and Bartholin’s gland ducts

*Jane Carlton Centre for Genomics and Systems Biology, New York University*
TV prevalence increases with age

References: Females - Hobbs M. ISSTDR presentation Vienna 2013

Risk factors for TV in England

Distribution and risk factors of *Trichomonas vaginalis* infection in England from Genitourinary Medicine Clinic Activity Dataset (GUMCAD) between 2009-2011

Rates highest in: London and West Midlands
Older age vs aged 20-24 years
Non-white ethnicity (particularly black)
Current gonorrhoea or chlamydia

Further research required to assess public health impact and cost-effectiveness of introducing **targeted screening** for women at high risk of infection in areas of higher prevalence

* Mitchell et al. Epidemiol Infect 2014*
Symptoms and signs of TV in females

Main symptom vaginal discharge
- Profuse purulent discharge seen in <50%
- More frequently grey colour resembling BV
50% also notice malodour; 25-50% have vulval pruritis
External dysuria and dysparunia may also be present
Asymptomatic in 10-50% of women

TV in males

256 male contacts of TV (female positive on microscopy or culture)
TV in males detected by urethral or urine culture, or urine PCR
- TV detected in 72% (177/256)
- 77% were asymptomatic (136/177)
Symptoms were urethral discharge and/or dysuria

Circumcision and TV

Incidence lower in circumcised men and their partners
HIV-ve men circumcised or not circumcised
TV at 21 months significantly lower in circumcised group
Ad OR 0.49 (95% CI 0.25-0.93)

Sobngwi-Tambekou et al. Sex Transm Inf 2009

Female partners of above men
TV at 1 year significantly lower in circumcised group
Ad RR 0.52 (0.05-0.98)


Lower incidence of TV in HIV-ve peripartum women with
circumcised male partner  Ad HR 0.49 (0.31-0.79)

Pintye J et al. Sex Transm Inf 2017

Diagnosis of TV

Females
TV detected in 51/590 (8.6%) by conventional tests
TV detected in 93/590 (15.8%) by PCR  P = <0.001

Paterson et al. Sex Transm Inf 1998

1086 genital specimens:
TV detected in 7% by conventional tests
TV detected in 14.5% by TMA  P = 0.003


Sensitivity of different tests:
Wet-mount 50.8%
Culture 75.4%
TMA 98.4%

Huppert et al. J Clin Microbiol 2009
Diagnosis of TV with NAATs

246 symptomatic UK women tested using 5 methods
True positive if positive by two or more of these tests
24 patients with TV (prevalence 9.8%)

In-house PCR sensitivity 88%
Aptima TMA TV sensitivity 92%
OSOM Trichomonas Rapid Test sensitivity 92%
Culture sensitivity 88%
Microscopy sensitivity 38%

Highlights number of infections routinely missed (even in symptomatic women) if only microscopy is used


Utility of TV NAATs

3503 symptomatic and asymptomatic patients tested in Birmingham
Prevalence of TV: 1.4% in men and 3.6% in women
Higher in black Caribbean versus white
Detected extra 16 infections (38%) in symptomatic women versus culture
UK TV prevalence low so universal screening unlikely to be cost effective
Testing symptomatic patients with targeted testing of high-risk asymptomatic groups using NAATs should be considered

Hathorn et al. Sex Transm Infect 2015

TV NAAT added to 9186 symptomatic and asymptomatic women having CT/NG testing in GUM and primary care in SW England
Prevalence of TV: GUM – symptomatic 4.5%; asymptomatic 1.7%
Primary care – sympt 2.7%; asymptomatic 1.2%
Associated with older age, black ethnicity and deprivation
Testing symptomatic women with TV NAATs costs £260 per positive case versus £716 using microscopy and culture

Nicholls et al. Sex Transm Infect 2018
### Treatment of TV

**Current guidelines**
- Metronidazole 400mg bd for 5-7 days 95% cure
- Metronidazole 2 gm single oral dose 90% cure
- Topical vaginal treatment inappropriate as first line

**Partner treatment essential**
- If partner treated simultaneously >95% quoted cure

**Meta-analysis single dose versus multi-dose metronidazole**
- Single dose cure rates 82.0-93.8%
- Multi-dose cure rates 91.5-97.3%
- Single dose treatment failure Pooled RR 1.87 (1.23-2.82)
  
  *Howe et al. Sex Transm Dis 2017*

**RCT of single dose versus multi-dose metronidazole**
- Single dose failure rate 19%
- Multi-dose failure rate 11%
- Multidose superior RR 0.55 (95% CI 0.34-0.70)
  
  *Kissenger et al. Lancet Infect Dis 2018*

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### Treatment of TV in HIV

Treatment failure following metronidazole 2gm stat:
- 7% in HIV-ve; 10% in HIV+ve  
  
  *Kissinger et al. CID 2008*

Metronidazole for 7 days more effective than 2gm stat in HIV+ve women: RR 0.5 at TOC and RR 0.46 at 3/12
  
  *Kissinger et al. JAIDS 2010*

More treatment failures on ART: 16.4% vs 6.3%; p=0.03
- Failure 2gm stat: On ART 23.3% vs 7.7% not on ART; p=0.05
- Failure 7 days: On ART 9.6% vs 4.8% not on ART; p=0.39

ART usage associated with higher TV persistence with single-dose treatment but not with 7 days  
  
  *Adamski et al. CID 2014*

Current guidelines
- Metronidazole 400mg bd for 7 days is the preferred treatment for HIV+ women
Factors predicting recurrent TV

- Recurrence mainly from:
  - inadequate treatment from poor compliance
  - reinfection from an untreated partner

- About 5% due to metronidazole-resistance by becoming aerotolerant
- Molecular mechanism of clinical resistance poorly understood
- *In vitro* evidence of cross resistance with metronidazole and tinidazole

Treatment of recurrent TV

If infection persists and re-infection excluded no universally effective therapy:

1. Repeat metronidazole 400mg bd for 7 days
   - 40% should respond; if no response
2. Either metronidazole or tinidazole 2gm daily for 5 days or metronidazole 800mg tds for 7 days
   - 70% should respond; if no response
3. Tinidazole 2gm bd for 14 days +/- ampicillin 500mg tds or doxycycline 100mg bd +/- clotrimazole pess 500mg od
   - 90% should respond

*BASHH Guidelines 2014*
Treatment of recurrent TV

If these fail:

- Paromomycin intravaginally 250mg once or twice daily for 14 days - 56-58% cure rate reported
- Furazolidone intravaginally 100mg twice daily for 12-14 days - 33% cure rate reported
- Acetarsol pessaries 500mg nocte for 2 weeks
- 6% Nonoxynol–9 pessaries nightly for 2 weeks
- Boric acid pessaries 600mg nocte for 60 nights
2/2 patients cured

Munzy et al. Sex Health 2012
Backus et al Sex Transm Dis 2017

Association of TV with other STIs

Associated with other STIs:

- 30% will have GC and/or CT


- Associated with incident HSV-2, HSV-2 seropositivity and HSV-2 shedding


- HIV acquisition: Adjusted risk 1.64 (95% CI 1.26-2.09)

Hilber et al. PLoS ONE 2010

- HIV acquisition: Adjusted risk 1.5 (95% CI 1.30-1.7)

Masha et al. Sex Transm Infect 2019
TV and HIV transmission

TV increases detectable HIV VL in genital tract
- Detectable vaginal VL: TV aOR 4.07 (95% CI 1.78-9.37)
  - BV aOR 5.65 (95% CI 2.64-12.01)
  - TV and BV aOR 8.63 (95% CI 6.71-51.72)
Compared with no diagnosis of TV or BV, and adjusting for age, antiretroviral therapy status, and plasma viral load.
  *Fastring et al. Sex Transm Dis 2014*

Treatment reduces genital tract shedding
- Men with urethritis treated with metronidazole had reduced semen VL
  *Price et al. Sex Transm Dis 2003*
- Women with TV less likely to shed HIV vaginally 3/12 after treatment compared to no change for TV negative women: RR 0.34 (95% CI 0.12-0.92)
  *Kissinger et al. Sex Transm Dis 2009*

HIV infections attributable to TV in USA

Mathematical model based on probability TV-positive woman would acquire HIV and result of increased HIV infectiousness of TV-infected male partner
- Estimated 746 new HIV infections in women each year due to TV
- Lifetime cost of treating these HIV cases about $167 million
  *Chesson et al. Sex Transm Dis 2004*

Annual TV screening and treatment is cost-effective and cost-saving in HIV-positive women in US
  *Bratton et al. Sex Transm Dis 2014*
TV and pregnancy

Systematic Review

Preterm birth 1.42 (1.15-1.75) 81,101 women
PPRM 1.41 (1.10-1.82) 14,843 women
Small for gestation 1.51 (1.32-1.73) 14,843 women
Confirmed not treated 1.83 (0.98-3.41) 1795 women

Two treatment trials - Ross 1983, Klebanoff 2001 metronidazole cleared TV in pregnant women but failed to prevent PTB

Conclusions – TV is a STI with unpleasant symptoms and associated with adverse outcomes, including facilitating HIV transmission. Prudent to treat symptomatic women during pregnancy.

Gülmezoglu AM, Azhar M. Interventions for trichomoniasis in pregnancy. Cochrane Database of Systematic Reviews 2011

Best investigations for accurate diagnosis of vaginal infections

Look at appearance of vaginal discharge
Perform vaginal pH and amine whiff test

Take a wet-mount smear posterior fornix \{ “wet and
Take Gram-stain smear mid-low lateral wall \} dry”

Perform candida culture and species if positive
Perform TV NAAT
Conclusions

• BV, Candida infections and TV are very common conditions
• Recent improvements in understanding of their aetiology and pathogenesis
• Best diagnostic techniques are not always used
• No treatments with acceptable long term cure rates
• Improvements in knowledge of aetiology and pathogenesis help our understanding of recurrences
• Recurrent BV and Candida are associated with psychological and psychosexual problems
• BV and TV predispose to other STI/HIV acquisition and transmission
• BV, TV and possibly Candida are associated with adverse pregnancy outcomes