VAGINITIS

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CASE 1

- 31 yo HIV uninfected cisgender white heterosexual female presents in the Fall of 2018 with primary complaint of ”I’ve had a yeast infection for three years!”

- HPI: vulvovaginal irritation with excessive discharge that began three years ago while living in Florida. She sought care at the local Planned Parenthood and then a variety of gynecologists.

CASE 1

- She conveys being aware of “fluconazole resistant” yeast since early in the course of her therapy.
- Treatments: fluconazole, topical azoles, boric acid, flucytosine, intravaginal ampho B, posaconazole, Gentian violet
- Work up for vulvovaginal trichomoniasis: negative
- Had a vaginal culture performed that revealed Group B strep and she received some amox.

CASE 1

- Sexual practices: last sex with a cisgender male person was one year ago. Vaginal-penile sex and receptive oral sex is exceptionally uncomfortable. No anal sex.
- She uses topical lidocaine routinely just for comfort.
- No unusual intra-vaginal practices: no douches, no dildos/toys
- She was told by many different providers to: avoid hot yoga, tight jeans, swimming pools

CASE 1

- PMHx: some sinus infections in childhood, prior genital HSV, depression/anxiety
- Travel: remotely to Nicaragua, Barbados, Virgin Isles
- Soc Hx: +smoker; no alcohol; no illicit substances

CASE 1

- MEDS: bupropion, valacyclovir
- PExam:
  - Gyn: no external vesicles noted; vaginal walls with creamy whitish discharge noted

CASE 1

- MICRO

  11/12/2018: mod *C albicans* (R to fluconazole; S to micafungin)

WHAT WOULD YOU DO NEXT?

- A. higher dose fluconazole for extended therapy
- B. another trial of boric acid
- C. voriconazole
- D. micafungin
- E. compounded intravaginal preparation of combined flucytosine and ampho B

VULVOVAGINAL CANDIDIASIS (VVC)

- 50% of all women will experience >1 episode of vulvovaginal candidiasis by 25 years of age
- Upwards of 40-45% of women will have more than 2 episodes over their life time

Makanjuola O, et al. J Fungi 2018

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VVC

- Treatments are historically limited to azoles
  - Topical azoles
  - Oral fluconazole 150 mg x 1
- Use of non-azole therapies in general except in the setting of azole-resistance (or azole intolerance)

RECURRENT VVC

- Three or more episodes of symptomatic infection within one year (per the CDC's STD Treatment Guidelines 2021)
- Vaginal cultures should always be obtained to confirm the diagnosis and identify less common *Candida* species, if present

Sobel JD. Am J Obstet Gynecol. 2016; Nyirjesy P, et al. Clin Infect Dis 2022

RECURRENT VVC

- Recurrent VVC tends to occur in otherwise healthy women
- Estimating the incidence and prevalence of recurrent infection is challenging because the symptoms are not exclusive to Candida infection and many women self-treat.
- In an internet survey study of over 7,000 women across seven countries, the estimated probability of RVVC, by age 50, ranged from 14 to 28 percent, with a mean of 23 percent

Blostein F, et al. Ann Epidemiol 2017

RECURRENT VVC

- Potential association of recurrent VVC with vaginal mucosal immune hyper-reactivity to the fungus
- Vaginal hyper-reactivity involves interleukin-22 (IL-22), IL-10, and IL-17 producing regulatory T cells. IL-17 plays a role in controlling *C. albicans* infection as it induces vaginal epithelial cells to produce antimicrobial peptides
- RVVC has also been associated with decreased in vivo concentration of mannose binding lectin (MBL) and increased concentration of IL-4. The prevalence of a variant MBL gene is higher in women with RVVC than in controls without candidiasis

De Luca A et al. PLoS Pathog 2013; Liu F et al. Int J Gynaecol Obstet 2006

TREATMENT FOR RECURRENT VVC

- Maintaining clinical and mycologic control, a longer duration of initial therapy (e.g., 7–14 days of topical therapy or a 100-mg, 150-mg, or 200-mg oral dose of fluconazole every third day for a total of 3 doses [days 1, 4, and 7]) is recommended, to attempt mycologic remission, before initiating a maintenance antifungal regimen
- Oral fluconazole (i.e., a 100-mg, 150-mg, or 200-mg dose) weekly for 6 months is the indicated maintenance regimen

CDC STD Treatment Guidelines 2021

COMPLICATED VULVOVAGINAL CANDIDIASIS

- Severe symptoms
- Recurrent infection
- Non-albicans species
- Host factors: pregnancy, difficult to control diabetes mellitus, immunosuppressed, etc.

CDC STD Treatment Guidelines 2021

Treatment of complicated vaginal candidiasis

Severe vaginitis symptoms
Oral fluconazole 150 mg every 72 hours for two or three doses (depending on severity).
OR
Topical azole antifungal therapy daily for 7 to 14 days. A low potency topical corticosteroid can be applied to the vulva for 48 hours to relieve symptoms until the antifungal drug exerts its effect.
Recurrent vulvovaginal candidiasis
Induction with fluconazole 150 mg every 72 hours for three doses, followed by maintenance fluconazole 150 mg once per week for six months.
If fluconazole is not feasible, options include 10 to 14 days of a topical azole or alternate oral azole (eg, itraconazole) followed by topical maintenance therapy for six months (eg, clotrimazole 200 mg [eg, 10 g of 2%] vaginal cream twice weekly or 500 mg vaginal suppository once weekly).
Nonalbicans *Candida* vaginitis
Therapy depends upon species identified:
▪ *C. glabrata*: Intravaginal boric acid* 600 mg daily for 14 days
• If failure occurs: 16% topical flucytosine cream, 5 g nightly for 14 days
▪ *C. krusei*: Intravaginal clotrimazole, miconazole, or terconazole for 7 to 14 days
▪ All other species: Conventional dose fluconazole (150 mg)
Compromised host (eg, poorly controlled diabetes, immunosuppression, debilitation) and *Candida* isolate susceptible to azoles
Oral or topical therapy for 7 to 14 days
Pregnancy
Topical clotrimazole or miconazole for 7 days

Boric acid capsules and flucytosine cream are not commercially available, but can be made by a compounding pharmacy.

* Boric acid capsules can be fatal if swallowed.

Data from: Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis 2009; 48:503.

UpToDate®

TREATMENT FOR AZOLE RESISTANT VVC

- Think about ***control*** *over cure*
- Extended lengths of therapy
- Pursue micro to ensure *C albicans* species (over other candida) and consider work up (pathology) for non-vaginitis conditions

BORIC ACID

- Typically studied for use in cases of vaginitis secondary to *C glabrata* (off label use).
- Clinical experts support boric acid towards “maintenance” therapy for patients with azole resistant recurrent VVC
- Regimens vary with some data review revealing average length of boric acid use of 13 mos with high satisfaction (76.9%) and few notable side effects

Powell A, et al. Sex Trans Dis. 2019
Iavazzo C, et al. Jnl Women’s Health (Larchmnt) 2011
Sobel J, et al. Clin Infect Dis 1993

BACK TO THE CASE

- Intra-vaginal boric acid with close follow up fungal cultures
- Why not micafungin?

BACK TO THE CASE

We moved forward in the following manner:

- boric acid vaginal suppository via inserter/applicator QHS x 7 days
- clinical exam/symptom check with me on 12/7/18 (KOH, fungal culture)

- If her KOH is negative/fungal culture is no growth but she has ongoing symptoms then she needs evaluation for another condition (pathology for etiologies including lichen sclerosus, erosive lichen planus).

- If she has presence of yeast (by KOH, culture) and hopefully some improvement (even mild) then press forward with ongoing boric acid. Continue for 4-6 weeks and then can move to QOD for the next 2-3 months and then twice a week to span out to the six month point.

RESISTANCE

- MICRO

  11/12/2018: mod C albicans (R to fluconazole with an MIC of 64; S to micafungin)

  12/7/2018: rare yeast forms

  12/18/18: no fungi isolated

  1/3/2019: no fungi isolated

  2/4/2019: no fungi isolated

MY PATIENT'S COURSE

- Extraordinary improvement
- I had made contact with a pharmaceutical company (Scynexis) that was pursuing clinical trials for patients with azole resistant VVC
- No further yeast noted on vaginal fungal smears/cultures
- Relief of discomfort meant return of sexual function

TREATMENT FOR AZOLE RESISTANT VVC

- Ibrexafungerp (commercial name Brexafemme) is a single-day (two tabs twice in one day) oral triterpenoid antifungal for use in females with vulvovaginal candidiasis
- First in its class
- Azoles inhibit fungal growth whereas Ibrexafungerp acts by inhibiting formation of the fungal cell wall
- Lack of safety data in pregnancy and breast feeding
- *Did not make it into the 2021 CDC STD Treatment Guidelines but is in UpToDate*

Schwebke Jane, et al. Clin Infect Dis 2022

NEXT CASE

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CASE 2

- 23 yo white cisgender heterosexual female unable to tolerate oral pills who presents with persistent *Trichomonas vaginalis* infection x two years

- States extreme nausea/vomiting with “most pills.”

CASE 2

- Two years ago, she began experiencing the combination of yellowish/greenish profuse vaginal discharge with malodor.
- She also began having vaginal bleeding that continued "every day" in moderate quantity. She was tested, found to have *T vaginalis* and offered therapy.
- She was unable to tolerate oral metronidazole. She was then offered a course of intravaginal metronidazole.
- +Symptoms persisted. Testing continued to support infection.

CASE 2

- She was then tried on oral tinidazole (crushed with ice cream) with pre-anti-emetics. This therapy made her vomit.
- Ongoing voluminous frothy greenish/yellowish discharge.
- She is not sexually active (and has not been so since this started two years ago).
- She uses pads daily to absorb the discharge.

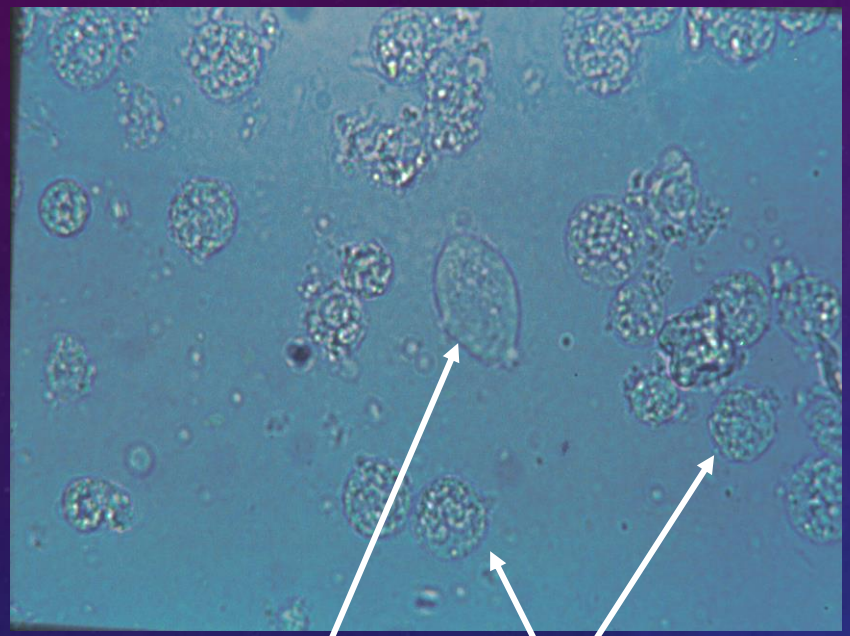
TESTING

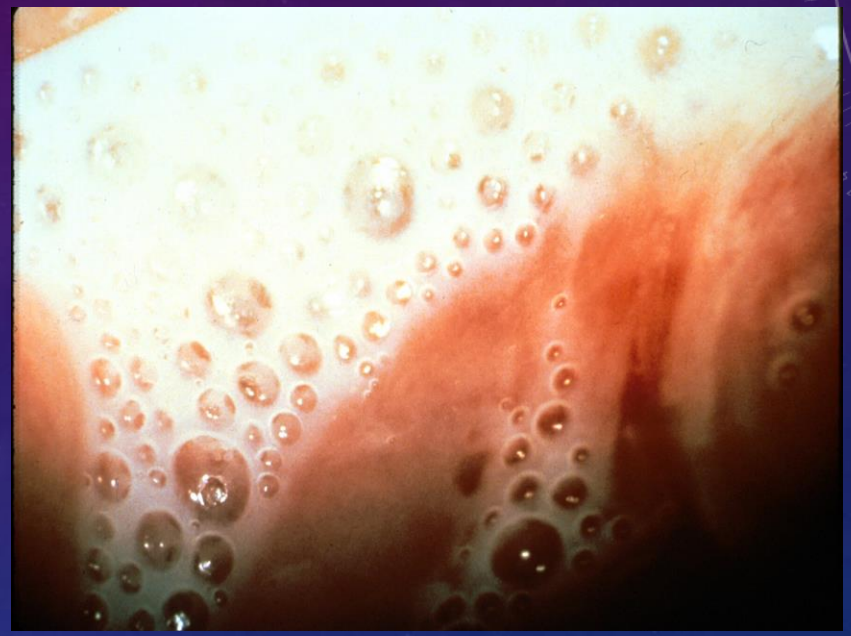
- Vaginitis exam: trich Antigen +
- (Evaluations repeatedly for BV, VVC, CT, GC negative)

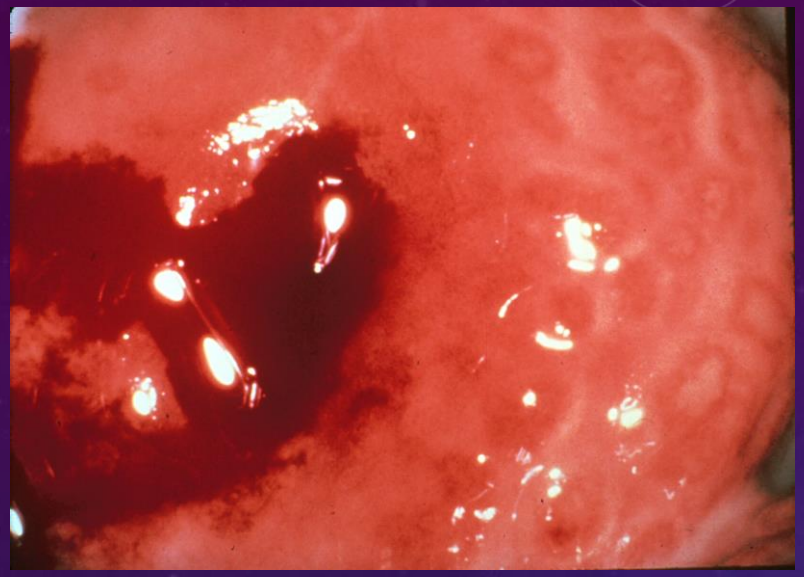
EXAM/TESTING

- Patient declined examination
- Self-collected vaginal swab
- Vaginal specimen on day of visit: *Trichomonas vaginalis* amplified RNA +

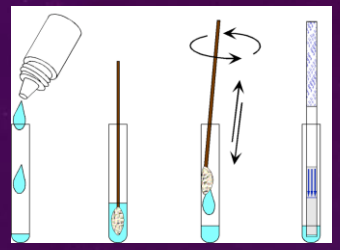
Saline microscopy & typical discharge







Cervicitis due to *Trichomonas vaginalis*



TESTING OPTIONS FOR TRICH

- APTIMA TMA *Trichomonas Vaginalis* assay (Gen-Probe)
  - Nucleic Acid Amplification Test
  - Similar to APTIMA Combo 2 (for chlamydia and gonorrhea)
  - May use same specimen type as used with APTIMA Combo 2 (i.e. vaginal swab, endocervical swab, urine)
    - sensitivity of 95.3%–100% and specificity of 95.2%–100%, compared with wet mount and culture

- Self-collected vaginal sampling: always more optimal
- Wet mount – cheap and easy
- Rapid antigen test (OSOM; Genzyme)

- InPouch culture

NAAT FOR TRICH

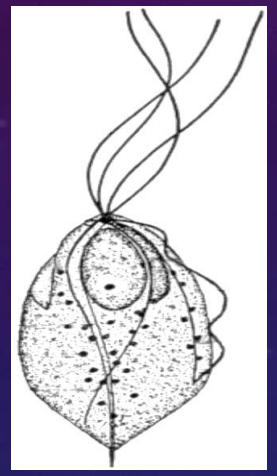
	Sensitivity	Specificity
Wet mount	55	100
Culture	75	100
ATV vaginal swab	**97**	**100**
ATV cervical swab	90	100
ATV urine	88	100

Nye, AJOG 2019

Comparison of APTIMA *Trichomonas vaginalis* transcription-mediated amplification to wet mount microscopy, culture, and polymerase chain reaction for diagnosis of trichomoniasis in men and women

Melinda B. Nye, PhD; Jane R. Schwebke, MD; Barbara A. Body, PhD

TRICHOMONAS VAGINALIS EPIDEMIOLOGY



- Prevalence is 2.1% among women ages 14-49 with a prevalence of 9.6% among African American women
- Asymptomatic in 50-60% of women and 90% of men
- Infection increases risk of PID, pre-term birth
- Increases risk of HIV acquisition and transmission

CDC 2022, Workowski 2010, Cherpes 2006, Kissinger 2009, McClelland 2007

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PREVALENCE OF *T VAGINALIS* AND COINFECTION

- Study of discarded urogenital samples from 7,593 women (ages 18-89) undergoing NAAT testing for chlamydia and gonorrhea. Samples tested with NAAT.

- Prevalence:
  - *T. vaginalis*: 8.7%
  - *C. trachomatis*: 6.7%
  - *N. gonorrhoeae*: 1.7%

Ginocchio et al. JCM 2012

BACK TO THE CASE – WHAT COULD BE THE ISSUE?

- Symptomatic chronic trich that has not been penetrated by any appropriate dose delivery of first line therapy with metronidazole or tinidazole.

- Resistant *T vaginalis*.

WHAT WOULD YOU DO NEXT?

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NEXT STEPS

- Patient declined re-challenge with abundant pre-treatment antiemetics of either another trial of either tinidazole or obtaining secnidazole PLUS vaginal paromomycin (6.25% cream, 5 gm applicator x 14 days).

- Parenteral metronidazole (500 mg IV daily x 5 days)

Alessio C and Nyirjesy P, Current Infectious Disease Reports 2019

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COURSE

- Patient completed IV metronidazole course without any notable side/adverse effects
- Some (but not full) symptomatic improvement in excessive vaginal discharge

TESTING

- Six weeks after treatment course completed: T vag amplified RNA +

TESTING

- Ten weeks after treatment course completed: T vag amplified RNA +

CHALLENGE

- One class of antimicrobials known to be effective against trichomonas
- Metronidazole resistance occurs in 4-10% of cases
- Tinidazole is less studied but present in 1% in one study

Schwebke JR, et al. Antimicrob Agents Chemother 2006

Trichomonas Susceptibility

CDC-10239

Synonym(s)	*Trichomonas*, trich, parasite
CDC Pre-Approval Needed	**Evan Secor** **(404) 718-4141** **was4@cdc.gov** **Peter Augostini** **(404) 718-4142** **pfa9@cdc.gov**
Supplemental Information Required	**A supplemental form is required. Please call the CDC POC to request a testing kit that will include the supplemental form and an InPouch TV culture media device for specimen submission. Alternatively, send mailing address and phone number to the CDC POC to request a kit. Please include the metronidazole treatment history and the supplemental form with the specimen.**
Supplemental Form	**Provided with the collection kit**
Performed on Specimens from	Human
Acceptable Sample/ Specimen Type for	This test order is currently not accepting any specimens until further notice.

RESULTS

Aerobic MLC	Metronidazole	Tinidazole
Patient isolate	3.1 ug/ml	0.8 ug/ml

Based on the in vitro susceptibility testing, this isolate shows no resistance to metronidazole and tinidazole. I have reviewed the previous course and note her GI

- NO resistance noted
- I offered another trial of tinidazole (with abundant anti-emetics, etc.)
- She failed to follow up to pursue this