Recurrent Candidasis, Bacterial Vaginosis and Trichomonas

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Disclaimer

- No financial relationships or conflict of interest to disclose
- May discuss off-label or non-FDA approved uses for some medications

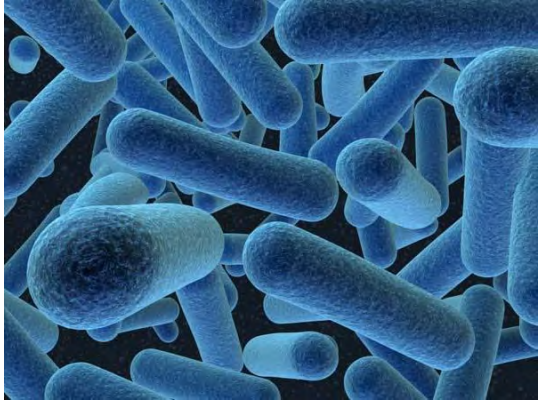
Educational Objective

Develop strategies for treatment of persistent, recurrent or complicated vaginal infections with candida, BV, and trichomonas in pregnant and non-pregnant women

Overview of Vaginitis

- The normal vagina
- Recurrent Yeast vaginitis
- Recurrent Bacterial Vaginosis
- Recurrent Trichomoniasis

The Normal Vagina

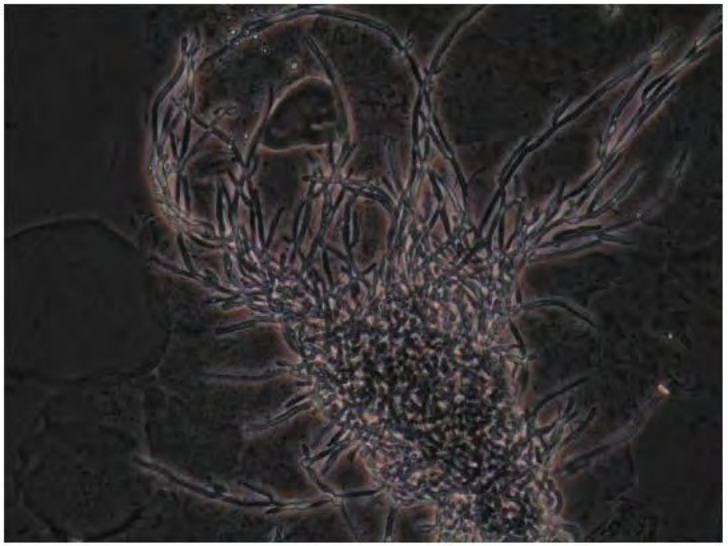


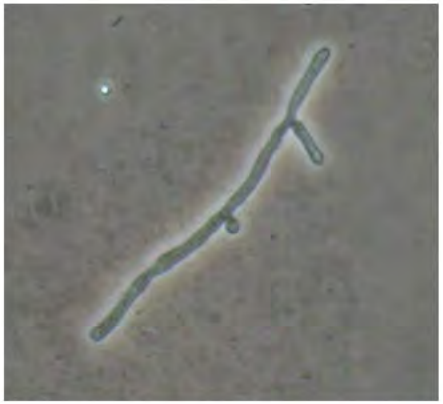
- Complex ecosystem of variable organisms
- Predominance of Lactobacilli (facultative gram + bacteria) maintain low pH between 3.5-4.5
- Suppress pathogenic bacteria
- 60% produce hydrogen peroxide which protects against pathogens
- Staph, strep, enterococci, E.coli, Proteus, Klebsiella, anaerobes, candida albicans in 20-70% of healthy asymptomatic women

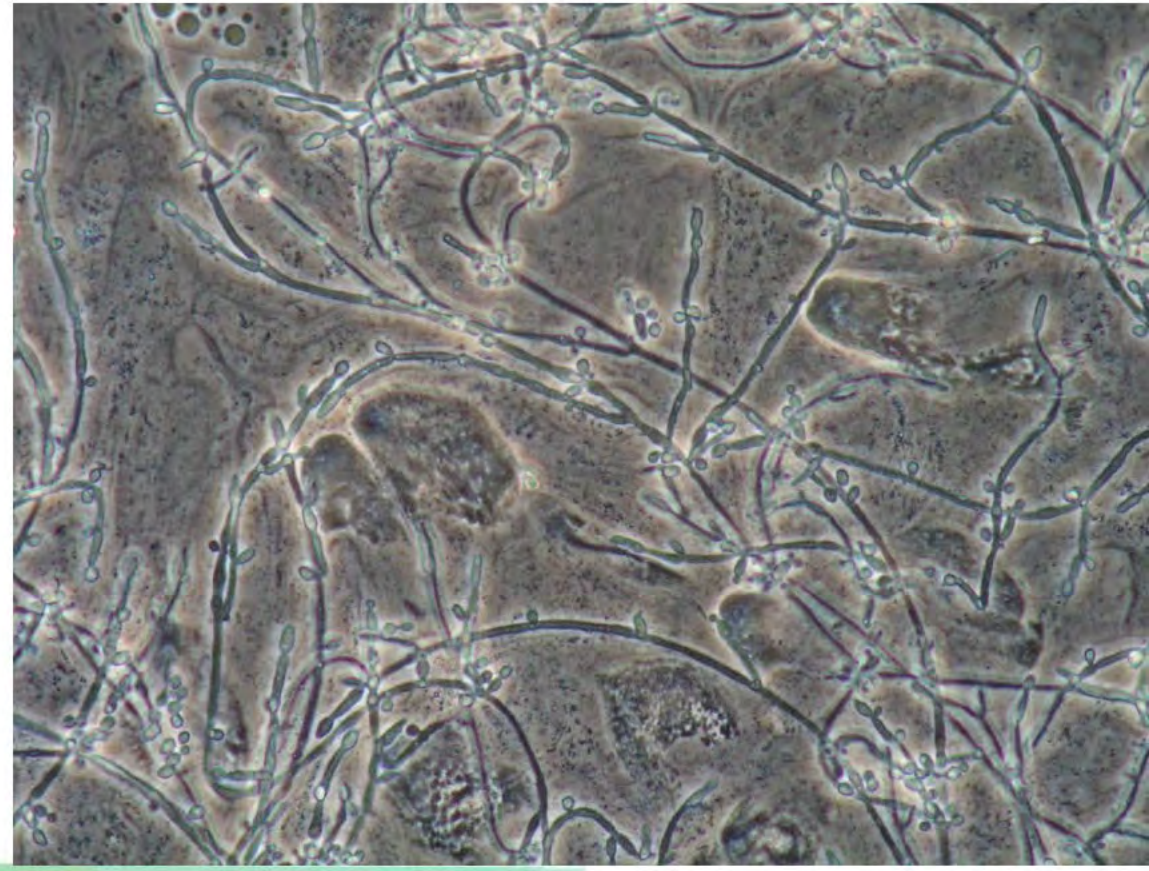
Standard Therapy for Uncomplicated Infections

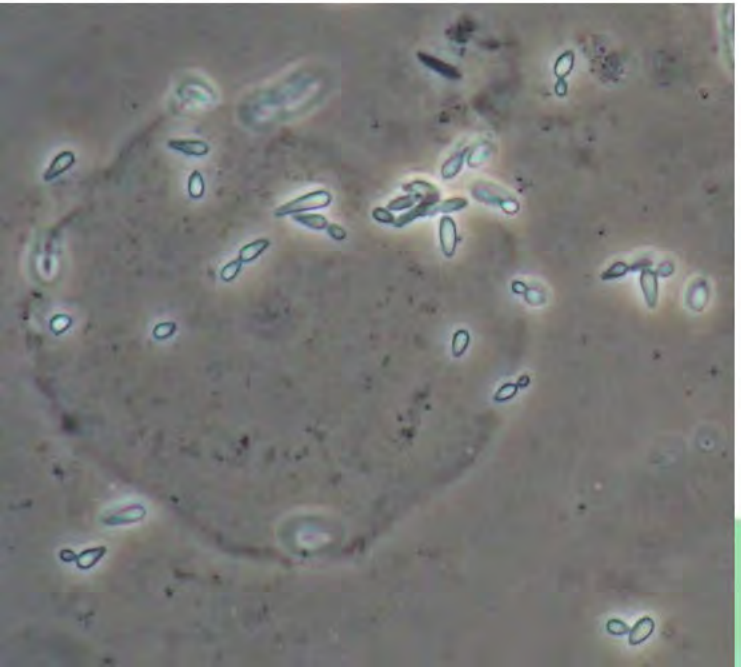
- ***Consistent, good quality, patient oriented evidence for:***
  - Oral and vaginal imidazoles are equally effective (80-90%) for treatment of uncomplicated ***Candida***
  - Oral and vaginal clindamycin and oral and vaginal metronidazole are equally effective for eradicating symptoms of ***bacterial vaginosis***
  - Nitroimidazole drugs (metronidazole or tinidazole) given orally in a single dose results in parasitological cure of ***trichomonas*** in 90% of cases

Vulvovaginal Candidiasis









Definitions

- ***Recurrent***:
  - Three or more proven cases in 12 months, at least one by culture, OR
  - At least three episodes unrelated to antibiotics within one year
  - 8-10% of women will have recurrent episodes
- ***Chronic***:
  - A proven episode of candidiasis that does not respond to conventional antifungal therapy within 2 weeks

-Sobel JC. Lancet 2007;396:1961-71.

Definitions

- ***Uncomplicated***:
  - Sporadic or infrequent vulvovaginal candidiasis
  - Mild to moderate symptoms or findings
  - Likely to be candida albicans
  - Non-pregnant, non-diabetic woman
- ***Complicated:***
  - 4 or more vulvovaginal candida recurrences per year
  - Severe symptoms or findings
  - Suspected or proven non-albicans infection
  - Impaired host immune system (diabetes, pregnancy, immunosuppression, other vulvovaginal conditions

Powell, A and Nyirjesy, P.:Clinical Obstet & Gynaecol 2014;28(7):967-976

Factors which promote recurrent symptomatic infection

- Uncontrolled diabetes mellitus (glucosuria)
- Topical or systemic corticosteroid use or other immunosuppression
- Postmenopausal vaginal estrogen use
- Antibiotic use (if already colonized)
- Frequent coitus, orogenital sex
- OCP and IUD use, contraceptive sponge, diaphragm with spermicide
- ***No clear risk factors in 50% of women with recurrent infections***

Topical Treatment Considerations

- 1 day preparations can cause burning
- Some preparations more irritating than others
- Itching and burning can occur after repeated use. If they get worse after treatment instead of better, consider them as irritants or allergens and try different therapy
- Patients who don't improve may have concurrent dx:
  - Contact dermatitis 21%
  - Atrophic vulvovaginitis 15%
  - Localized provoked vulvodynia 13%
  - Physiologic discharge 9%
    - Nyirjesy 2014

Topical Agents (First-Line Therapy) for the Treatment of Candidiasis*= prescription

DRUG	BRAND NAME	FORMULATION	DOSAGE
Butoconazole *	Gynazole-1®*	2% vaginal cream	1 app (5 gm) vaginally x1 day
	Mycelex-3®	2% vaginal cream	1 app (5 gm) vaginally x3 days
Clotrimazole	Gyne-Lotrimin 7®, Mycelex-7®	1% vaginal cream	1 app vaginally for 7 days
	Gyne-Lotrimin 3®	2% vaginal cream	1 app vaginally for 3 days
	Gyne-Lotrimin 3®	200 mg vaginal supp	1 vaginal supp daily for 3 days
Clotrimazole Combination Pack	Gyne-Lotrimin 3®	200 mg supp + 1% topical cream	1 supp daily for 3 days. Use cream externally as needed.
	Mycelex-7®	100 mg supp + 1% topical cream	1 supp daily for 7 days. Use cream externally as needed.
Clotrimazole + Betamethasone*	Lotrisone®	1% clotrimazole with 0.05% betamethasone vaginal cream	Apply cream topically twice daily (Maximum use 2-4 weeks)

Miconazole	Monistat-7®	100 mg vaginal supp	1 supp daily for 7 days
	Monistat®	2% topical cream	Apply externally as needed
	Monistat-3®	4% vaginal cream	1 app vaginally for 3 days
	Monistat-7®	2% vaginal cream	1 app vaginally for 7 days
Miconazole Combination Pack	Monistat-3®	200 mg vaginal supp + 2% topical cream	1 supp daily for 3 days. Use cream externally BID as needed. (Max use 2-4 weeks)
	Monistat-7®	100 mg vaginal supp + 2% topical cream	1 supp daily for 7 days. Use cream externally BID as needed. (Max use 2-4 weeks)
	Monistat® Dual-Pack	1200 mg vaginal supp + 2% topical cream	1 supp once daily for 1 day. Use cream externally BID as needed. (Max use 2-4 weeks)
Terconazole *	Terazol 3®	80 mg vaginal supp	1 supp daily for 3 days
	Terazol 7®	0.4% vaginal cream	1 app vaginally for 7 days
	Terazol 3®	0.8% vaginal cream	1 app vaginally for 3 days
Tioconazole	Monistat-1®, Vagistat-1®	6.5% vaginal ointment	1 applicatorful vaginally, once
Econazole Nitrate *	Spectrazole®	1% topical cream	Apply cream twice daily
Nystatin *	Pyolene Nystatin/Generic	100,000 unit vaginal tablet	1 tablet daily for 14 days (best choice for 1st trimester pregnancy)
Nystatin Powder*	Mycostatin®	100,000 units/gram	Apply to vulva twice daily for 14 days

Hope Haefner, "Recurrent and Resistant Yeast and BV", ISSVD Vulvovaginal Disease Update, 5/31/2013

Oral Treatments

- ***Fluconazole***: 150 mg PO X 1 dose (FDA approved)
- ***Itraconazole***: 200 mg PO BID X 1 day or 200 mg PO QD X 3 days

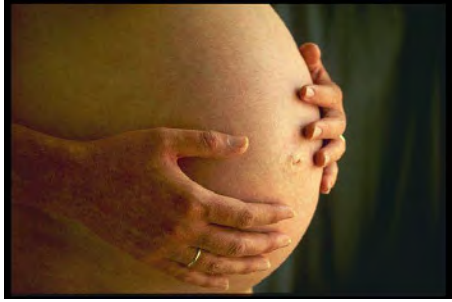
- Side effects of fluconazole: headache 13%, nausea 7%, abdominal pain, rare elevation of liver enzymes

Oral Treatment Considerations

- **Fluconazole has drug-drug interactions:**
  - Behavioral health medications
    - Alprazolam, cytalopram, fluoxetine, sertraline, trazadone, clonazepam, escitalopram, venlafaxine, amitriptyline,
    - OK with duloxetine, lamictal, lamotrigine, lorazepam
  - Proton Pump Inhibitors and GERD medications
    - Omeprazole, cimetidine
  - Statins and cardiac medications
    - Simvastatin, avorastatin, verapamil
    - OK with pravastatin
  - Sulfonylureas
    - Glimepiride

  -Warfarin, phenytoin, rifampin, cyclosporine, methadone

What if she's pregnant?



- Candida during pregnancy may be associated with PROM, preterm birth, chorioamnionitis, congenital cutaneous candidiasis
- No evidence that one imidazole is more effective than another
- Treatment of choice: clotrimazole or miconazole cream vaginally X 7 days, especially in 1st trimester
- Compounded vaginal nystatin X 14 days

Fluconazole in Pregnancy

- High dose oral azoles in the first trimester (400-800 mg/d), pattern of birth defects including abnormalities of cranium, facies, bones and heart
- Amount of teratogenic risk unknown
- First trimester use of a single dose of 150 mg fluconazole has not been associated with an increased risk of birth defects-
  Mastroiacovo P, et al. Am J Obstet Gynecol 1996;175:1645-50
- Vaginal treatment preferable to oral treatment in the first trimester
- No studies of long term suppressive maintenance therapy in pregnancy. Episodic treatment preferred.

Complicated and Recurrent Infections

- May need longer treatment duration:
  - 7-14 days of topical therapy
  - Fluconazole 150-200 mg days 1, 4, and 7

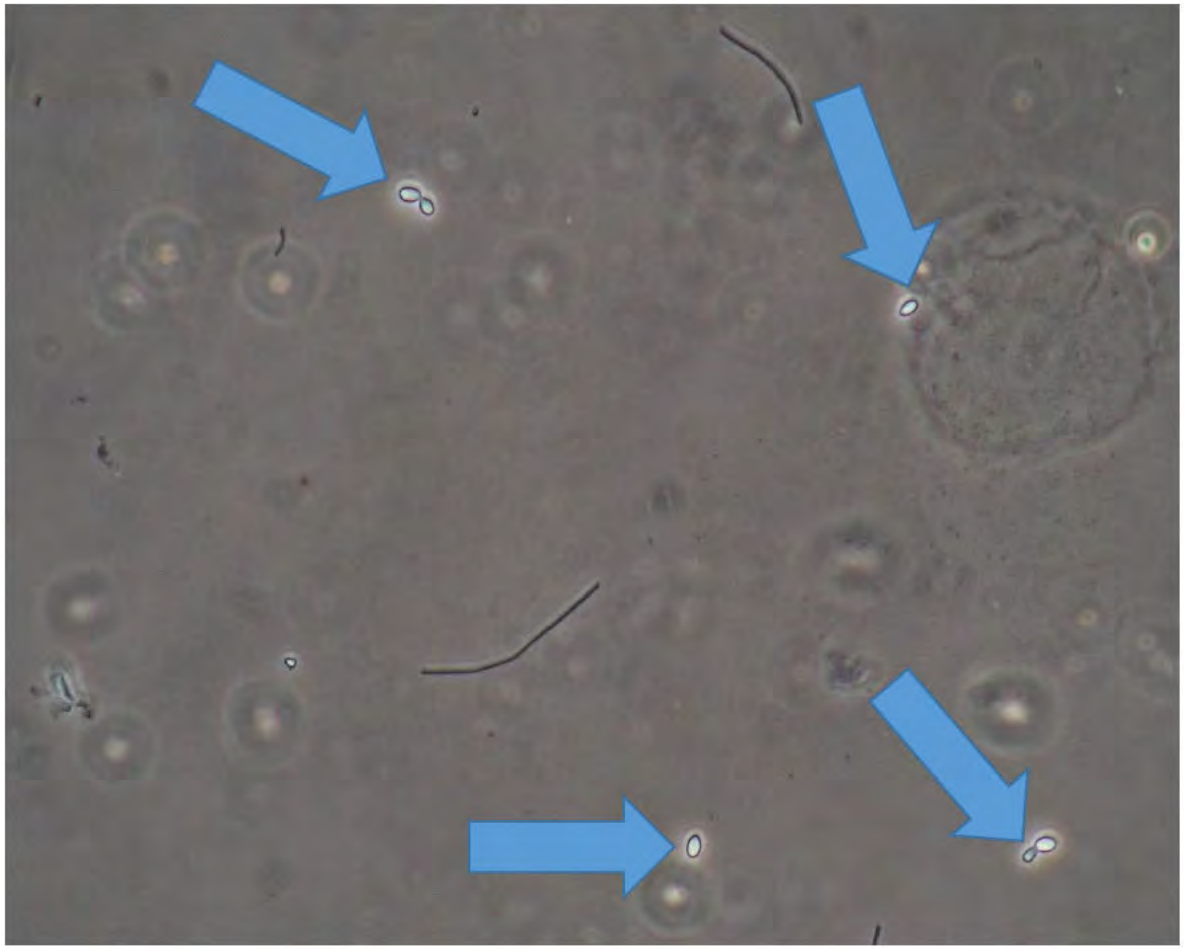
- Culture if:
  - Non-albicans candida species suspected (10-20%)
  - Recurrent symptoms with negative wet prep
  - Resistance suspected (obtain sensitivities)

Long Term Suppression

- Fluconazole 100 mg, 150 mg or 200 mg PO once per week for 6 months is 93% effective
  - Check LFT's if using fluconazole X 6 months
- Vaginal clotrimazole 1% cream or miconazole 2% cream 5 grams vaginally 2 times per week X 6 months
- Boric acid 600 mg capsules or suppositories per vagina 2 times per week X 6 months

30-50% of women will recur after suppression. May continue longer than 6 months

Non-albicans Candida



Treatment considerations: Non-albicans candida species

- Resistant to all currently available azoles
- **600 mg boric acid capsules** vaginally X 14 days cures 70% of c. glabrata infections. Contraindicated in pregnancy. Inhibits hyphal formation, virulence factors, biofilm formation
- Topical **flucytosine 15.5-17%** compounded in hydrophilic cream base, insert 5 grams PV qhs X 14 nights for c. glabrata & c. tropicalis ($$$) or 50 mg suppositories PV X 14
- **Gentian violet** 0.25% or 0.5% or 1.0% aqueous solution in office once per week up to 4-6 applications. May irritate, blister or erode. Permanent purple stain on clothing. Fungicidal. Is pregnancy category B
- **Fluconazole 200 mg** twice weekly X 1 month (c. parapsilosis)
  - Nyirjesy 2014

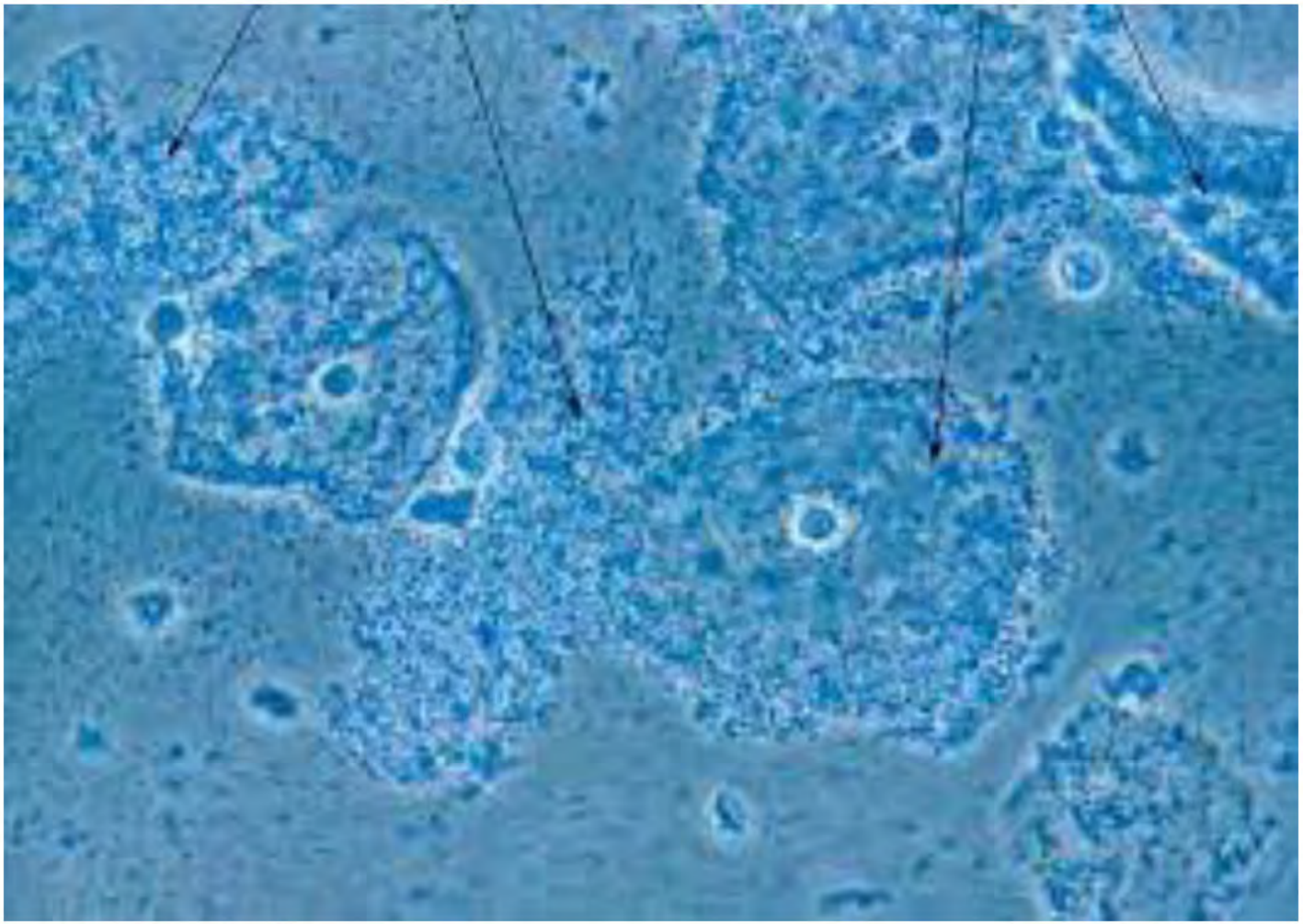
Treatment for Non-Albicans Yeast

- Itraconazole 100 mg PO BID X 14
- Amphoterocin B 50 mg vaginal suppositories PV QHS X 14
- Fluconazole 400 mg PO daily X 14
- Caspofungin vaginal cream 100 mcg/4 gm in sodium carboxy gel, 5 gm QHS X 14
- Nystatin 100,000 u in compounded tablet PV QHS X 21
- Ketoconazole 100 mg PO BID X 30 days (ALT pre & post)
- **50% of the time non-albicans yeast is an innocent bystander and is not causing the pt's symptoms**
  - Nyirjesy 2016

Treatment of Fluconazole Resistant Yeast

- Itraconazole 100 mg PO BID X 14 days
  - Test ALT before and after
- Amphoterocin B 3% cream, 4 gm PV QHS X 7-14 days
- Posaconazole 300 mg PO Q 12 H X 2 doses to load, then 300 mg PO daily X 7-14 days
  - Check EKG before treatment (prolongs QT)

Bacterial Vaginosis



BV Pathogenesis

- Polymicrobial change in vaginal ecosystem →
- Absence or decrease of lactobacillus species
  - L. crispatus, L. jensenii (and others produce H2O2)

- High concentrations of facultative and obligate anaerobes
  - Gardnerella vaginalis
  - Mobiluncus species
  - Prevotella species
  - Mycoplasma hominis
  - Bacteroides species
  - Peptostreptococcus species
  - Atopobium vaginae
  - -Fusobacterium species
  - -BV associated bacterium 1,2,3
  - -Megasphaera species
  - - Eggerthella species
  - -Leptotrichia species

Implications of BV Infection

- Associated with ***obstetrical complications***:
  - preterm labor, PPROM, low birth weight, post partum endometritis, spontaneous abortion
- Associated with ***surgical complications***:
  - Post-abortal endometritis, vaginal cuff cellulitis or abscess after hysterectomy, PID
- Increased risk of ***acquiring other infections***:
  - HIV, HSV 2, Neisseria gonorrhoeae, Chlamydia trachomatis, Trichomonas vaginalis, UTI's

Diagnosis: Amsel's Criteria

Must have 3 of the following 4:

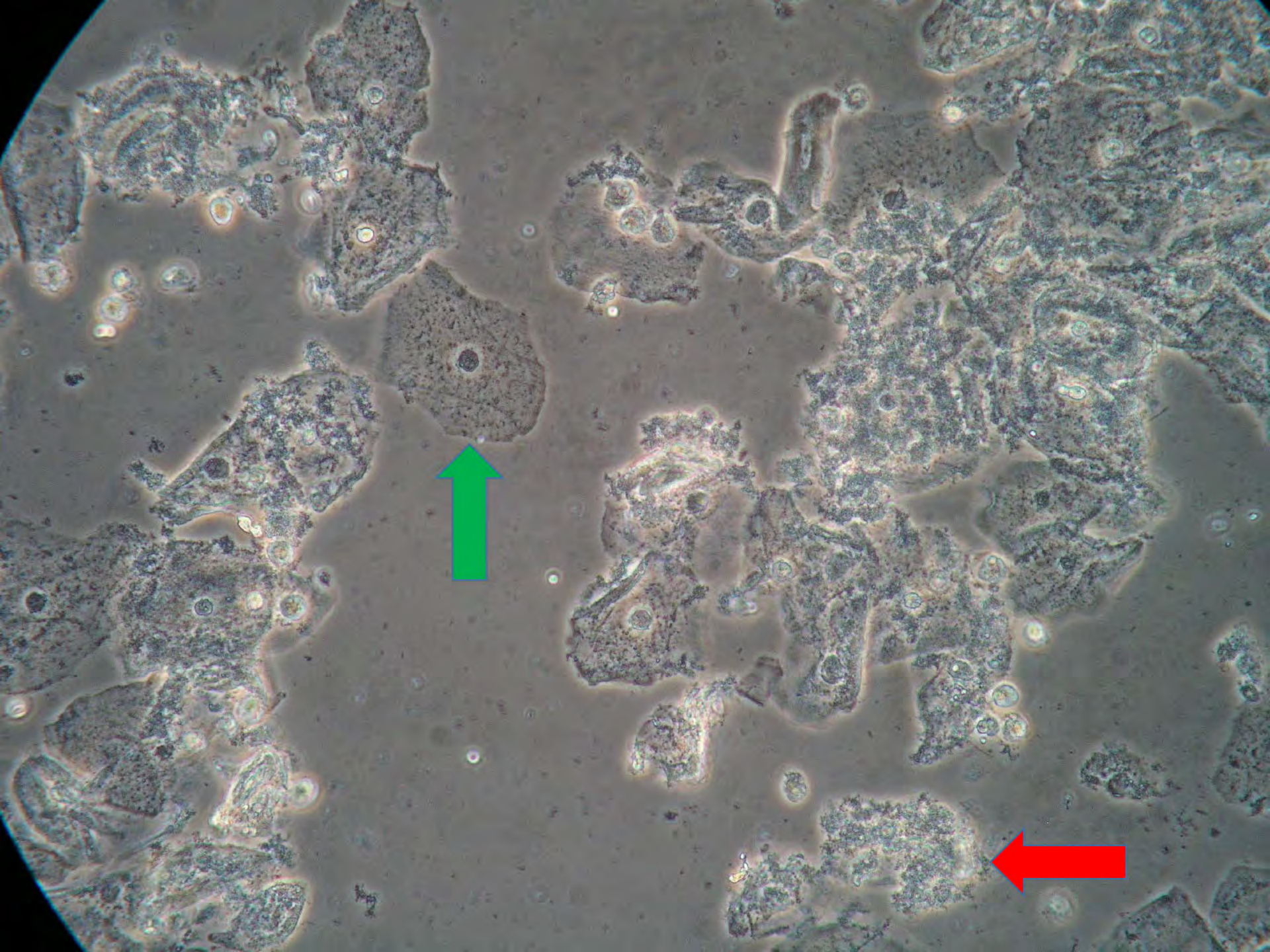
- ***Elevated pH*** greater than 4.5
- Gray white ***discharge*** smoothly coating vaginal walls
- More than 20% ***clue cells*** on microscopy
- ***Positive whiff test***: fishy amine odor after addition of 10% potassium hydroxide (putrescine, cadaverine and trimethylamine)

Other Diagnostic Tests

- Gram Stain
- Affirm VP III (Becton Dickinson, Sparks, MD): DNA hybridization probe
- OSOM BV Blue Test (Sekisui Diagnostics, Framingham, MA): detects vaginal fluid sialidase activity

Diagnosis: The Finer Points

- Vaginal cultures are not helpful (Gardnerella can be normal flora)
- Only treat Gardnerella found on pap smear if patient meets Amsel's criteria
- BV is not inflammatory, should not have elevated WBC's or parabasal cells on wet prep.
- BV doesn't usually cause dyspareunia, may cause itching or irritation



BV Treatments

- Metronidazole 500 mg PO BID X 7 days
- Metronidazole 0.75% gel, 5 gm PV X 5 days
- Clindamycin 2% cream, 5 gm PV X 7 days
- Clindamycin 300 mg PO BID X 7 days
- Clindamycin 100 gm ovules PV QHS X 3 days
- Tinidazole 1 gm PO QD X 5 days
- Tinidazole 2 gm PO QD X 2 days

- All regimens equally effective; may respond to a second course of same therapy if first ineffective

BV: Alternate Treatment Regimens

- Metronidazole 750 mg extended release tablets PO QD X 7 days
- Clindamycin bioadhesive cream 2%, 5 grams vaginally X1
  - Clindamycin cream can degrade latex condoms
- Boric Acid 600 mg capsules PV QHS X 21 days

What if she's pregnant?

- Metronidazole gel 0.75%, 5 grams vaginally X 5 days
- Metronidazole 500 mg PO BID X 7 days
- Metronidazole 250 mg PO TID X 7 days
  - Metronidazole is not teratogenic or mutagenic
  - Cure rate 70%

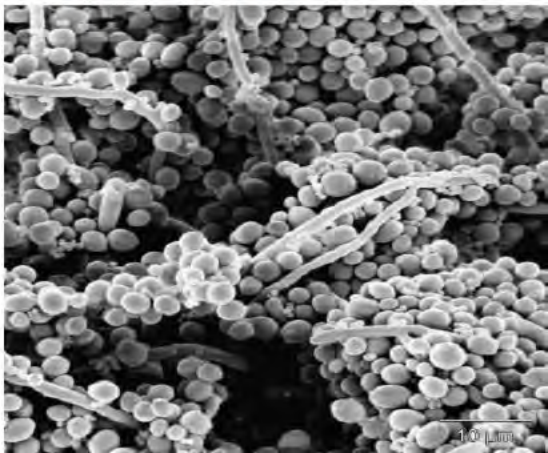
- Clindamycin 2% cream, 4 grams vaginally X 7 days
- Clindamycin 300 mg PO BID X 7 days
  - Cure rate 85%

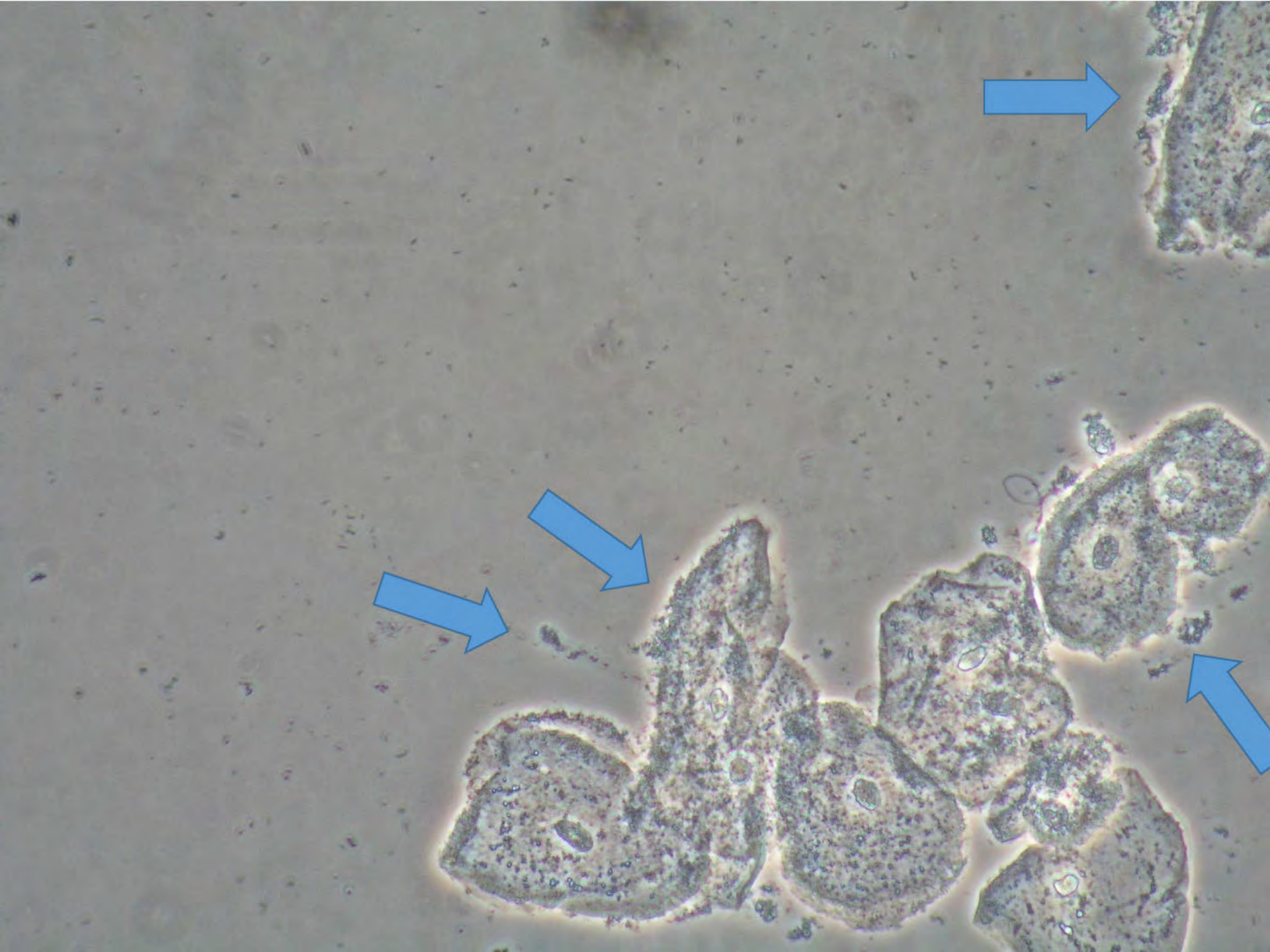
The Problem of Recurrence

- Recurrence is common: 15-30% within 3 months after treatment, 50-70% within 12 months.
- Risk factors:
  - prior history of BV,
  - having a regular sex partner,
  - having female sex partner,
  - presence of both G. vaginalis and A. vaginae
- Mechanisms:
  - reinfection by sexual activity,
  - failure to re-establish normal lactobacillus predominant flora
  - formation of "biofilms"

Biofilms

- Highly organized sessile microbial communities of bacteria, fungi, or both
- Decrease susceptibility to antimicrobial agents
- Enhance the spread of antimicrobial resistance
- Provide a safe haven for other opportunistic pathogens to thrive and be a source of infection
- “Clue Cells” are desquamated cells coated with bacterial biofilm





Biofilm Defense

- Free floating organisms adhere to cell surface
- Adherent cells up-regulate genes involved in matrix production
- Biofilm formation begins: physical architecture for microbial interactions, facilitates feedback
- Open water channels for nutrient circulation
- Biofilms are highly resistant to antimicrobial agents and host defenses

How Biofilms Do It

- Incomplete penetration of antibiotics and host immune cells into the matrix
- Physiologic changes in cells in the matrix promoting spore formation, anaerobic niches
- Communication between cells in the matrix
- Efflux pumps which remove antibiotics from cells
- Enzymes and pH changes which deactivate antibiotics, change drug target structures
- “Persister cells” able to survive antibiotic concentrations well above the MIC

Preventing BV Recurrence

- Try a different agent or regimen for recurrence
- Try vaginal metronidazole if oral metronidazole not tolerated
- Probiotics: (oral, intravaginal, +/- antibiotics) mixed results, can delay time to recurrence: L. acidophilus, L. rhamnosus, L. fermentum, L. gasseri best

Preventing BV Recurrence

- Partner treatment is controversial
- Clean shared sex toys
- Consistent condom therapy for 3-6 months
- Vaginal Boric Acid may influence biofilms

Maintenance Therapies for BV

- Metronidazole 0.75% vaginal gel QHS X 10, then twice weekly X 4-6 months
  - Sobel 2006
- Monthly oral metronidazole 2 gm PO with fluconazole 150 mg
  -CDC
- 500 mg metronidazole or tinidazole PO BID X 7 days, then 600 mg vaginal boric acid capsules QHS X 21 days, then twice weekly vaginal metronidazole gel X 16 weeks
  -Nyirjesy. Management of Persistent Vaginitis. Obstet Gynecol 2014; 124 (6):1135-1146.

Abstain from alcohol for 24 hours after completion of metronidazole or 72 hours after completion of tinidazole

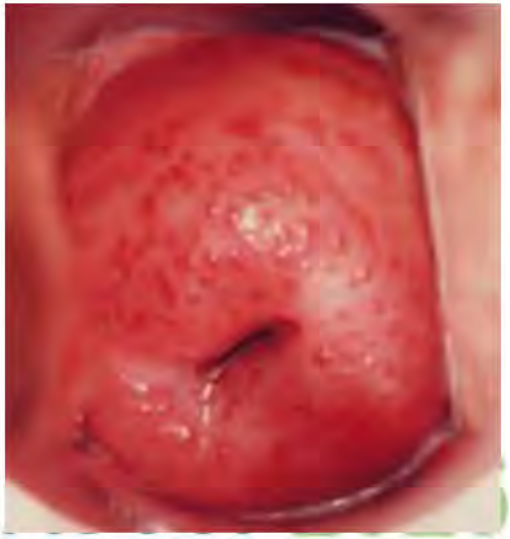
Trichomonas

Trichomonas Vaginitis

- *Trichomonas vaginalis*: flagellated motile anaerobic protozoan organism which colonizes the vagina and urethra, para-urethral and Skene glands
- Transmission primarily sexual
- Can transmit via fomites, hot tubs, pools
- Must treat orally to address all reservoirs
- Must treat patient and partner to prevent reinfection, condoms until treatment complete

Trichomonas: Clinical Presentation

- Discharge, irritation, itching, burning, soreness, dyspareunia
- Dysuria and lower abdominal pain common
- Copious yellow or green frothy vaginal discharge
- Inflammation and erythema of vestibule and vagina, “strawberry cervix” and vaginal mucosa (punctate hemorrhages)
- Vaginal pH >5



Risk Factors for Trichomonas Infection

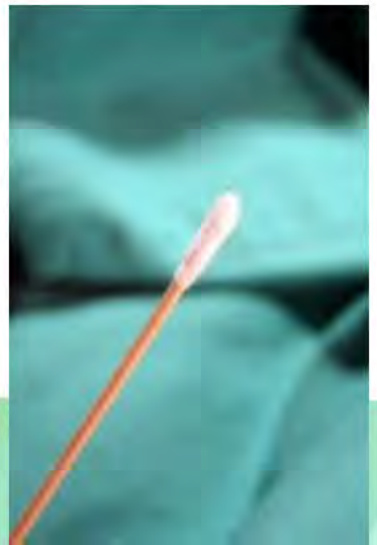
- Change in sexual partners
- Frequent sexual intercourse
- Having three sexual partners or more in a month
- Coexistent sexually transmitted infections (HIV)
- Illicit drug use, smoking
- Lack of barrier contraception
- Low socio-economic status

Implications of Trichomonas Infection

- ***Pregnancy complications***:
  - Premature rupture of membranes
  - Preterm birth,
  - Low birth weight
- ***Gynecological complications***:
  - Often coexists with other STD's, HPV and BV
  - PID and tubal infertility
  - Endometritis after delivery, abortion or surgery
  - Facilitates acquisition and transmission of HIV

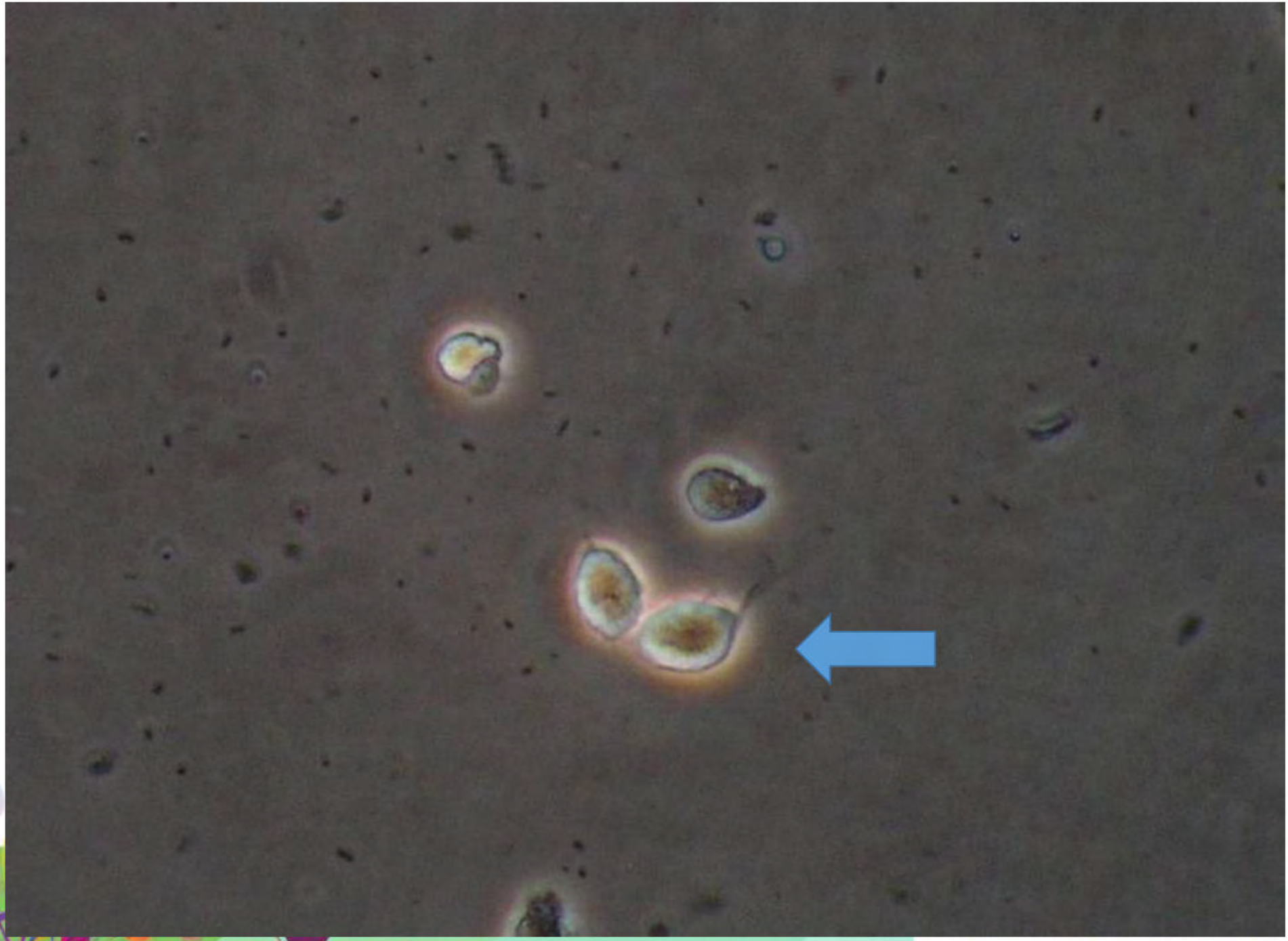
Testing for Trichomonas

- ***Test for Trichomonas if wet mount is negative and***:
  - History of Trichomonas infection with persistent symptom after treatment
  - Increased vaginal pH and WBC's on microscopy
  - Trichomonas reported on pap test
  - Patient request
  - If pt symptomatic, pH elevated, and microscopy not available



Testing Options

- ***FDA-approved NAATS (transcription amplification of RNA)***
  - **APTIMA T. vaginalis assay** (Hologic Gen Probe, San Diego, CA). Vaginal swab, urine. Sensitivity 95-100%, Specificity 95-100%
  - **BD Probe Tec TV Qx Amplified DNA assay** (Becton Dickinson, Franklin Lakes, NJ). Endocervix, vaginal, urine.
- ***Point of care antigen detection test***
  - **OSOM Trichomonas Rapid Test** (Sekisui Diagnostics, Framingham, MA). 10 minute assay. Sensitivity 82-95%, Specificity 97-100%
- ***DNA hybridization probe***
  - **Affirm VP III** (Becton Dickinson, Sparks, MD. 45 minute assay. Sensitivity 63%, Specificity 99.9%
- ***Culture*** (vaginal swab preferred, older gold standard)
  - Sensitivity 75-96%, Specificity 100%.
- ***Wet Mount***
  - Sensitivity 51-65%, decreasing to 20% after 1 hour



Trichomonas on Wet Mount

Inflammatory Effects of T. vaginalis

- Lipophosphoglycan (LPG) on organism's surface allows adherence to host cells
- LPG triggers inflammatory response and chemokine upregulation in the host and gene upregulation in the parasite
- Trichomonas cysteine proteases digest host IgG, IgM, IgA and anti-inflammatory mediators, and induces apoptosis in vaginal epithelial cells and multiple immune cell types
- Induces host cells to produce galectin-1 which promotes viral attachment and replication (HIV)

Treatment for Trichomonas: Treat all partners

- Metronidazole 2 gm PO single dose. NOT VAGINAL GEL
- Tinidazole 2 gm PO single dose
- Metronidazole 500 mg PO BID X 7 days (same for initial treatment failure)
- **Cure rates of 90-95%**

- Tinidazole more expensive, higher serum levels, longer half life, fewer GI side effects than metronidazole.
- Abstain from sex until both partners treated and symptoms resolved. Test for other STD's and HIV
- Retest 3 months after treatment

What if she's pregnant? Treat all partners

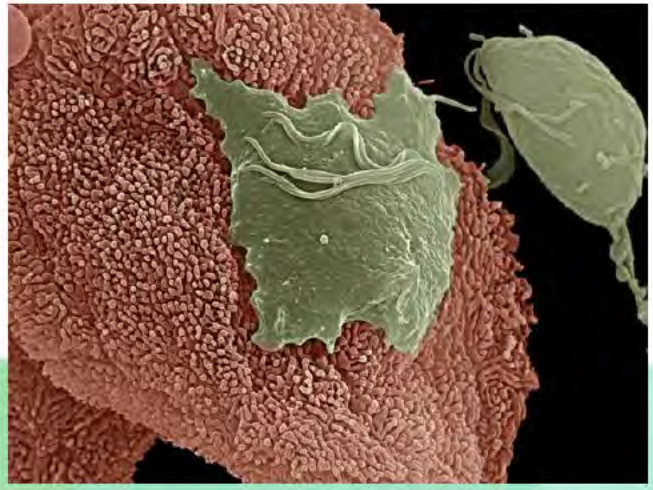
- Metronidazole 2 gm orally in a single dose in any trimester
  - Metronidazole is pregnancy risk category B
  - Metronidazole is secreted in breastmilk in lower concentrations than used to treat neonatal infections
  - Withhold breastfeeding until 12-24 hours after single 2 gm dose of metronidazole
- Tinidazole is pregnancy risk category C and is not sufficiently studied. Animal studies suggest moderate risk: avoid in pregnancy and defer lactation for 72 hours after single 2 gm dose of Tinidazole

Trichomonas and HIV

- Up to 53% of HIV + women have trichomonas. Screen at entry to care and at least annually thereafter
- Treatment of trichomonas if HIV+ decreases viral load and viral shedding, decreases PID
- Treat with metronidazole 500 mg PO BID X 7, NOT single dose therapy
- Treat HIV+ pregnant women with trichomonas to reduce vertical transmission of HIV
- Retest HIV+ women with trichomonas 3 months after treatment with NAAT testing

Trichomonas Treatment Failures

- Causes of treatment failure:
  - patient non-compliance,
  - reinfection, multiple sex partners, lack condom use
  - metronidazole resistance (4%-10%), tinidazole resistance (1%)
- If patient allergic to metronidazole: oral or parenteral desensitization to metronidazole followed by treatment is highly effective



Persistent or Recurrent Trichomoniasis (treat all partners)

1. If 2 gm metronidazole PO single dose therapy fails:
2. Metronidazole 500 mg PO BID X 7 days. If this fails:
3. Therapy for repeated treatment failure:
   - Metronidazole 2 gm PO QD X 7 days
   - Tinidazole 2 gm PO QD X 7 days

For Repeated Treatment Failures

- Consider testing organism for metronidazole resistance
  - CDC: 404-718-4141
  - http://www.cdc.gov/std

Treatment for nitroimidazole-resistant infections:

Tinidazole 1 gm PO BID to TID X 14 days, plus intravaginal tinidazole 500 mg/d X 14 days.

Summary

- Oral and vaginal antifungals are equally effective for the treatment of uncomplicated vulvovaginal candidiasis. 6 months of weekly or semiweekly maintenance therapy needed for suppression of recurrent infections
- Clindamycin and metronidazole are equally effective for BV. Recurrences are common and may require combined therapies for suppression
- Nitroimidazole drugs orally in a single dose or longer courses effective for trichomonas
- Treatment in pregnancy prevents complications