The 2015 CDC STD Treatment Guidelines In Action:

A Case-Based Approach to STD Management in Adolescents & Young Adults

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Disclosures

- In the past 12 months, Drs. Hsu, Heller, and Hardy have **NOT** had significant financial interests or other relationships with manufacturer(s) of product(s) or provider(s) of service(s) that will be discussed in this presentation
- This presentation may include discussion of pharmaceuticals or devices that have not been approved by the FDA
  - "Off-label" use of extra-genital (rectal and pharyngeal) nucleic acid amplification tests (NAATs) for gonorrhea and chlamydia
  - "Off-label" use of HIV assays for diagnostic purposes

Before we begin …

Goals

- Distinguish relevant updates to epidemiology, diagnosis, and treatment for STD syndromes and specific infections (e.g. PID, vaginitis, HSV, HPV, urethritis)
- Highlight areas of CDC STD Treatment Guidelines that should be read carefully for detailed recommendations
- Accomplish this in an **interactive** fashion …

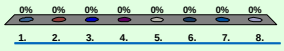
CDC STD Treatment Guidelines Development

- Evidence-based on principal outcomes of STD therapy
  1. Microbiologic eradication
  2. Alleviation of signs & sx
  3. Prevention of sequelae
  4. Prevention of transmission
- Recommended regimens preferred over alternative regimens
- Alphabetized unless there is a priority of choice
- Reviewed April 2013; published 2015
- www.cdc.gov/std/treatment
  - Pocket guides, teaching slides, charts, app

Language in yellow highlighted boxes reflects changes between 2010 and 2015 guidelines

What do *YOU* want to hear about most?

1. Dealing with HSV
2. BV and recurrent BV
3. Recurrent genital lesions
4. Persistent urethritis
5. STD screening for MSM
6. Rectal pain and tenesmus
7. Persistent chl+
8. Tricks for trich



There are second chances in life …

1. Dealing with HSV
2. BV and recurrent BV
3. Recurrent genital lesions
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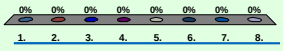


Cases

1. 17 yo female with first-time genital lesions
2. 19 yo female with vaginal discharge
3. 20 yo female with recurrent genital lesions
4. 20 yo male with dysuria and discharge
5. 24 yo male who has male partners
6. 25 yo male with rectal pain and tenesmus
7. 16 yo female with persistent chlamydia positivity
8. 27 yo female with trichomoniasis

Resources and End Slides

Case 1

Case History

A 17 year old presents with first time genital ulcerations:

She has never had any prior genital symptoms. She has had one partner in her lifetime. She has no other history of STD. What else would you like to know?

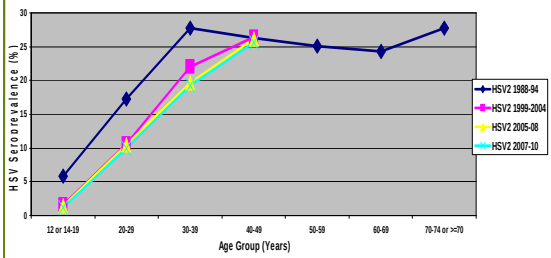
What diagnostic testing do you perform today?

1. Nothing - it's most likely herpes
2. Herpes culture
3. Herpes PCR
4. Herpes serology
5. Syphilis serology

0% 0% 0% 0% 0%

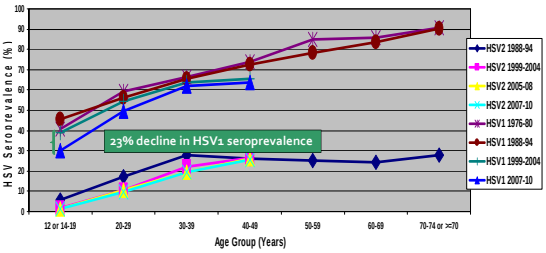
1. 2. 3. 4. 5.

NHANES HSV2 Seroprevalence



Johnson et al. *NEJM* 321:7-12, 321, 1989
Schillinger et al. *STD* 31:753-60, 2004
Fleming et al. *NEJM* 337:1105-11, 1997
Xu et al. *JAMA* 296:964-73, 2006
Xu et al. *MMWR* 59:456-9, 2010
Bradley et al. *JID 209:325-33*, 2014

NHANES HSV1&2 Seroprevalence



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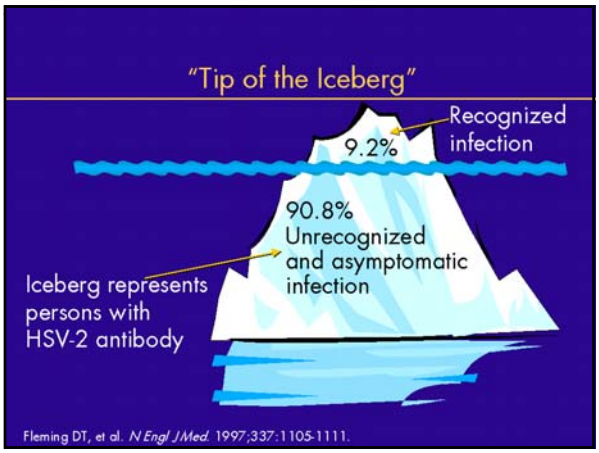
Bradley et al. *JID 209:325-33*, 2014

"Almost 1 in 10 adolescents who 10 years ago already would have acquired HSV1 earlier in life now are vulnerable to getting a primary infection as they enter their sexually active years." Kimberlin, JID 2013

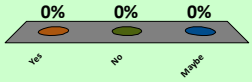


Genital Herpes Manifestations

- Classic multiple painful vesicular or ulcerative lesions often absent
- Systemic manifestations (fever, headache, and malaise) can occur
- Local manifestations (pain, itching, dysuria, vaginal or urethral discharge, and tender local inguinal adenopathy) common, and can be subtle with recurrent genital herpes
- Complications include aseptic meningitis, autonomic nervous system dysfunction, transverse myelitis, sacral radiculopathy, and fungal superinfection

Your clinical experience: Does HSV1 recur less often than HSV2?

A. Yes
B. No
C. Maybe

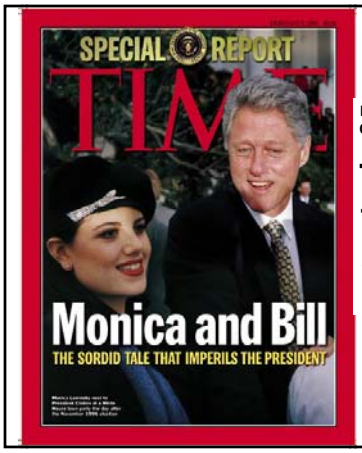


What About Genital HSV-1?

- **HSV1 now causes MOST of first genital HSV episodes in young adults**
  - Among >3400 HSV double-seronegative women 18-30 yrs from control arm of herpes vaccine trial who acquired disease during a 20 month period:
    - 5.3% became infected
    - HSV1 2.3x *more common* than HSV2 infection
    - Genital HSV1 2.5x *more common* than oral HSV1
  - Increasing proportion of anogenital herpetic infections have been attributed to HSV-1 infection in women and MSM
- Primary genital HSV1 and HSV2 remain *indistinguishable* clinically, and are treated with the same antiviral regimens
- Genital HSV1 does not recur as often as genital HSV2 **(?)**

What are the implications for genital HSV vaccine development?

Bernstein DI et al., *CID* 2013
Whitley RJ, *CID* 2013
Ryder N et al., *STI* 2009
Roberts CM et al., *STD* 2003



Monica Lewinsky & Bill Clinton Feb. 2, 1998

They are in the majority, *not* the minority …

Treatment First Clinical HSV Episode

- Acyclovir 400 mg PO tid
- Acyclovir 200 mg PO 5x per day
- Famciclovir* 250 mg PO tid
- Valacyclovir** 1 g PO bid

for 7-10 days or until clinical resolution

*not licensed for <18 yrs
**not licensed for pre-pubertal

Treatment
Episodic Recurrent HSV

- Acyclovir 400 mg PO tid
- Acyclovir 800 mg PO bid
- Valacyclovir** 1 g PO qd
- Famciclovir* 125 mg PO bid all for 5 days, OR
- Valacyclovir** 500 mg PO bid for 3 days, OR
- Acyclovir 800 mg PO tid for 2 days, OR
- Famciclovir* 1 g PO bid for 1 day, OR
- Famciclovir* 500 mg PO x 1 dose, then 250 mg PO bid for 2 days

Start during prodrome or within 1 day of lesion onset

*not licensed for <18 yrs
**not licensed for pre-pubertal

CDC 2015 STD Treatment Guidelines

Treatment:
HIV+ Episodic Recurrent HSV

- Acyclovir 400 mg PO tid
- ~~Acyclovir 800 mg PO bid~~
- Valacyclovir* 1 g PO ~~qd~~ **bid**
- Famciclovir** ~~125 mg~~ **500 mg** PO bid

all for 5 – 10 days, OR

- ~~Valacyclovir* 500 mg PO bid for 3 days, OR~~
- ~~Acyclovir 800 mg PO tid for 2 days, OR~~
- ~~Famciclovir** 1 g PO bid for 1 day~~
- ~~Famciclovir** 500 mg PO x 1 dose, then 250 mg PO bid x 2 days~~

Short course therapy not advised for HIV-infected

Start during prodrome or within 1 day of lesion onset

*not licensed for pre-pubertal
**not licensed for <18 yrs

Treatment
Daily Suppressive HSV Therapy

- Among patients with frequent recurrences (≥6/yr), reduces frequency by 70-80%
- Safe and efficacious
  - Acyclovir up to 6 yrs documented experience
  - Valacyclovir and famciclovir up to 1 yr
- Regimens
  - Acyclovir 400 mg PO bid
  - Famciclovir* 250 mg PO bid
  - Valacyclovir** 1 g PO qd
  - Valacyclovir** 500 mg PO qd
    (may be less effective in those with ≥10 episodes/yr)
- *Discuss need to continue therapy annually with patient*

***not licensed for <18 yrs**
****not licensed for pre-pubertal**

Treatment:
HIV+ Daily Suppressive HSV Therapy

- Efficacious in decreasing clinical manifestations of HSV in HIV-infected persons
- **Regimens for persons with HIV**
  - **Acyclovir 400 - 800 mg PO bid to tid**
  - **Valacyclovir* 500 mg PO bid**
  - **Famciclovir** 500 mg PO bid**

Discuss need to continue therapy annually with patient

*not licensed for pre-pubertal
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Counseling

- Discuss natural history
  - Potential for recurrence
  - Asymptomatic shedding
  - Sexual transmission risk
- First episode
  - Discuss episodic or suppressive therapy
- Encourage partner notification
  - But they may already be infected and asymptomatic, and should be offered serology to determine if risk for HSV acquisition exists
- Abstain from sex when lesions or prodrome present
- Condoms reduce risk of transmission
- Transmission can occur when asymptomatic
  - More shedding with HSV2 than with HSV1
  - More shedding in first yr after acquisition of HSV2
  - Risk of HSV2 transmission reduced with suppressive therapy
- Risks for neonatal infection
  - Discuss with men and women
  - Counsel pregnant women not known to be infected with either HSV1 or 2, to avoid genital exposure
- Asx persons dxed with HSV2 by type-specific serology should receive same counseling messages as persons with sx
- HSV2-infected persons are at greater risk for HIV acquisition following exposure

CDC 2015 STD Treatment Guidelines

Counseling

- Study from 2004 showed that patients were satisfied with their care if they had 15 minutes face-to-face with practitioner
- Most felt that a follow-up visit was helpful to answer questions and clarify key points
- Much of the initial information <u>was not retained 48 hours after visit</u>

Patrick et al. *Sexually Transmitted Infections* 2004;80:192-197

I HAVE WHAT ?!?

Initial visit suggestions for confirmed cases

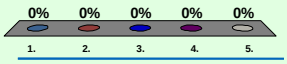
- The 4 T's
  - Transmission (Acquisition)
  - Treatment
  - Telling your partner
  - Therapist

Marshall, Contraceptive Tech, Boston 2010

Case 2

19 yo sexually active female, vaginal discharge x 3 days. What is most likely diagnosis?

1. Yeast
2. ✓ BV
3. Trich
4. Chlamydia
5. Not sure



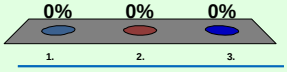
Etiologies of Vaginitis

	National	Anderson et al.
Yeast	20-25%	17-39%
BV	40-50%	22-50%
Trich	15-20%	4-35%
Undiagnosed	30%	7-72%

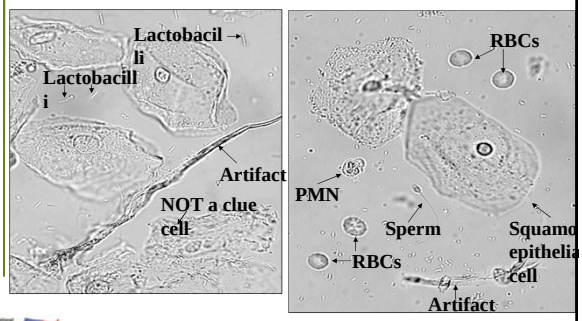
Anderson, M. R. et al. *JAMA* 2004;291:1368-1379

Do you still have a microscope in your office?

1. No
2. Yes, but it's not working
3. Yes, and it even works!



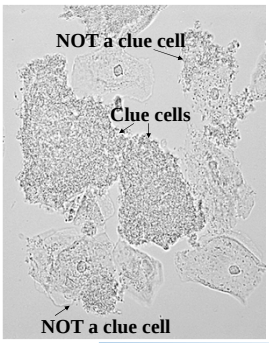
Wet Prep: Normal Findings, Saline, 40x objective



Source: Seattle STD/HIV Prevention Training Center at the University of Washington

Wet Prep: Bacterial Vaginosis

Saline: 40X objective



Source: Seattle STD/HIV Prevention Training Center at the University of Washington

Sensitivity and Specificity of Clinical Criteria for BV

	Sens	Spec
Thin homogenous discharge	79%	54%
pH ≥ 4.5	89%	74%
Positive amine test	67%	93%
Clues cells (>20%)	74%	86%
pH ≥ 4.5 and discharge	69%	86%
pH ≥ 4.5 and amine odor	64%	95%
pH ≥ 4.5 and clue cells	69%	92%
Clue cells and amine odor	63%	95%
Clue cells and discharge	61%	91%
Amine odor and discharge	58%	94%
Amsel's criteria (≥ 3 of 4)	69%	93%

Gutman et al. Obstet Gynecol 2005;105:551-6

Bacterial Vaginosis

- Screening: No changes to recs for screening in pregnancy (still not routinely recommended)
- Treatment of non-pregnant women: no changes

Proposed
BV in pregnancy: oral therapy not superior to topical therapy, either oral or topical regimens can be used

Treatment

- Recommended
  - Metronidazole 500 mg PO BID x 7 days OR
  - Metrogel 0.75% 5 g intravaginally qhs x 5 days OR
  - Clindamycin cream 2% 5 g intravaginally qhs x 7 days
    - Oil-based, might weaken latex condoms and diaphragms for 5 days after use
- Alternative
  - Tinidazole 2 g PO qd x 2 days
  - Tinidazole 1 g PO qd x 5 days
  - Clindamycin 300 mg PO BID x 7 days OR
  - Clindamycin ovules 100 mg intravaginally qhs x 3 days
- Pregnant
  - Metronidazole 500 mg PO BID x 7 days OR
  - Metronidazole 250 mg PO TID x 7 days OR
  - Clindamycin 300 mg PO BID x 7 days
- Suppressive treatment:
  - Metrogel 0.75% twice weekly for 4-6 months
  - Oral nitroimidazole followed by boric acid intravaginally and suppressive metronidazole gel

2010 CDC STD Treatment Guidelines

Recurrent BV

- Recurrent disease remains common
  - Rates up to 70% within 3 months
- Reasons for recurrence unclear
  - Re-infection
  - Failure of lactobacilli to re-colonize
  - Inadequate length of therapy
  - Persistence of unidentified host factor
- Despite comparable early cure rates, higher recurrence rates associated with shorter treatment
  - Single-dose 2 g metronidazole no longer recommended
  - 3-day clindamycin course no longer recommended

Recurrent BV: Treatment

- Limited data on best approach
- First recurrence
  - Repeat same *OR* use different first-line regimen
- Multiple recurrences following initial tx
  - 0.75% metronidazole gel twice weekly x 4–6 months: (benefit might not persist when therapy discontinued)
  - Metronidazole or tinidazole 500 mg PO bid x 7 days, then boric acid 600 mg intravaginally* daily x 21 days, then 0.75% metronidazole gel twice weekly x 4–6 months
  - Monthly metronidazole 2 g PO administered with fluconazole 150 mg PO has also been evaluated as suppressive therapy (reduced incidence of BV and promoted colonization with normal vaginal flora)

*requires compounding pharmacy

2010 CDC STD Treatment Guidelines

Partner Management

- Routine treatment of male sexual partners of women with BV is not recommended
- After multiple occurrences, some consider empiric treatment of male sex partners to see if recurrence rate diminishes, but this approach has not been validated.
- Female partners of women with BV should be examined and treated if BV is present

SUMMARY: Utility of Hx and Exam for Vaginitis

- **No single symptom has enough predictive power to confidently diagnose any of 3 main causes of vaginitis**
- **Symptoms & signs can *suggest* a dx**
  - **Yeast: assoc w/ itching, cheesy d/c, redness and self-dx; watery d/c or odiferous d/c makes it less likely**
  - **BV: assoc w/ sensation of increased d/c and c/o of odor; absent d/c makes it less likely**
  - **Inflammation relatively specific for yeast, but not always there, and sometimes assoc w/ trich**

Anderson, M. R. et al. JAMA 2004;291:1368-1379

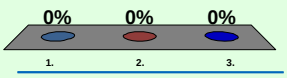
SUMMARY: Office Lab Tests for Vaginitis

- **Wet mount remains best way to make dx**
  - **No yeast or trich on microscopy does not mean no yeast or trich as cause**
  - **Presence of clue cells makes yeast unlikely**
  - **Lack of lactobacilli and presence of bacilli with corkscrew motility highly assoc with BV**
  - **Other diagnostics (e.g. Affirm™ VPIII) useful in settings without microscopes or microscopic expertise**
  - **Microbiome sequencing not ready for prime time yet**
- **Use pH testing**
  - **Yeast: normal pH!!!**

Anderson, M. R. et al. JAMA 2004;291:1368-1379

Where do you typically obtain vaginal wet mount samples?

1. Lateral side wall of vagina
2. From the lower tongue of the speculum you just removed
3. Not consistent/not sure



Workshop Readiness

- How to obtain pH
  - Swab lateral wall of vagina 1/3-1/2 way in
  - Roll swab on narrow range pH paper (3.8-5.5)
  - Compare color to reference
  - Note - pH may be affected by cervical mucus, blood, sperm

Workshop Readiness

- Wet mount method #1
  - Swab lateral vaginal wall and place in 0.5 cc room- temperature saline
  - Agitate swab in saline to mix; place drop on slide, add coverslip and read under microscope
- Wet mount method #2
  - Place drop of saline on slide
  - Collect sample from vagina, mix into saline
- KEY POINT: keep sample warm and wet on the way to the microscope!

Workshop Readiness

- KOH preparations
  - swab lateral wall of vagina
  - roll swab onto slide
  - add 10% KOH and mix with swab
  - whiff immediately- fishy odor is “positive”
  - add coverslip and wait 2-5 minutes for KOH to digest cells

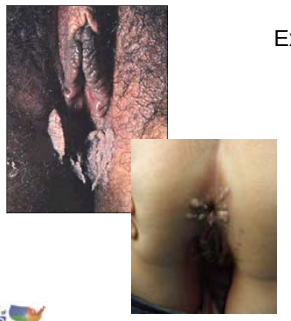
Back To Case Menu ...

Case 3

Dora

- 20 year-old woman G_2P_0 presents with genital lesions increasing in size for 2 weeks
- 5 lifetime sexual partners, her most recent partnership began 3 months ago
- H/o genital warts 1 yr ago. She broke up with her partner because she thought warts indicated that he was cheating on her
- Using oral contraceptives for birth control

Dora’s Exam

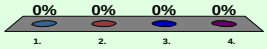


Exam shows multiple nontender exophytic lesions on the labia perineum, and external anus

STD Atlas, 1997

Why did Dora's warts come back?

1. Her original HPV infection has recurred
2. She was infected with a new HPV type
3. She has become immunocompromised
4. Any of the above ✓



Recurrent Genital Warts

- Reasons for late recurrence:
  - ♦ Reactivation of initial infection
  - ♦ Reinfection with new HPV types
  - ♦ Intercurrent immunodeficiency
- Test for pregnancy
- Screen for GC, chlamydia, syphilis
- Annual Pap smear
- Recommend HIV test

HPV DNA Tests

Qiagen Hybrid Capture II®
- RNA probes: 13 high risk types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 & 68

Hologic Cervista®
- 14 high risk types (as above plus type 66)
- Separate HPV 16/18 test

Roche Cobas HPV®
- 14 high risk types
- Separate HPV 16/18 test

GenProbe Aptima HPV®
- 14 high risk HPV types

Package Inserts

When should I order an HPV test?

- ✓ Triage of ASC-US Pap result (if age ≥21)
- ✓ Co-test with Pap in women age 30+
- ✓ Very selective follow up situations

When should I NOT order an HPV test?

- ✗ Screening in women under 30
- ✗ Any use in women under 21
- ✗ Diagnosis of genital warts
- ✗ Testing in males
- ✗ ASC-H, LSIL or higher grade lesions
- ✗ Before vaccination
- ✗ STD screening

2012 Updated Consensus Guidelines for Management of Abnormal Cervical Cancer Screening Tests and Cancer Precursors. www.ASCCP.org

Dora's results

- Not pregnant
- GC/CT-negative
- Syphilis-negative
- HIV-negative
- But she still has warts…

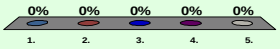
What next???

Pretreatment Education

- Goal is removal of symptomatic warts
- Warts may resolve on their own (10-30%)
- Multiple treatments are usually required
- Recurrence is common (20-50% by 6 mo)
- Removal of warts likely reduces but probably doesn't eradicate infectivity
- Treatment may have uncomfortable side effects
- Treatment may cause persistent hypo or hyperpigmentation (e.g. ablative modalities, Imiquimod)

Which wart treatment do you prescribe most often?

1. Podofilox 0.5% solution or gel (Condylox)
2. Imiquimod 5% cream (Aldara)
3. Sinecatechins 15% ointment (Veregen)
4. I do office-based therapy
5. I don't have a favorite



Genital Warts: Treatment

- No best or curative therapy
- All therapies have potential side effects and high recurrence rates
- Consider:
  - Provider's experience
  - Patient's preference and abilities
  - Size, number and location of warts
  - Potential side effects
  - Availability and expense of therapy

Genital Warts: Treatment

Recommended patient-applied therapy:

- Podofilox 0.5% BID x 3 d, 4 days off; up to a total of 4 cycles
- Imiquimod 5% QHS (wash off after 6-10 hours) 3x/week for up to 16 weeks
- **NEW:** Sinecatechins 15% ointment apply TID x 16 weeks (DO NOT wash off)

Recommended provider-applied therapy:

- TCA, BCA or podophyllin resin
- Cryotherapy with liquid nitrogen
- Surgical removal

Alternative: intralesional interferon, photodynamic therapy, topical cidofovir

2010 CDC STD Treatment Guidelines

New Genital Wart Treatment

- Sinecatechins (Veregen) a green tea extract ointment (15% strength) approved for treatment of genital warts
- Cost $251 for 15 grams
- Not recommended in pregnancy, HIV, HSV
- May weaken condoms/diaphragms

Imiquimod Vs. Sinecatechins

- Age
  - Imiquimod FDA-approved down to age 12 years
  - Sinecatechins FDA approved 18 years and older
- Sinecatechins dosed more frequently
- No head-to-head trials
  - Similar efficacy rates in separate trials
    - Week 16 complete clearance rates
      - Men 30-50% (vehicle 5-30%)
      - Women 60-70% (vehicle 20-40%)
  - Similar adverse events profile in separate trials
    - ~50% developed erythema, itching, burning
    - ~30-50% developed pain, erosions/ulcerations

More HPV recs

- *New tx for genital warts: Imiquimod 3.75% cream, apply daily*
- *Move podophyllin out of the box of recommended therapy to alternative (due to reports of severe toxicity)*

Dora's Clinical Course

- You treat Dora in the office with TCA treatments every 1-2 weeks
- After 4 treatments her warts have resolved
- She asks if she could get the HPV vaccine to prevent getting warts in the future!

Dora: Key Counseling Messages

- A diagnosis of genital warts is not indicative of a partner's infidelity
- Unknown how long HPV remains contagious after warts are treated
- Her current partner does not need to be tested for HPV
- Informing her future sex partners about prior history of genital warts may not benefit the health of those partners
- She should continue Pap screening at recommended intervals regardless of her genital wart or vaccination history

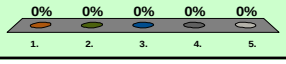
Case 4

20yo heterosexual male was treated with doxycycline for NGU 2 weeks prior.

- **His initial chlamydia and GC tests were negative. His urethral symptoms never fully resolved and he now returns for evaluation. NGU is demonstrated again.**
- **He reports compliance with treatment and sexual abstinence.**

What's next on your differential for persistent urethritis?

1. *T. vaginalis*
2. *M. genitalium*
3. *U. urealyticum*
4. HSV
5. *N. meningitidis*



Recurrent and Persistent Urethritis

- Check first for objective signs of urethritis
  - Mucoid, mucopurulent, or purulent discharge on exam
  - Gram, methylene blue, or gentian violet stain of urethral secretions: ≥2 WBC per oil immersion field
  - Positive leukocyte esterase test on first void urine
  - Urine micro of first void urine sediment: ≥10 WBC per high-power field
- If urethritis confirmed, re-treat with initial regimen if initially non-compliant or if re-exposed to untreated partner
  - Not this patient's case, but this is the usual next step

DDx for Recurrent and Persistent Urethritis

- Consider azithromycin or doxycycline-resistant *U. urealyticum* or *M. genitalium*
  - May benefit from treatment with moxifloxacin 400 mg orally once daily for 7 days
- Consider *T. vaginalis*
  - More common in heterosexual men
    - Test using first-void urine or urethral swab, send for culture (not always available) or NAAT (now commercially available)
    - May benefit from treatment with metronidazole or tinidazole
  - Low probability in MSM
- Consider HSV if recurrent

Mycoplasma genitalium: Epidemiology

- First identified in the early 1980's
- Cause of male urethritis
  - 15-20% of non-gonococcal urethritis (NGU) cases
  - 20-25% of non-chlamydial NGU
  - 30% of persistent or recurrent urethritis
  - More common than *N. gonorrhoeae* but less common than *C. trachomatis*
  - Co-infection with *C. trachomatis* is not uncommon
- Unknown whether it can cause male infertility or other male anogenital tract disease syndromes
- Pathogenic role in women also less clear

Mycoplasma genitalium: Diagnostics

- Very slow-growing organism
  - Culture can take up to 6 months
  - Only a few laboratories in the world are able to recover clinical isolates
- Nucleic acid amplification testing (NAAT) is the preferred method to detect *M. genitalium*
  - Research settings
  - In-house PCR assays (?)
  - None commercially available (YET)

Mycoplasma genitalium: Treatment

- 7-day doxycycline regimen recommended for treatment of urethritis is largely ineffective against *M. genitalium* with a median cure rate of approximately 31%
- 1 gram single dose azithromycin significantly more effective against *M. genitalium* than doxycycline in two randomized trials
  - However, resistance to azithromycin appears to be rapidly emerging: median cure rate for both men and women is approximately 85%, but was only 40% in the most recent trial
  - Individuals with treatment failures after 1g azithromycin regimen frequently have macrolide resistant strains suggesting that single dose azithromycin therapy may select for resistance
- Moxifloxacin (400mg x 7, 10 or 14 days) successfully used to treat *M. genitalium* treatment failures in men and women, with cure rates of 100% in initial reports
  - However, moxifloxacin has been used in a relatively small number of cases and the drug has not been tested in clinical trials

Treatment of MG: RCTs Comparing Doxycycline vs. Azithromycin

Study	Year	N	Drugs & Dosages	Micro Cure
Mena	2009	36 42	DOXY 100mg PO BID X7d AZM 1g PO X1	45% 87% ←
Schwebke	2011	39 45	DOXY 100mg PO BID X7d AZM 1g PO X1 +/- Tinidazole	31% 67% ←
Manhart	2013	35 35	DOXY 100mg PO BID X7d AZM 1g PO X1	30% 40% ←

Mena 2009 *Clin Inf Dis*; 48:1649; Schwebke 2011 *Clin Inf Dis*; 52:163; Manhart 2013 *Clin Inf Dis*;56:934

- Observational studies suggest that longer courses of AZM (e.g. 500 mg PO X1 followed by 250 mg QD X 4d) yield higher cure rates and may lead to decreased emergence of resistance

Reviewed by Manhart 2013 Infect Dis Clin N Am 27;:779

Treatment of MG: Fluoroquinolones

- Ofloxacin, ciprofloxacin, and levofloxacin not highly active Takahashi 2011 *J Infect Chemother*;17:392
- Moxifloxacin
  - No RCTs
  - Observational studies suggest high efficacy of 400mg PO X 7-10d Reviewed by Manhart 2013 *Infect Dis Clin N Am* 27;:779
  - Recent emergence of fluoroquinolone resistant mutations with suggestion of clinical and microbiologic treatment failures

Tagg 2013 *J Clin Microbiol* 51:22; Couldwell 2013 *Int J STD AIDS*; 10:822

Trich Testing in Men

- No approved point of care tests
  - Wet prep not sensitive
- Culture available- urethral swab, semen or urine
  - No conclusive studies on sensitivity/specificity
- Urine and urethral swab NAAT offered through certain labs using analyte-specific reagents (check before sending)

**MSM- *T. vaginalis* does not infect oral sites, rectal prevalence low. Do not test these sites.

Newer Testing Options for Trich

- Microscopy is inferior to new options, including
  - Rapid antigen testing (OSOM)
  - APTIMA TMA Trichomonas Vaginalis
    - Nucleic Acid Amplification Test
    - Utilizes same technology as APTIMA Combo 2 (for CT/GC)
    - May use same specimen type as used with APTIMA Combo 2 (i.e. vaginal swab, endocervical swab, urine)

Huppert CID 2007

Test	Sens	Spec
APTIMA TMA	98.2%	98%
OSOM	90%	100%
Culture	83%	100%
Wet prep	56%	100%

Slide courtesy of Marrazzo, IDSA 2011

Table 3. Differences in test sensitivity stratified by the presence or absence of vaginal symptoms.

Test method	Sensitivity, % (95% CI)		
	All patients (*n* = 330)	Vaginal symptoms present (*n* = 210)	Vaginal symptoms absent (*n* = 120)
Wet mount	50.8 (37.7–63.9)	57.5 (40.8–72.9)	38.1 (18.1–61.5)
Culture	75.4 (62.7–85.5)	77.5 (61.5–89.1)	71.4 (47.8–88.7)
Rapid test	82.0 (70.0–90.6)	92.5 (79.6–98.4)	61.9 (38.4–81.9)
TMA	98.4 (91.2–99.9)	97.5 (86.9–99.9)	100 (83.8–100)

NOTE. The comparator was any test result positive for Trichomonas vaginalis infection. TMA, transcription-mediated amplification.

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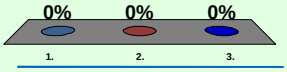
Case 5

Jeremy

- 24 year-old web designer presents for STD and HIV testing
- He reports exclusively male partners, 5 in past 6 months, insertive and receptive oral sex, occasionally anal sex (condoms)
- Good health, no complaints, GC ~3 years ago, last tested for HIV/STD 8 months ago

Do you screen MSM differently than MSW for STI/HIV?

1. Yes
2. No
3. Sometimes



STD Screening for MSM*

Screen at least annually, q 3-6 mos if high risk*
- HIV
- Syphilis
- Urethral GC and CT
- Rectal GC and CT (if anal sex)
- Pharyngeal GC (if oral sex)

Also screen for:
- Hepatitis C (*in HIV+ MSM: repeat as indicated by risk)*

Proposed: Anal Cancer in HIV+ MSM: Annual digital rectal exam may be useful, some centers perform anal Pap and HRA for ASC-US or worse.

* High risk: multiple and/or anonymous partners, drug use, or high risk partners

CDC 2010 STD Tx Guidelines www.cdc.gov/std/treatment

HIV and Syphilis Rates in MSM

- Numerator based upon national 2008 surveillance data on new HIV and syphilis diagnoses
- Denominator based upon estimated proportion of men who engaged in same-sex behavior in past 5 years (3.9%)
- HIV diagnosis rate = 672/100,000 MSM
  - 67x rate of other men
  - 58x rate for women
- 1º and 2º syphilis diagnosis rate = 154/100,000 MSM
  - 71x rate of other men
  - 96x rate for women

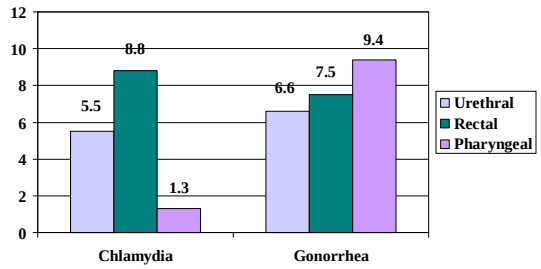
Purcell et al., *Open AIDS J*, 2012

HIV and Syphilis Diagnoses Have Increased in Young MSM

- Survey of trends in HIV and syphilis diagnoses in 73 large metro areas, 2004/2005 and 2007/2008
- Primary and secondary syphilis rates increased in 70% of areas
- Average increases in young black men
  - HIV: 68%
  - Syphilis: 203%

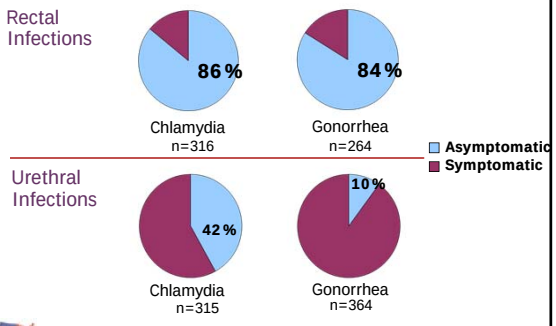
Torrone et al, *JAIDS*, 2011.

How common are CT and GC infections among MSM seeking STD testing?



Kent CK et al, Clin Infect Dis 2005;41:67–74

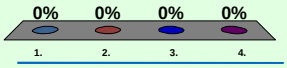
Majority of Rectal Infections in MSM are Asymptomatic



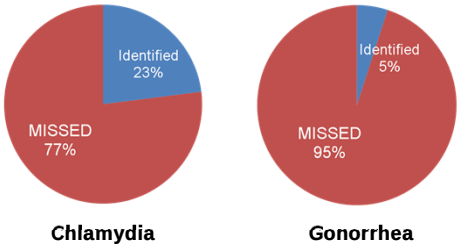
Kent CK et al, Clin Infect Dis July 2005

What proportion of CT/GC infections may be missed if extragenital sites in MSM are not screened?

1. 10%
2. 25%
3. 50%
4. ✓ Over 50%



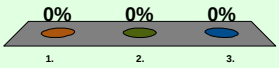
Proportion of CT and GC infections MISSED among 3398 asymptomatic MSM if screening only urine/urethral sites, San Francisco, 2008-2009



Marcus et al, *STD* Oct 2011; 38: 922-4

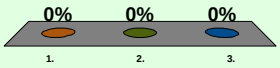
Is GC/Chlamydia NAA testing for non-genital sites available at your site?

1. Yes
2. No
3. Unsure



What is your usual first-line screening test for syphilis?

1. RPR
2. Syphilis EIA
3. Not sure



Syphilis Screening Paradigm

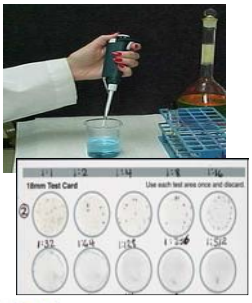
EMERGING NEW…

Treponemal tests (e.g., EIA, CIA, MBIA)
- SPECIFIC TO *TP*
- QUALITATIVE
- REACTIVITY PERSISTS OVER LIFETIME
- REACTIVITY DECLINES WITH TIME

reflex to

Non-treponemal tests (e.g., RPR, VDRL)
- NON-SPECIFIC ANTIBODY TO LIPOIDAL ANTIGENS
- QUANTITATIVE
- REACTIVITY DECLINES WITH TIME

Why switch to EIA/CIA?



180 tests per hour, no manual pipetting

Which algorithm?

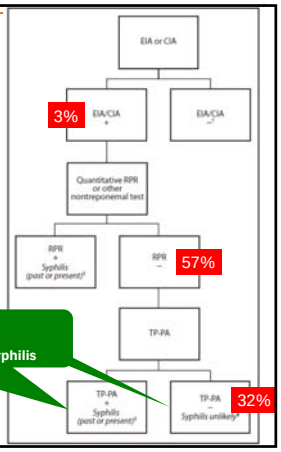
- Traditional algorithm
  - Detects active infection
  - High rate of biologic false positives
    - Confirmation with treponemal test
      - Use of both tests results in a high positive predictive value
  - Can miss early primary and treated infection
- Reverse sequence algorithm
  - Detects early primary and treated infection that might be missed with traditional screening
  - Nontreponemal test needed to detect active infection
  - Ideally, EIAs and CIAs should have perfect specificity
    - EIAs and CIAs are nonspecific
    - High rate of false positive results
    - Varies by risk of population

CDC-Recommended Algorithm for Reverse Sequence Syphilis Screening

Radolf JD et al. ***MMWR***, 2011

Probable false positive EIA
•If high risk: repeat RPR in several weeks

Assess for hx of treated syphilis, sx/signs
•If treated, no further action
•If untreated, consider tx for latent syphilis



CDC Recommendations

•All reactive EIA/CIAs should be reflexed to a quantitative non-treponemal test (e.g. RPR, VDRL)
- •Confirm reactive EIA/CIA
- •Detect active infection

•Discordant specimens (e.g. EIA+/RPR-) should be confirmed with a 2nd treponemal test

•Confirmatory treponemal test should ideally be similarly sensitive and more specific than EIA/CIA
- •TP-PA recommended
- •FTA-ABS test not recommended (lower specificity than other treponemal tests and probably lower sensitivity; also requires trained personnel and a dedicated fluorescence microscope)

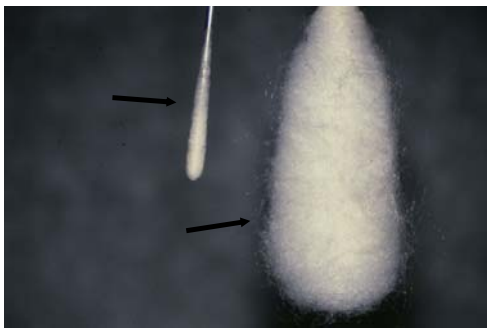
•Results of all 3 tests (EIA, RPR, TP-PA) should be reported simultaneously to provider

MMWR / February 11, 2011 / Vol. 60 / No. 5

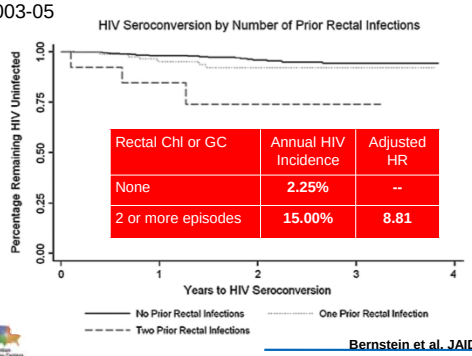
Don't forget the "triple dip" for MSM

- HIV/Syphilis/ HepC Serologies
- Pharyngeal GC NAAT*
- Urine GC/CT NAAT
- Rectal GC/CT NAAT*

*Off-label use . Not FDA-approved for testing at extragenital sites, but many reference labs have validated the assay for use.



MSM in SF City Clinic
Diagnosed with Rectal Chlamydia or Gonorrhea
2003-05



Rectal Chl or GC	Annual HIV Incidence	Adjusted HR
None	**2.25%**	--
2 or more episodes	**15.00%**	**8.81**

Bernstein et al. JAIDS, 2010

Consider HIV PrEP

Case 6

Back to Case Menu ...

Case History

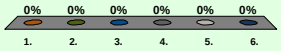
- A 25 year old male graduate student presents with a 6 day history of rectal pain and tenesmus. On a few occasions he has noted blood on the toilet tissue but not on the stool.
- No fever, sore throat, headache, abdominal pain, diarrhea.
- He has been in a monogamous relationship with his boyfriend for the last 5 months and they do not have sexual partners outside the relationship. They were both tested for STIs and were "negative" before they began to have unprotected sex.
- On exam there are three 4-8 mm external anal ulcers. Anoscopic exam revealed several <1 cm ulceration and erythematous friable mucosa in the distal rectum and anus. No purulence.

Proctitis vs. Proctocolitis vs. Enteritis

- Proctitis: rectum
  - Anal pain, tenesmus, constipation, bleeding, mucus streaking of stool
- Proctocolitis: rectum and colon
  - Proctitis symptoms plus diarrhea +/- abdominal cramps
- Enteritis: small bowel
  - Diarrhea, cramps, bloating, abdominal tenderness

While awaiting test results what would likely be the most effective treatment for this patient's ulcerative proctitis?

1. Ceftriaxone + azithromycin
2. Corticosteroid enema
3. Doxycycline
4. Valacyclovir
5. Penicillin IM
6. Some combination of above



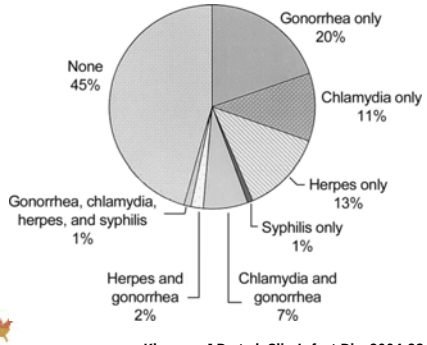
Proctitis: differential diagnosis

- Herpes simplex 1 or 2
- Chlamydia trachomatis
  - Serovars D-K
  - LGV serovars L1, L2, L3
- Gonorrhea
- Syphilis
- Inflammatory bowel disease
- ?HPV

Proctocolitis: differential diagnosis

- *Shigella spp.*
- *Campylobacter spp.*
- *Salmonella spp.*
- *E. coli*
- *Entamoeba histolytica*
- *Cryptosporidium spp.*
- Cytomegalovirus

Frequency of diagnosis of STDs in male patients with proctitis (n = 101), San Francisco City Clinic, 2001–2002



Klausner J D et al. Clin Infect Dis. 2004;38:300-302

HSV proctitis

- Distal proctitis
- Tenesmus, bleeding
- Usually multiple ulcerations on anoscopy.
- May be associated with bowel or bladder dysfunction symptoms
- HSV-1 or HSV-2
- HSV-1 from oral-anal contact or using saliva as lubricant

GC proctitis

- Purulent
- May be ulcerative
- Diagnosis:
  - NAAT
  - Culture if suspected treatment relapse
- Treatment: ceftriaxone 250 mg IM + azithromycin 1 gm

Syphilis proctitis

- Rectal pain, discharge, spasms during bowel movements
- May have multiple ulcerations
- Diagnosis: serology
- Treatment: Benzathine penicillin 2.4 million units x 1

Chlamydia proctitis

- Multiple ulcers, mucopurulent discharge, bleeding, tenesmus
- Biovar trachomatis (genotypes D-K)
- Biovar LGV (genotypes L1-3)
- NAAT testing does not distinguish biovars/genotypes
- If chlamydia is found on NAAT testing with presence of proctitis
  - Consider sending serum for LGV serology (complement fixation titers, microimmunofluorescence tests) – BUT … serologic test interpretation for LGV is not standardized
  - Treat for presumed LGV with doxycycline 100 mg BID x 21 days

What diagnostic tests does our patient need?

- Herpes simplex culture or PCR
- Rectal chlamydia NAAT
- Rectal GC NAAT
- Syphilis serology
- HIV antibody and antigen or PCR
  - Need current baseline - risk of HIV acquisition very high if not already positive
- Consider LGV serology (if HSV culture/PCR is negative)
- ?HSV serology (if needed to convince patient and partner how this could have happened if it does turn out to be HSV proctitis)

Results

- HSV-1 culture **positive**
- Chlamydia NAAT **positive**
- GC NAAT negative
- RPR negative
- HIV antibody negative

ALWAYS CONSIDER MULTIPLE INFECTIONS!

Rectal chlamydia treatment

- Single dose azithromycin 1 gram: 13-21% failure rate
- Doxycycline 100 mg BID x 7 d: 95-100% cure rate
- LGV treat for 21 days
  - If unable to determine if it is LGV and patient is treated with single dose azithromycin or with doxycycline x 1 week then retest to confirm cure

Steedman NM, McMillan A. Int J STD AIDS 2009;20:16-8
Hathorn E, et al. Sex Trans Infect 2012;88:352-4.

Consider HIV PrEP

Back To Case Menu...

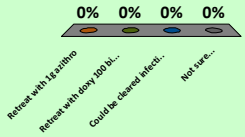
Case 7

16yo with chlamydia…

- You recently treated your 16yo patient for chlamydia with 1g azithromycin
- You treated her male partner with EPT at the same time (1g azithro)
- 4 weeks later you get a call from an urgent care provider because her chlamydia test is positive
- She denies any sexual activity since her treatment (she broke up with her boyfriend after the chlamydia)

What do you do?

A. Retreat with 1g azithro
B. Retreat with doxy 100 bid x 7d
C. Could be cleared infection but positive test, test again 3 months after infection
D. Not sure...



Time to clearance by NAAT: Not well defined

- 115 women with chlamydia, treated with 1g azithromycin
- Vaginal NAAT on day 0,3,7,14

Day after treatment (N=61)	% with negative NAAT
Day 0	0/61 (0%)
Day 3	7/61 (12%)
Day 7	28/61 (46%)
Day 14	48 (79%)

Linear regression predicted time to clearance 17 days (95 CI: 16-18 days)

Renault et al. Sex Health 2011;8:69-73

Azithromycin vs. Doxycycline

- CDC recommendation based on meta-analysis of 12 RCTs
  - Efficacy azithro 97%, doxy 98%
  - Less sensitive tests (vs NAATs) may underestimate treatment failure
  - Doxy adherence not assured
- Question raised about efficacy of azithro
  - 3 studies, efficacy <90%

RCT: Chlamydia Treatment Azithromycin vs. Doxycycline

Antibiotic group	Treatment failures	Efficacy
Doxycycline	0	100%
Azithromycin	5 (3.2%; 95%CI 0.4-7.4%)	97%

- Captive audience: juvenile detention facilities
- Difference in failure rates was 3.2%
- The non-inferiority of azithromycin was not established
- Both medications are effective
- Azithro had some treatment failures, but adherence is likely to be much greater with single-dose azithromycin

Geisler et al. NEJM 2015;373:2512-2521

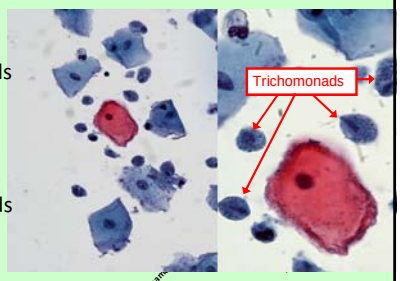
Case 8

Dehlia

- 27 y.o. woman presents for Pap
- Good health, no symptoms
- Unmarried, steady boyfriend for nearly a year
- No history of abnormal Pap or prior STDs
- IUD for pregnancy prevention

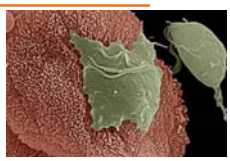
What do you see on cytology prep?

- ✓ A. Normal squamous epithelial cells
- B. Koilocytosis
- ✓ C. WBCs
- D. RBCs
- ✓ E. Trichomonads
- F. Not sure



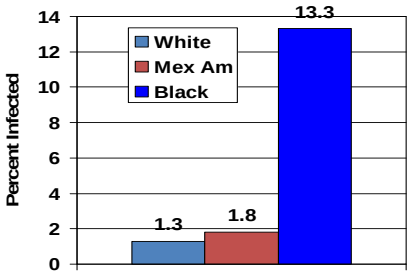
Source: http://fiveprime.org

Trichomoniasis



- Etiologic agent: *Trichomonas vaginalis*, flagellated anaerobic protozoa
- Most common non-viral STD in U.S.
- No surveillance or case reporting data
- Overall prevalence from NHANES 2001-2004, 3.1%
- Significant racial disparities

Trichomonas Prevalence by Race/Ethnicity, NHANES 2001-2004



Sutton M et al. CID 2007 Nov 15; 45(10) 1319-1326.

Epidemiology

- **Most common curable STD**
- Estimated 7.4 million cases/yr ($375 million) in the U.S.
- Estimated prevalence:
  - 50%-60% in female prison inmates and commercial sex workers
  - 18%-50% in females with vaginal complaints
  - **3% in U.S. women 14-49 years of age (NHANES data)***
    - **Factors associated with increased likelihood of infection in multivariable analysis**
      - Black, non-Hispanic race/ethnicity
      - Birth in United States
      - Greater number of lifetime sex partners
      - Increasing age
      - Lower educational level
      - Poverty
      - Douching
      - NOT symptoms

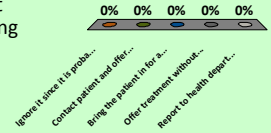
*Sutton et al. *CID* 2007; 45:1319-26

Trichomonas: Adverse Health Outcomes

- Adverse pregnancy outcomes
  - Low birth weight
  - Premature rupture of membranes
  - Premature delivery
- May increase risk of HIV acquisition
  - Trich infection in HIV-positive women may enhance HIV transmission by increasing genital HIV shedding
  - Treatment for *T. vaginalis* reduces HIV shedding

What should you do with Trich on a Pap?

A. Ignore it since it is probably a mistake
B. Contact patient and offer treatment if symptomatic
C. Bring the patient in for a confirmatory test (e.g., culture)
✔D. Offer treatment without conducting further testing
E. Report to health department



How Good is Pap for Trichomonas Detection

- Poor sensitivity
- High specificity and positive predictive value (PPV), especially with liquid based Pap
  - SurePath™-specificity 99.5%, PPV 98% (PCR as gold standard)
  - ThinPrep™-specificity 99.4%, PPV 96% (Culture as gold standard)
- False positives more likely in low-prevalence populations

Aslan DL et al. Diagn. Cytopathol. 2005;32: 341–344
Lara-Torre E et al. Am J Obstet Gynecol 2003; 188:354-6

Trichomoniasis: Diagnosis

- Saline Wet Mount
  - Motile trichomonads
  - pH > 4.5
  - Whiff test may be positive
- Culture (InPouch TV Test, BioMed Diagnostics)
- Point-of-care tests
  - OSOM trichomonas rapid test (Genzyme)
  - Affirm VP III (BD)
- **New:** Modified Nucleic Acid Amplification Tests
  - BD Probe Tec TV Qx Amplified DNA Assay
  - Hologic/Gen-Probe APTIMA Analyte Specific Reagents

Newer Testing Options for Trich

- Microscopy is inferior to new options, including
  - Rapid antigen testing (OSOM)
  - Nucleic acid amplification testing
    - APTIMA TMA *Trichomonas vaginalis* assay
    - BD ProbeTec TV Q^x Amplified DNA assay
    - May use same specimen types as used with gc/chl NAATs (i.e. vaginal swab, endocervical swab, urine)

Huppert CID 2007

Test	Sens	Sp
APTIMA TMA	98%	98%
OSOM	90%	100%
Culture	83%	100%
Wet prep	56%	100%

Slide courtesy of Marrazzo, IDSA 2011

Table 3. Differences in test sensitivity stratified by the presence or absence of vaginal symptoms.

Test method	Sensitivity, % (95% CI) All patients (*n* = 330)	Vaginal symptoms present (*n* = 210)	Vaginal symptoms absent (*n* = 120)
Wet mount	50.8 (37.7–63.9)	57.5 (40.9–72.9)	38.1 (18.1–61.5)
Culture	75.4 (62.7–85.5)	77.5 (61.5–89.1)	71.4 (47.8–88.7)
Rapid test	82.0 (70.0–90.6)	92.5 (79.6–98.4)	61.9 (38.4–81.9)
TMA	98.4 (91.2–99.9)	97.5 (86.9–99.9)	100 (83.8–100)

NOTE. The comparator was any test result positive for *Trichomonas vaginalis* infection. TMA, transcription-mediated amplification.

Trichomoniasis Treatment

Recommended regimen:

- ❖ Metronidazole 2 g PO x 1
- ❖ Tinidazole 2 g PO x 1

Safe at all stages of pregnancy
Avoid EtOH x 24 hrs after tx
If breastfeeding, consult guidelines

Pregnancy Category C, do NOT use!
Avoid EtOH x 72 hrs after tx
If breastfeeding, consult guidelines

HIV-infected women:

- ❖ Metronidazole 500 mg PO BID x 7d (consider)

Alternative regimen:

- ❖ Metronidazole 500 mg PO BID x 7d

Recommended regimen in pregnancy:

- ❖ Metronidazole 2 g PO x 1

Note: Topical vaginal therapy is ineffective

Trichomonas Treatment in HIV

- 270 women enrolled (New Orleans, Houston, Jackson; HIV-infected, positive for TV by culture)
- Randomized to either MTZ 2 g PO x 1 or 500 mg PO bid x 7 days
  - 255 women evaluated for test of cure (~1 mth)
  - 152 women negative or didn't return at TOC were eval. at ~3 mths

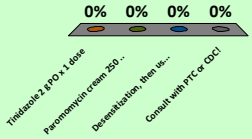
	TV+ rate overall, %	7-day dose, %	Single dose, %	RR (95% CI)	P
TOC visit (~1 mth)	12.5	8.5	16.8	0.50 (0.25, 1.00)	0.045
3 month visit	17.8	11.0	24.1	0.46 (0.21, 0.98)	0.03

- Secondary analysis: lack of single dose treatment efficacy found only among women with asymptomatic BV

Kissinger et al., *JAIDS* 2010
Slide courtesy of J Marrazzo, IDSA 2011

How would you manage trich in someone with severe MTZ allergy?

A. Tinidazole 2 g PO x 1 dose
✓B. Paromomycin cream 250 mg intravag. qd x 14 days
✓C. Desensitization, then use MTZ
✓D. Consult with PTC or CDC!



Management of Trichomoniasis in Patients with Serious Contraindications to Metronidazole

- Oral desensitization (Kurohara et al., *J All Clin Immunol* 1991)
- Paromomycin cream 250 mg intravag. daily x 14 days (Nyirjesy et al., *CID* 1998)
  - Can cause labial ulcers
- Furazolidone 100 mg BID intravag. x 10-14 days
- Zinc oxide douche
- NOT tinidazole
- Call your local PTC, or CDC!

Slide courtesy of J Marrazzo, IDSA 2011

Metronidazole-Resistant *T. vaginalis*

- Estimated 4-10% of clinical cases caused by *T. vaginalis* strains with at least some resistance to metronidazole
- Most of these strains have low or moderate resistance, therefore may respond to tinidazole or higher levels of metronidazole

Schmid et al. *J Reprod Med* 2001
Schwebke et al., *Antimicrob Agents Chemother* 2006

Trichomoniasis Treatment Failure

Exclude reinfection?!

First treatment failure, re-treat with:

- Metronidazole 500 mg PO BID x 7 days

If repeat failure, treat with:

- Metronidazole 2 g PO QD x 7 days
- Tinidazole 2 g PO QD x 7 days

Susceptibility testing: send isolate to CDC (Parasitic Laboratory, phone 404-718-4141)

Anecdotal experience with:

- Paramomycin 250 mg intravaginally x 7-14 days together with high dose tinidazole orally
- Boric acid intravaginally
- Nitazoxanide orally

2015 CDC STD Treatment Guidelines

Partner Management

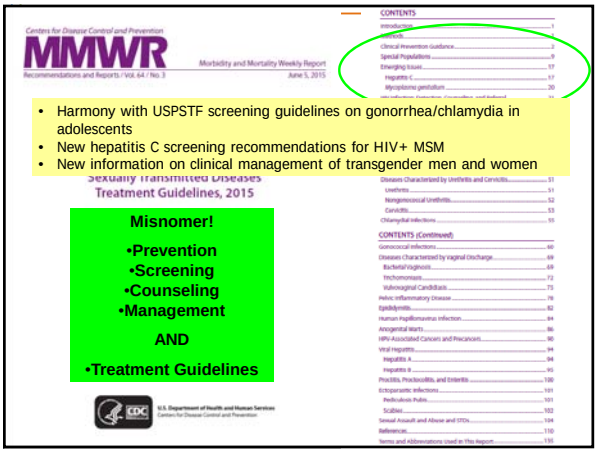
- Sex partners should be treated
- Patients should be instructed to avoid sex until they and their partners have completed therapy and symptoms have resolved
- Re-screening for *T. vaginalis* is recommended for all sexually active women within 3 months following initial treatment

Resources

CDC STD Treatment Guidelines Development

- Evidence-based on principal outcomes of STD therapy
  1. Microbiologic eradication
  2. Alleviation of signs & sx
  3. Prevention of sequelae
  4. Prevention of transmission
- Recommended regimens preferred over alternative regimens
- Alphabetized unless there is a priority of choice
- Reviewed April 2013; published 2015
- www.cdc.gov/std/treatment
  - Pocket guides, teaching slides, charts, app

Language in yellow highlighted boxes reflects changes between 2010 and 2015 guidelines



- Harmony with USPSTF screening guidelines on gonorrhea/chlamydia in adolescents
- New hepatitis C screening recommendations for HIV+ MSM
- New information on clinical management of transgender men and women

Want to know more about STDs?
There's an app for that.

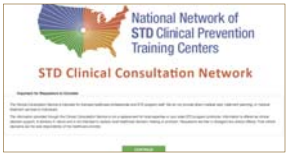
CDC STD Treatment Guidelines App for Apple and Android

Available now, **FREE!** (accept no competitors)

Search "STD Treatment" in App store

STD Clinical Consultation Network (STDCCN)

- NEW!!!!!
- Provides STD clinical consultation services within 1-5 business days, depending on urgency, to healthcare providers nationally
- Your consultation request is linked to your regional PTC's STD faculty
- Just a click away!
- www.STDCCN.org



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THANK YOU!


HPV


Syphilis


Chlamydia


HSV-2


HIV


Gonorrhea


Trichomoniasis