Gonorrhea, Chlamydia and Syphilis Update

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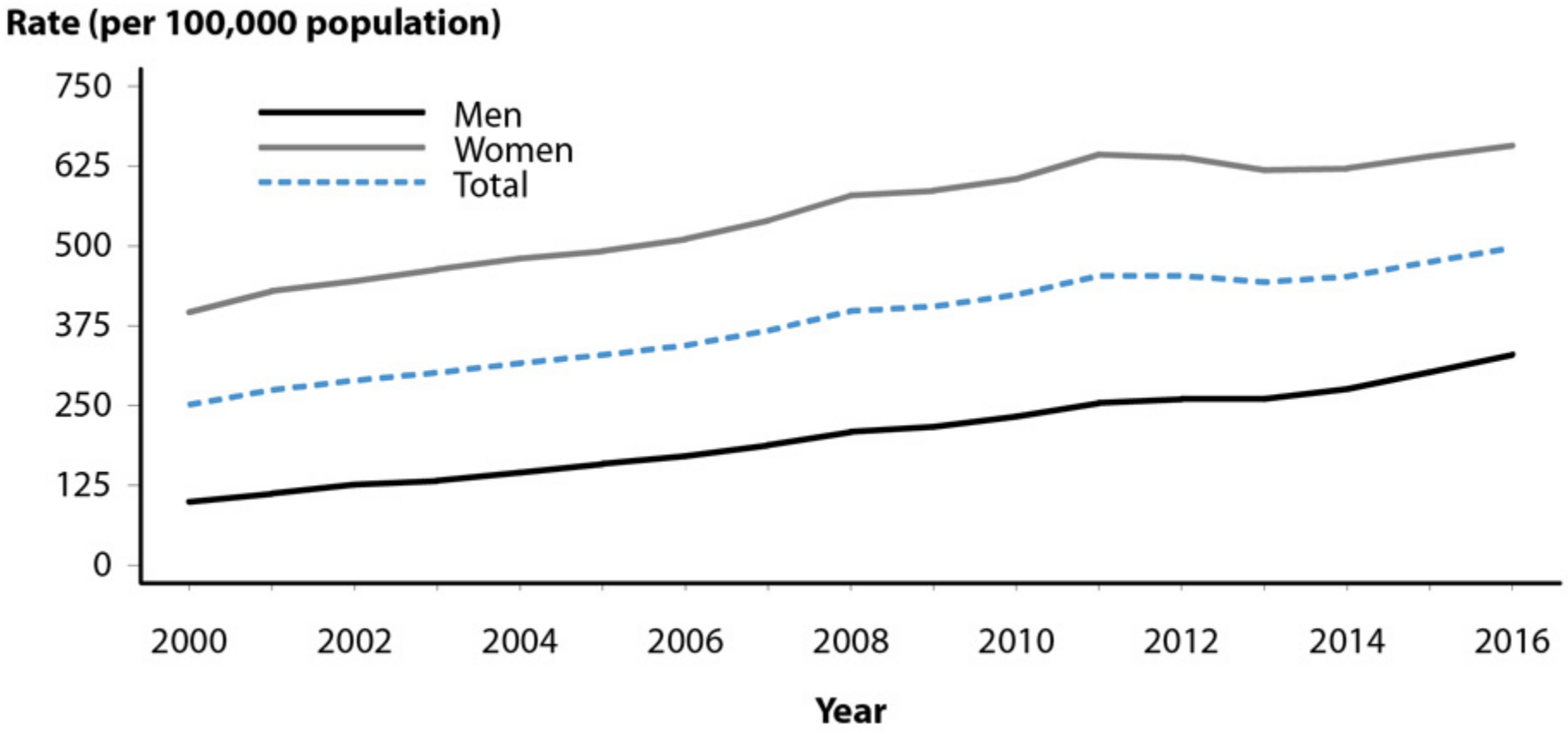
- Thank you to Stephen Berry, Khalil Ghanem, Anne Rompalo and Seema Nayak for many of these slides.

Outline

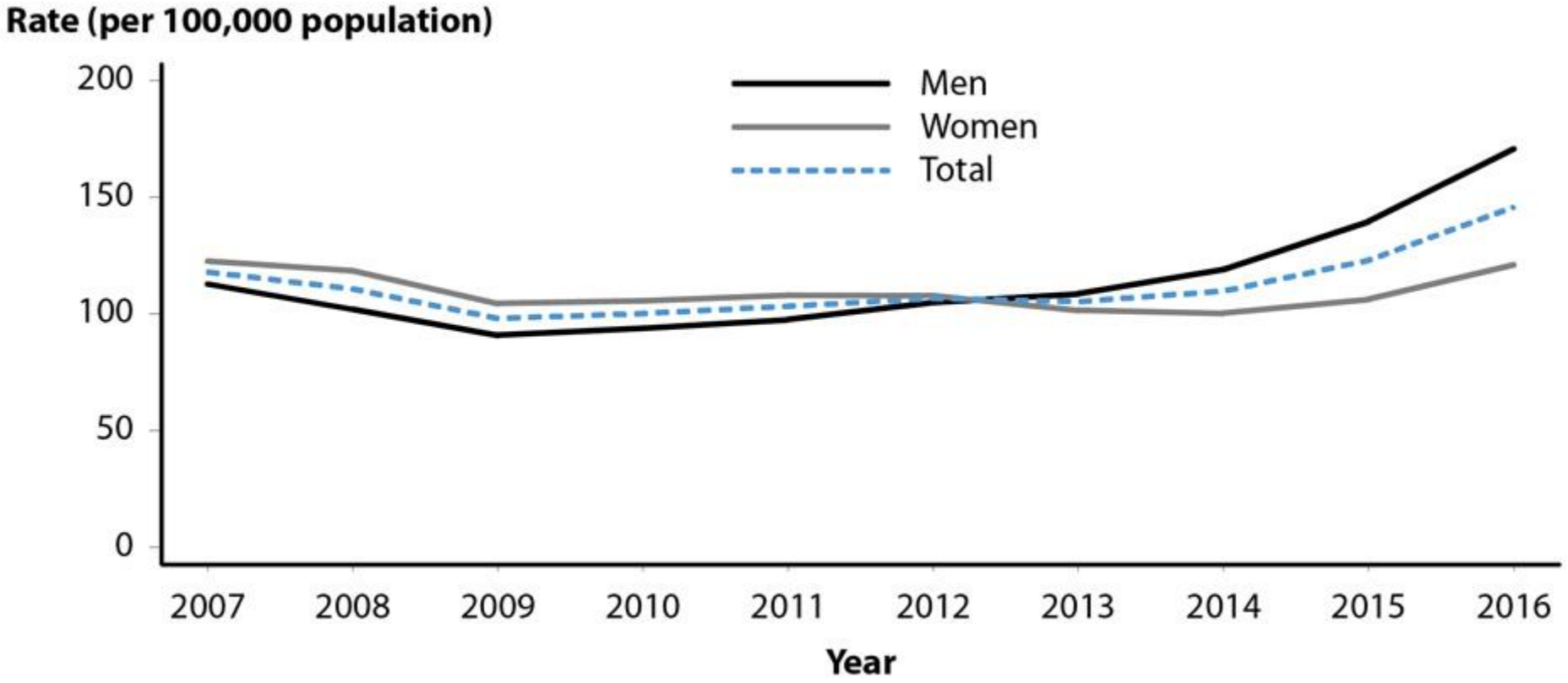
- Update on gonorrhea, chlamydia and syphilis trends in the U.S.
- GC/CT
  - Testing and screening, including extragenital screening for GC/CT
  - Drug resistant gonorrhea
  - Treatment recommendations
  - LGV
- Mycoplasma genitalium
- Syphilis
  - Screening recommendations
  - Ocular syphilis
  - Treatment

US Chlamydia Trends



4.7% increase during 2016! 497.3 cases/100,000
2.6% inc in women, 26.8% increase in men

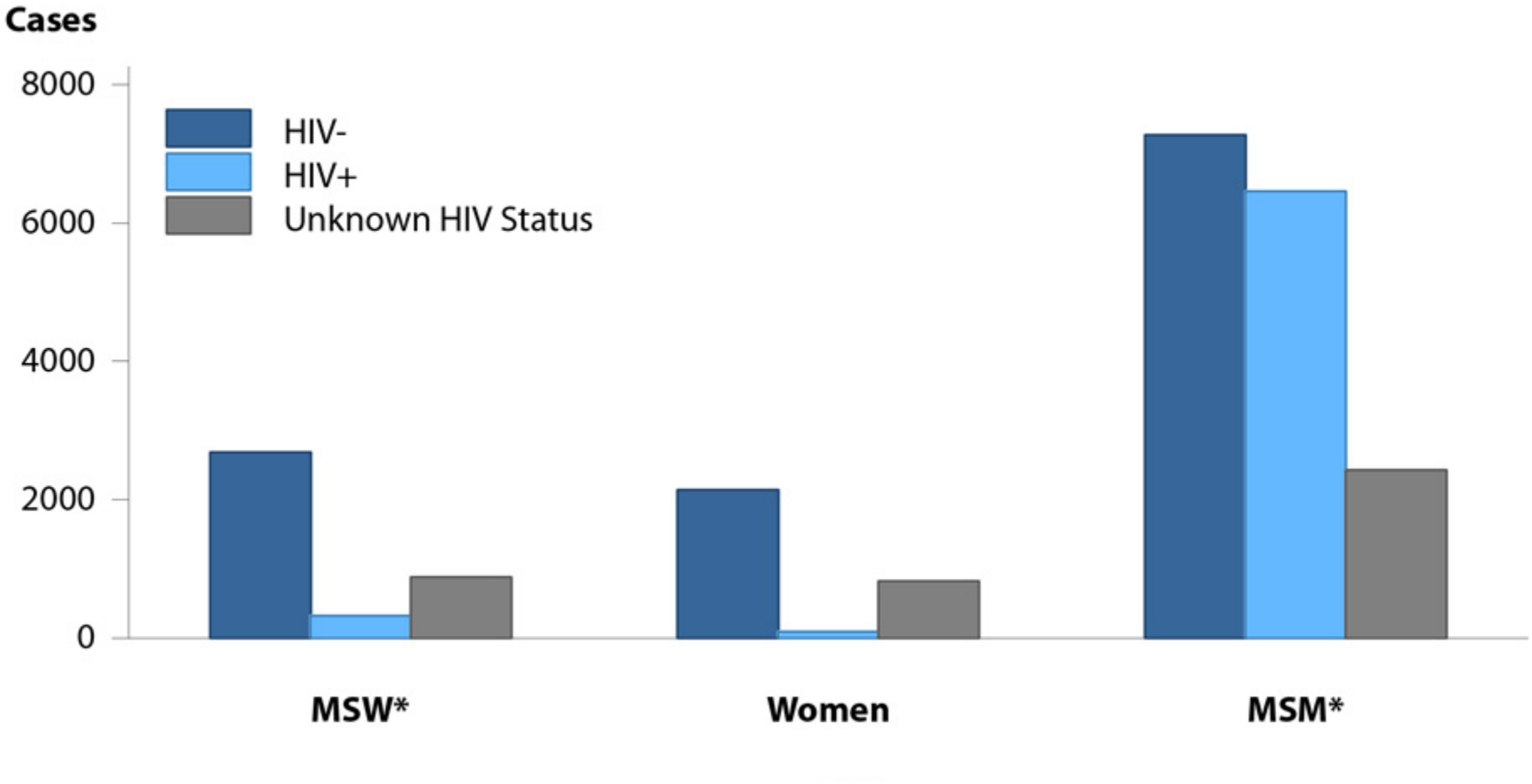
US Gonorrhea Trends



18.5% increase during 2016! 145.8 cases/100,000

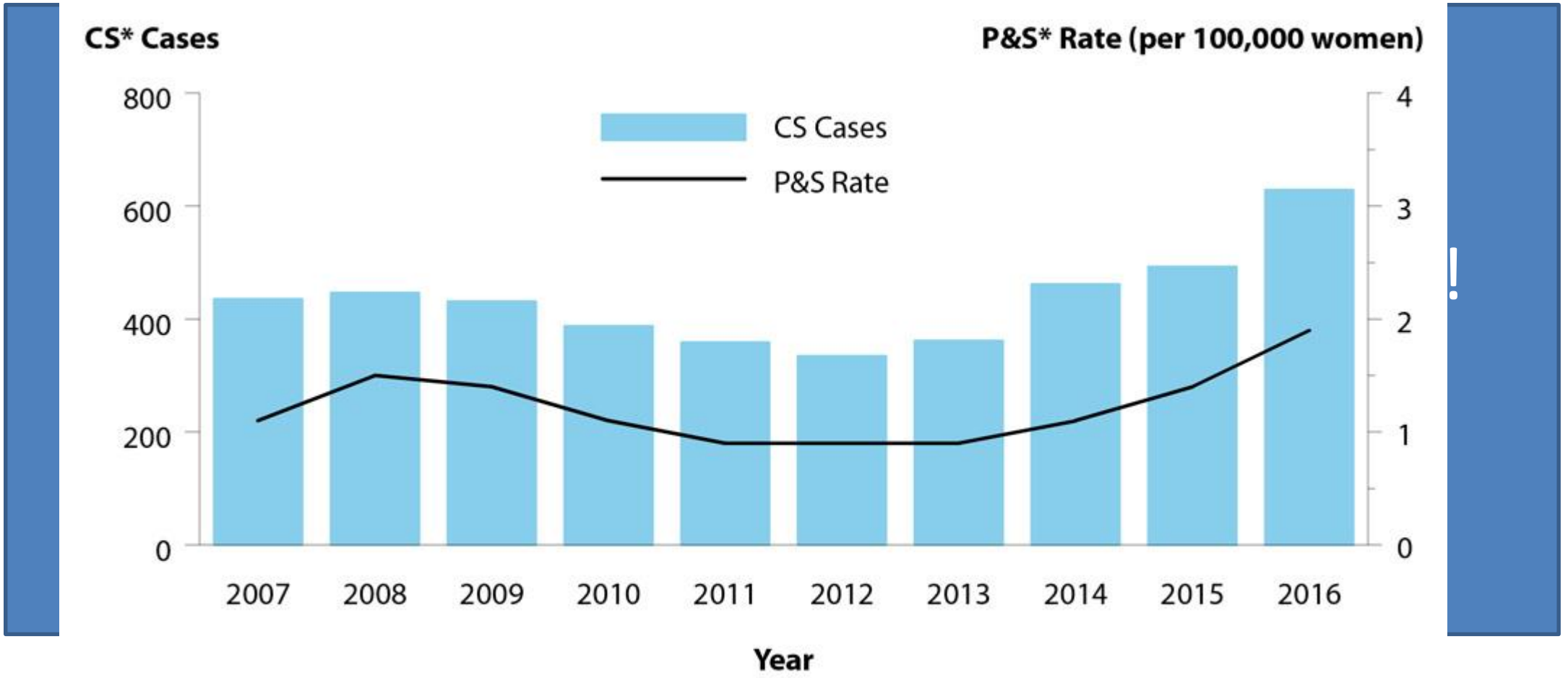
13.8% increase in women, 22.2% increase in men

US Primary and Secondary Syphilis Trends



17.6% increase 2016! 14.7% increase in men, 35.7% increase in women

Congenital Syphilis



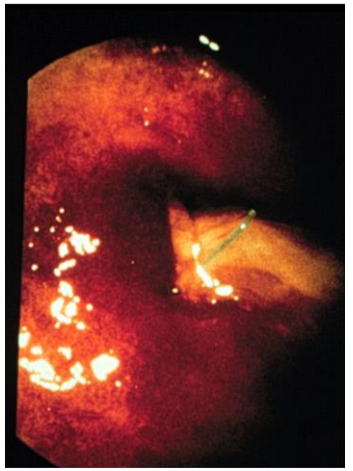
Case B: 45 y.o. HIV + man routine follow-up

- “Alan”
- On Genvoya, suppressed X 10 years
- No symptoms, just “wants to get checked for everything.”
- Hepatitis B vaccinated
- Worried about syphilis
  - Three episodes before, including CNS
  - Crack and crystal meth binges
  - MSM: multiple anonymous partners
  - Insertive and receptive oral and anal sex
  - Never had NG or CT, 3 previous urine NAT’s
  - No prior extragenital screening
- Exam unremarkable
- What STI screening tests should be ordered?
- A test was positive…

Case B: 45 y.o. HIV+ man routine follow-up

- Syphilis treponemal test: Positive, RPR: negative
- Oral NG/CT NAT: **POS CT**
- Urine NG/CT: Negative
- Rectal NG/CT: **POS NG**

Neisseria gonorrhea



- 2nd most commonly reported communicable disease in U.S. (>800,000 new cases/year)
- Men – usually symptomatic at urethral site
- Women – commonly asymptomatic or with non-specific symptoms
  - Complications – PID, tubal scarring, infertility, chronic pelvic pain

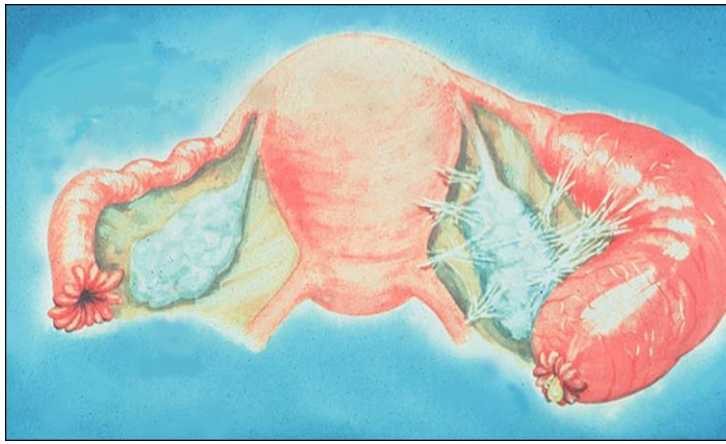
- **Clinical:**
  - Urethritis/Mucopurulent Cervicitis
  - Conjunctivitis – always symptomatic
  - Perirectal infections – proctitis—often Asymptomatic.
  - Pharyngeal infection – self limited, mild if any symptoms
  - Disseminated Gonococcal Infection

Gonococcal antibiotic resistance is a huge problem!

Chlamydia trachomatis

- Most commonly reported STD in U.S.
- Majority of genital chlamydial infections in BOTH males and females are asymptomatic
- 10-15% of untreated CT infections result in diagnosed clinical PID

- **Clinical:**
  - Urethritis/Cervicitis
  - Epididymitis/Prostatitis(men) and Pelvic Inflammatory Disease(women)
  - Proctitis/Proctocolitis-usually asymptomatic
  - Conjunctivitis
  - Auto-immune

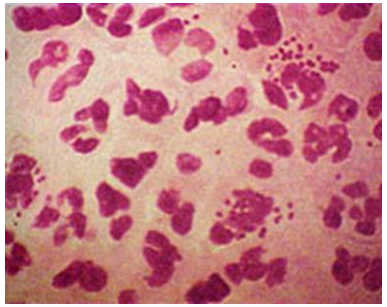


Testing for gonorrhea and chlamydia

Dx Urethritis/Cervicitis:POC

- **Male**: penile discharge
  - Swab of urethral secretions
    - >=2 WBC per hpf: **Non-gonoccal urethritis** (**NGU**)
      - Can also look for LE on first void urine or >10 WBC per hpf on spun first void urine.
      - 15-25% *M. genitalium*>=2 WBC + gram-neg intracellular diplococci: GC urethritis
    - >=2 WBC & gram-neg intracellular diplococci: **GC urethritis**

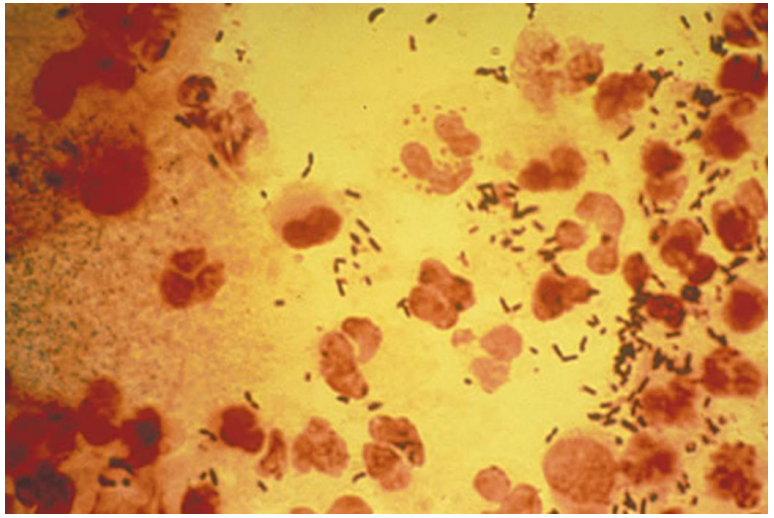
- **Female**: cervical discharge/friability
  - Gram's stain specific, but not sensitive for GC.

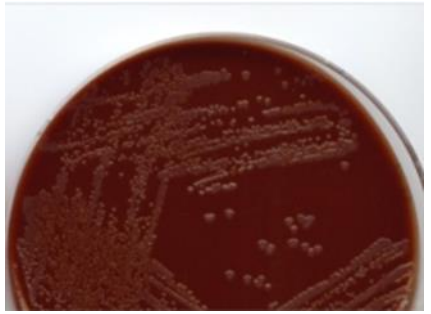


SO…Often will need to prescribe empiric therapy!

Dx NG/CT

- Culture for chlamydia insensitive.
- Gonococcal culture:
  - Requires endocervical or male urethral swab
  - If suspected or documented treatment failure, perform a culture and antimicrobial susceptibility testing





Diagnosis of NG/CT

Nucleic acid amplification tests (NAATs) are the most sensitive

Urethral CT/GC in men

- Urethral swab
- **First catch urine**

Cervical CT/GC in women

- Cervical swab
- Clinician collected vaginal swab
- **Self-collected vaginal swab**

Based on ease of collection and CT detection rates comparable to other specimens, optimal urogenital specimen types for CT using NAATS include first catch urine from men and vaginal swabs from women

Oropharyngeal CT/GC

- Routine screening for CT is not recommended since clinical significance is unclear

Rectal CT/GC

- NAATS have improved sensitivity and specificity compared with culture

Chlamydia trachomatis and *Neisseria gonorrhea* Screening Recommendations

- Screening of women for NG/CT is paramount and recommended:
  - **Annual of all sexually active women aged <25 years**
  - Older women with risk factors (e.g., those who have a new sex partner or multiple sex partners, and those reporting their sex partner may have a concurrent sex partner)
- Evidence for routine screening of young men for CT is insufficient:
  - Consider in clinical settings with high prevalence (e.g., adolescent clinics, correctional facilities, and STD clinics)
- MSM: screen at least annually for NG/CT if sexually active, q3-6 mos if risk behaviors
- HIV+:
  - Screen all sexually active men for NG/CT at least annually
  - Screen all sexually active women for NG/CT at least annually, emphasis on women <= age 25
  - In those with risk behaviors, especially MSM, screen q 3-6mos
- Pregnancy
  - NG/CT testing in third trimester (reinfection)
  - Untreated CT in pregnant women can lead to severe chlamydia pneumonia in the infant (transmitted during vaginal delivery)
  - Untreated GC in pregnant women can lead to conjunctivitis in infant.
- **Retest women/men 3 months post treatment**

CDC Screening Guidelines for Sexually Active Persons

	Syphilis	NG/CT	HIV
Women	Pregnancy	<25: annual ≥25: consider*	13-64 (opt-out) If other STI
MSW		Consider CT***	13-64 (opt-out) If other STI
MSM	≥ annual**	≥ annual** at sites of contact (urethra, rectum, pharynx) regardless of condoms	≥ annual if new partner(s) since last test
HIV+	≥ annual**	≥ annual**	

*** New or multiple partners, anonymous partners, transactional sex, history of or partners with STI's, illicit drug use, high local incidence**

** q3-6 months *based on risk factors above*

***Consider in clinical settings with high prevalence (e.g., adolescent clinics, correctional facilities, and STD clinics)

https://www.cdc.gov/std/tg2015/screening-recommendations.htm

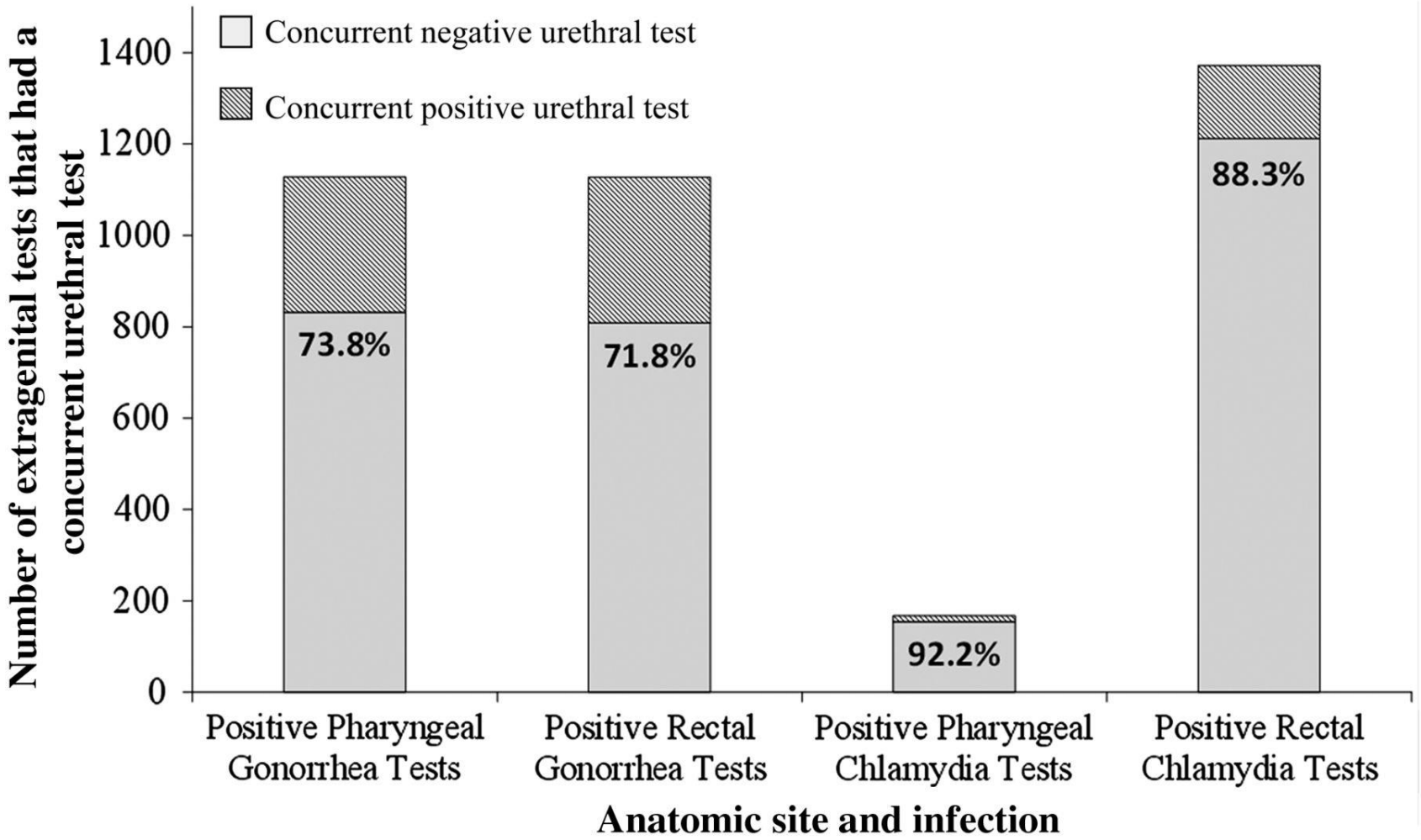
Why do NG/CT extragenital testing?

- From July 2003 until February 2007, 441 rectal test sets were collected from individuals attending a sexually transmitted disease clinic and three HIV clinics who gave a history of anal intercourse or were women at high risk for *Neisseria gonorrhoeae* or *Chlamydia trachomatis* infections.
- Over 60% and 80% of gonococcal and chlamydial infections, respectively, among men who have sex with men and over 20% of chlamydial infections in women would have been missed if the rectal site had not been tested.*
- Baltimore STD clinics: among women endorsing extragenital exposures, 30.3% of GC infections and 13.8% of CT infections would have been missed with urogenital-only testing.**

*Bachmann LH et al. J Clin Micro 2010:1827-1832; Trebach et al. STD 2015.

Proportion of extragenital gonorrhea and chlamydia infections associated with concurrent negative urethral tests.

21,994 MSM attending 42 STD Clinic in US 2011-2012



Monica E. Patton et al. Clin Infect Dis. 2014;58:1564-1570

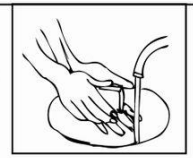
BUT….I don’t have time for all this screening and testing!

Self-Collection of Vaginal Swab

ATTENTION: Read ALL instructions before you begin!

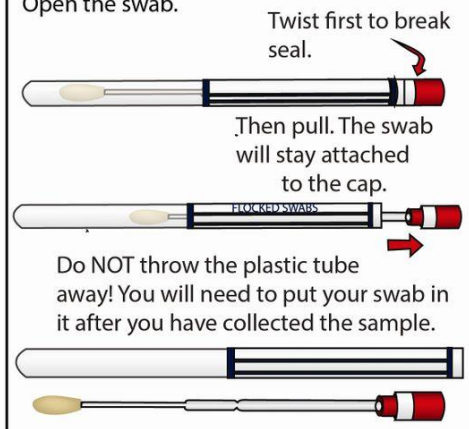
The Test kit is safe for pregnant women and effective when you're having your period.

STEP 1
Wash your hands thoroughly.

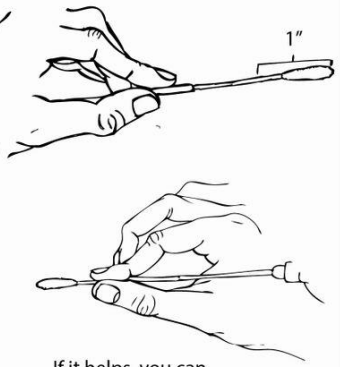


STEP 2
Undress from the waist down. Get into a position where you can comfortably insert a swab into your vagina- such as sitting on the toilet, or standing with one foot on a chair, or any position that you would use to insert a tampon.

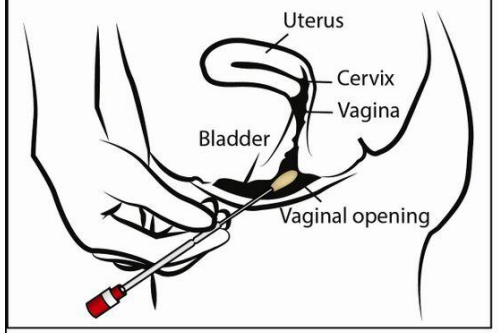
STEP 3
Take the sealed swab out of the package. Open the swab.



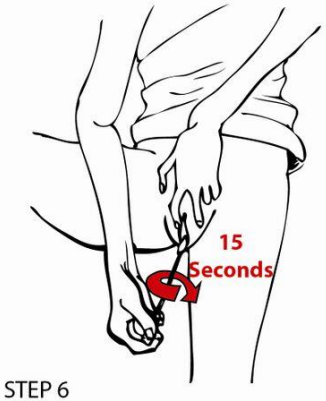
STEP 4
Insert the white tip of the swab about one inch inside the opening of your vagina.



If it helps, you can grip the swab 1" away from the end of the soft tip, so your fingers will touch your body when the swab is in far enough.

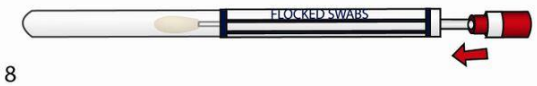


STEP 5
Rotate the swab for 15 seconds, making sure that the swab touches the walls of your vagina so that moisture is absorbed into the swab.



STEP 6
Remove the swab from your vagina. Don't let the tip of the swab touch anything else.

STEP 7
Place used swab back into the transport tube. Close tightly to prevent leakage.



STEP 8
Place closed tube into the red plastic zip-lock bag. Seal the bag.

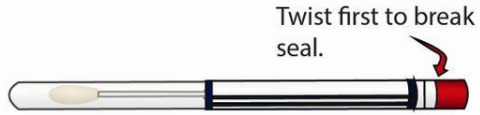
STEP 9
Place sealed zip-lock bag into the return mailer (white envelope with blue diamond-shaped sticker on the front). Seal the envelope and drop it in any mailbox. It's already addressed and postage is paid, so you don't need to do anything else.

Diagram designed by Garvi Sheth

Self-Collection of Penile Swab

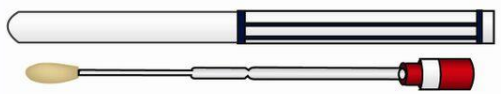
ATTENTION: Read ALL instructions before you begin!

STEP 1
Take the sealed swab out of the package.
Open the swab.

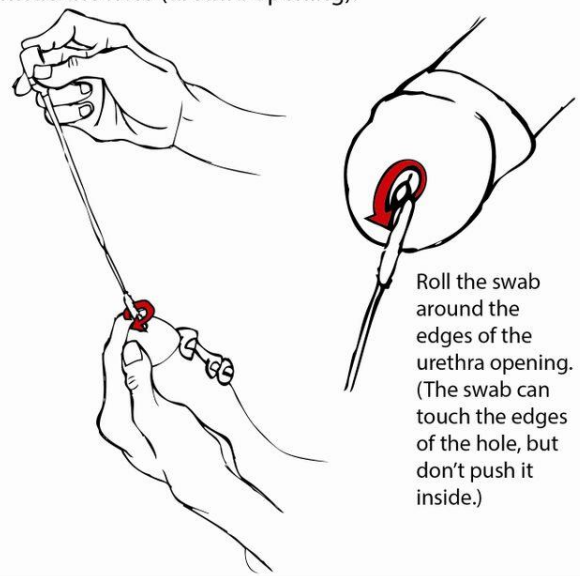


Then pull. The swab will stay attached to the cap.

Do NOT throw the plastic tube away! You will need to put your swab in it after you have collected the sample.



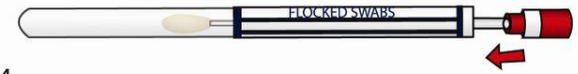
STEP 2
Roll the swab just at the tip or inside the opening to the penis through which you pass urine (pee). Roll the swab completely around the opening to get the best specimen. It is not necessary to put the swab deep inside the hole (urethra opening).



Roll the swab around the edges of the urethra opening. (The swab can touch the edges of the hole, but don't push it inside.)

Diagram designed by Garvi Sheth

STEP 3
Place used swab back into the transport tube. Close tightly to prevent leakage.



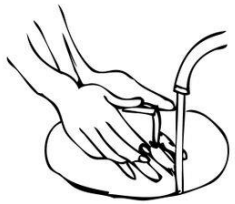
STEP 4
Place closed tube into the red plastic zip-lock bag. Seal the bag.

STEP 5
Place sealed zip-lock bag into the return mailer (white envelope with a blue diamond shaped sticker on the front). Seal the envelope and drop it in any mailbox. It's already addressed and postage is paid, so you don't need to do anything else.

Self-Collection of Rectal Swab

ATTENTION: Read ALL instructions before you begin!

STEP 1



Wash your hands thoroughly.

STEP 2

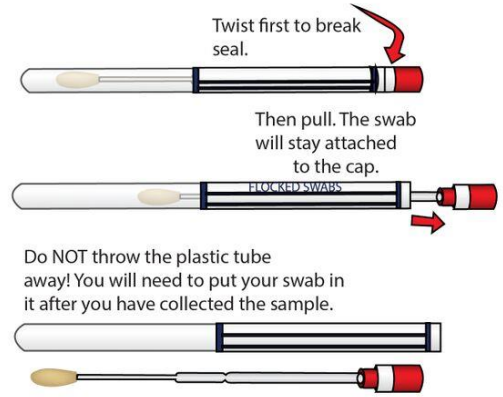
Either squat down, or lift one leg on a toilet, ledge, or chair (as shown). Pull underwear down or off.

Diagram designed by Garvi Sheth

STEP 3

Open the swab.

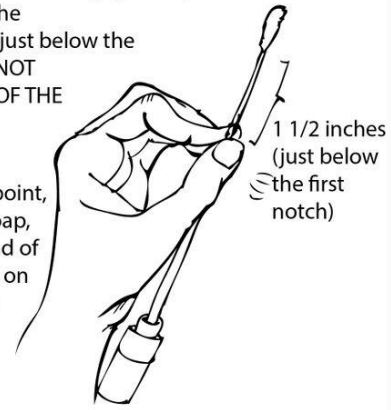
DO NOT TOUCH THE TIP OF THE SWAB.



STEP 4

With your dominant hand (right if you're right-handed, left if you're left-handed), grip the opened swab 1.5" away from the tip of the swab (just below the first notch). DO NOT TOUCH THE TIP OF THE SWAB.

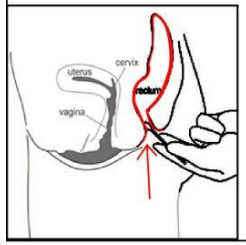
Do NOT, at any point, use anything (soap, saliva, or any kind of lubricant) either on your body or on the swab.



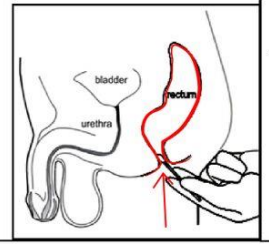
STEP 5

With your other hand, position your bare buttock and lift one cheek for easy access to the rectum. (DO NOT use anything on your rectum or the swab.)

Female Anatomy



Male Anatomy



STEP 6

Insert the swab 1.5 inches into your rectum until you feel your fingers touch your anus.

STEP 7

Once the swab is in, walk your fingers halfway down the swab (away from your body) and grip it there, for stability. (The swab should stay where it is- only your fingers should move.)

STEP 8

Gently rub the swab in a circle, touching the walls of your rectum, to collect the specimen.

STEP 9

When removing the swab from your rectum, slowly turn it in a circle while pulling it out.

STEP 10

Place used swab back into the transport tube. Close tightly to prevent leakage.

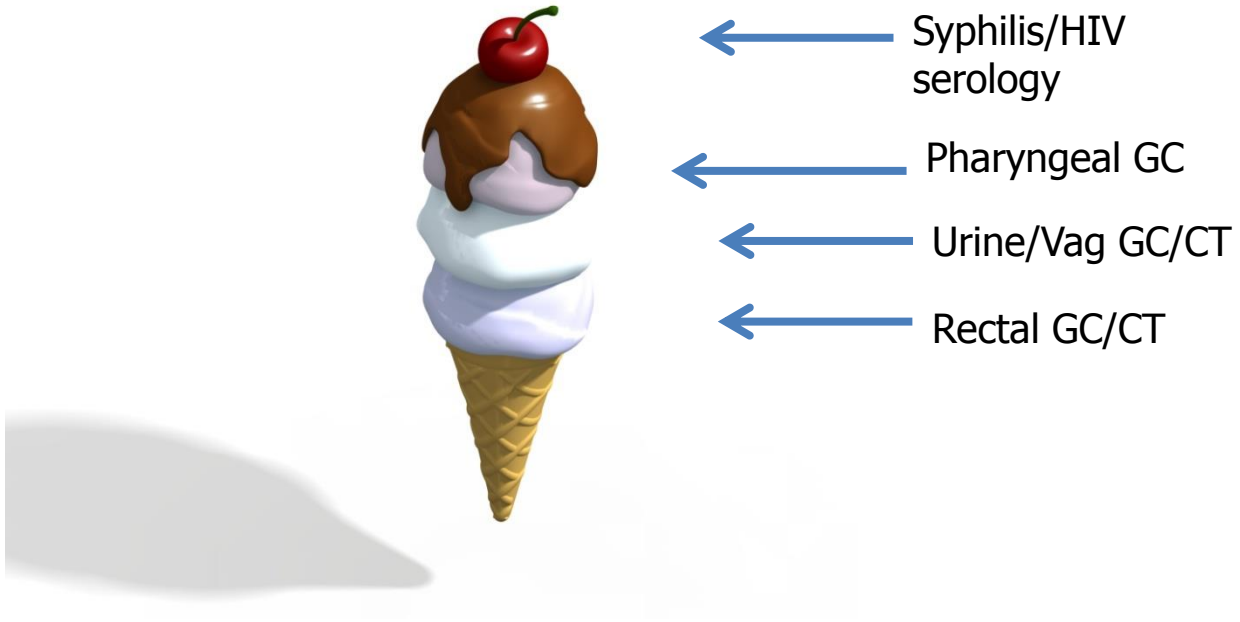
STEP 11

Place closed tube into the red plastic zip-lock bag. Seal the bag.

STEP 12

Place sealed zip-lock bag into the return mailer (white envelope with a blue diamond-shaped sticker on the front). Seal the envelope and drop it in any mailbox. It's already addressed and postage is paid, so you don't need to do anything else.

Don’t forget the triple dip

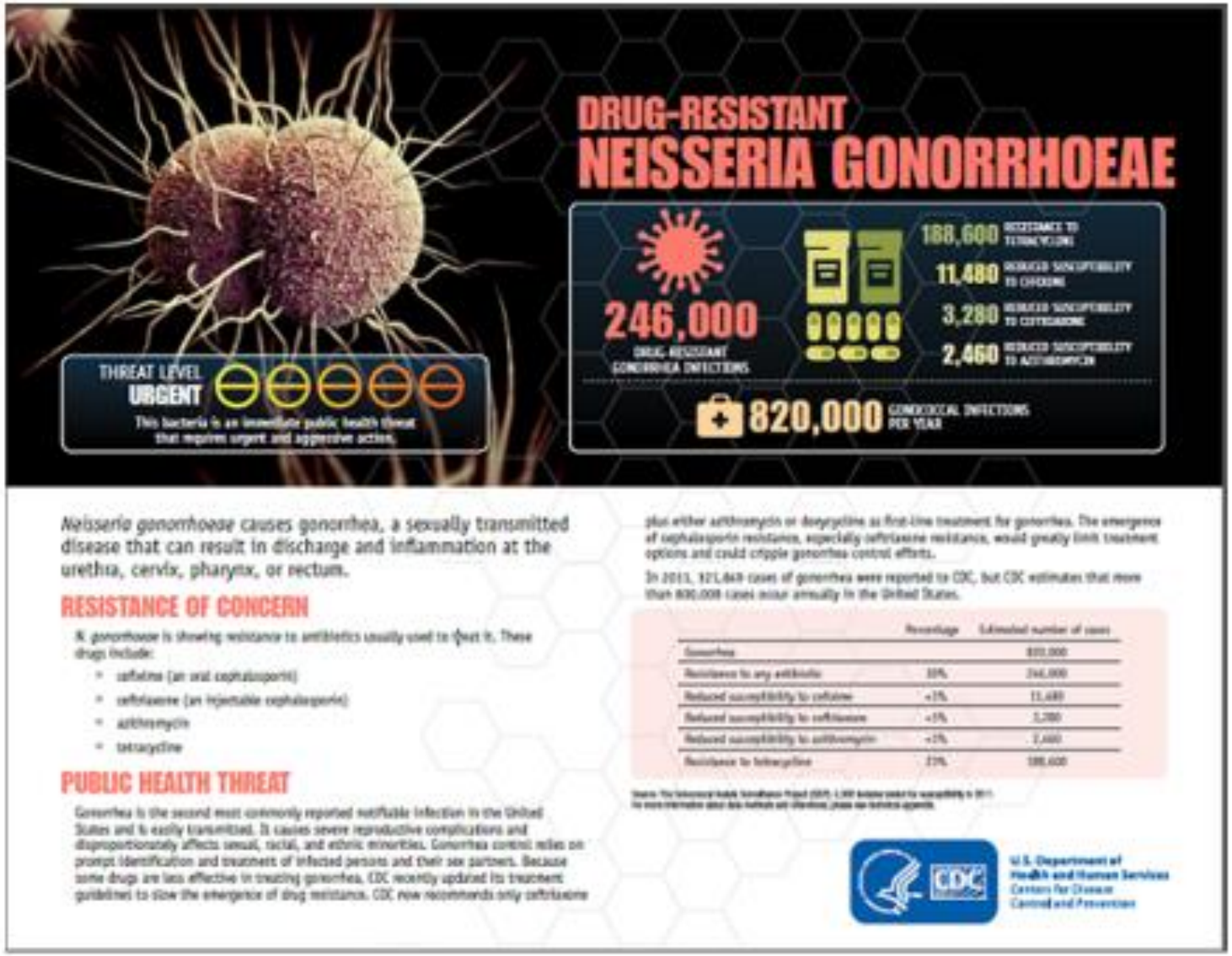


Case B: 45 y.o. HIV+ man routine follow-up

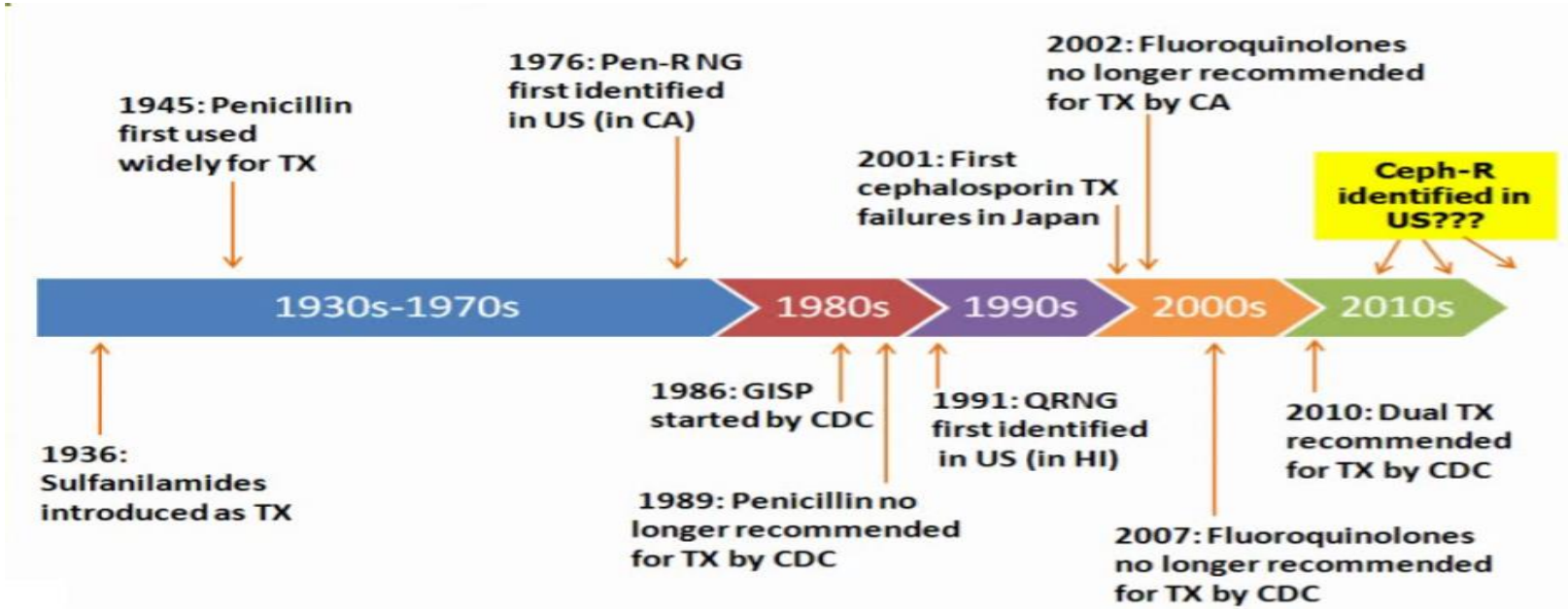
- Syphilis treponemal test: Positive, RPR: negative
- Oral NG/CT NAT: **POS CT**
- Urine NG/CT: Negative
- Rectal NG/CT: **POS NG**

How should ‘Alan’ be treated?

Gonorrhea Treatment



Gonorrhea Drug Resistance



- 2006 – 2011: increasing resistance to cefixime in U.S; Cefixime failure in Europe, South Africa and Canada
  - 2010: Doxycycline or Azithromycin plus a cephalosporin (oral or IM)
  - 2012: No more cefixime (oral) as first-line treatment (just Ceftriaxone IM plus azithromycin or doxycycline.)

GC Drug Resistance

- But wait! **GC with elevated MICs to cefixime are also likely to be resistant to tetracyclines (doxycycline) BUT susceptible to azithromycin**
- AND BEWARE!!! Ceftriaxone treatment failures for pharyngeal infections have been reported in Australia, Japan, and Europe. Isolates with high-level cefixime and ceftriaxone MICs have been identified in Japan, France, and Spain.

Gonorrhea Treatment: 2015
Uncomplicated Genital, Rectal, or Pharyngeal Infections

Ceftriaxone 250 mg IM in a single dose

PLUS*

Azithromycin 1 g orally

or

~~Doxycycline 100 mg BID x 7 days~~

* Regardless of CT test result

Doxycycline has been **REMOVED** from recommended to alternative treatment

Why two agents to prevent resistance?

Why it may work

- CTX and Azi have different mechanisms of action and should prevent emergence of resistance
  - Based on mathematical principal applied to rate of chromosomal mutation in bacteria
  - Works for TB and HIV

Why it may not

- Unlike TB that develops resistance through chromosomal mutations, GC is highly social, acquires foreign DNA in large chunks – like in plasmids – and can transform its DNA by incorporating naked DNA it acquires for the environment.
- Plus it mutates its DNA commonly and acquires resistance that way too.
- CTX and Azi are not always used in combination (Z-pack), Azi longer ½ life
- Both ABX have potential to select resistance to each other
- Pharyngeal GC: Poor drug penetration + environment for acquiring drug resistance

Rice LB. Sex Transm Infect 2015;91:238-240

More News

- NEJM: June 2016: Fifer et. al. Failure of dual antimicrobial therapy in treatment of gonorrhea:

  IM Ceftriaxone + Azithromycin: urogenital Gonorrhea was successfully treated but Pharyngeal persisted.

NG Treatment Alternatives (not 1st line)

- Cefixime 400mg PO x1 + azithro 1g PO (**only if ceftriaxone is not available**)
- Doxycycline 100mg PO BID x 7 days (**as the 2nd agent, if azithromycin allergic**)

Test of cure (NAT or culture) at 14 days if treating pharyngeal NG with alternative regimen (need culture if 2nd NAT pos)

Remember to re-screen at 3 months after treating

MMWR June 5, 2015;64(RR3):1-137

2015 Gonorrhea Treatment Penicillin Allergy:

Gentamicin 240mg IM
OR
Gemifloxacin 320mg po X1

+

Azithromycin 2g po X1

AZITHROMYCIN 2 gm x 1 with test of cure is NO LONGER RECOMMENDED

Gonorrhea Treatment: What's Next?

On The Horizon?

Solithromycin
Delafloxacin (Just FDA approved for tx of SSI)
Zoliflodacin (AZ D0914)
Gepotidacin (BTZ116576)

BUT: Timeline to new antibiotics: three years minimum

Intriguing…sort of…

Effectiveness of a group B outer membrane vesicle meningococcal vaccine against gonorrhoea in New Zealand: a retrospective case-control study

Helen Petousis-Harris, Janine Paynter, Jane Morgan, Peter Saxton, Barbara McArdle, Felicity Goodyear-Smith, Steven Black

Estimate vaccine effectiveness of MeNZB against gonorrhoea after adjustment for ethnicity, deprivation, geographical area, and sex was 31% (95% CI 21–39)

Case B: 45 y.o. HIV+ man routine follow-up

- Syphilis treponemal test: Positive, RPR: negative
- Oral NG/CT NAT: **POS CT**
- Urine NG/CT: Negative
- Rectal NG/CT: **POS NG**

How should ‘Alan’ be treated?

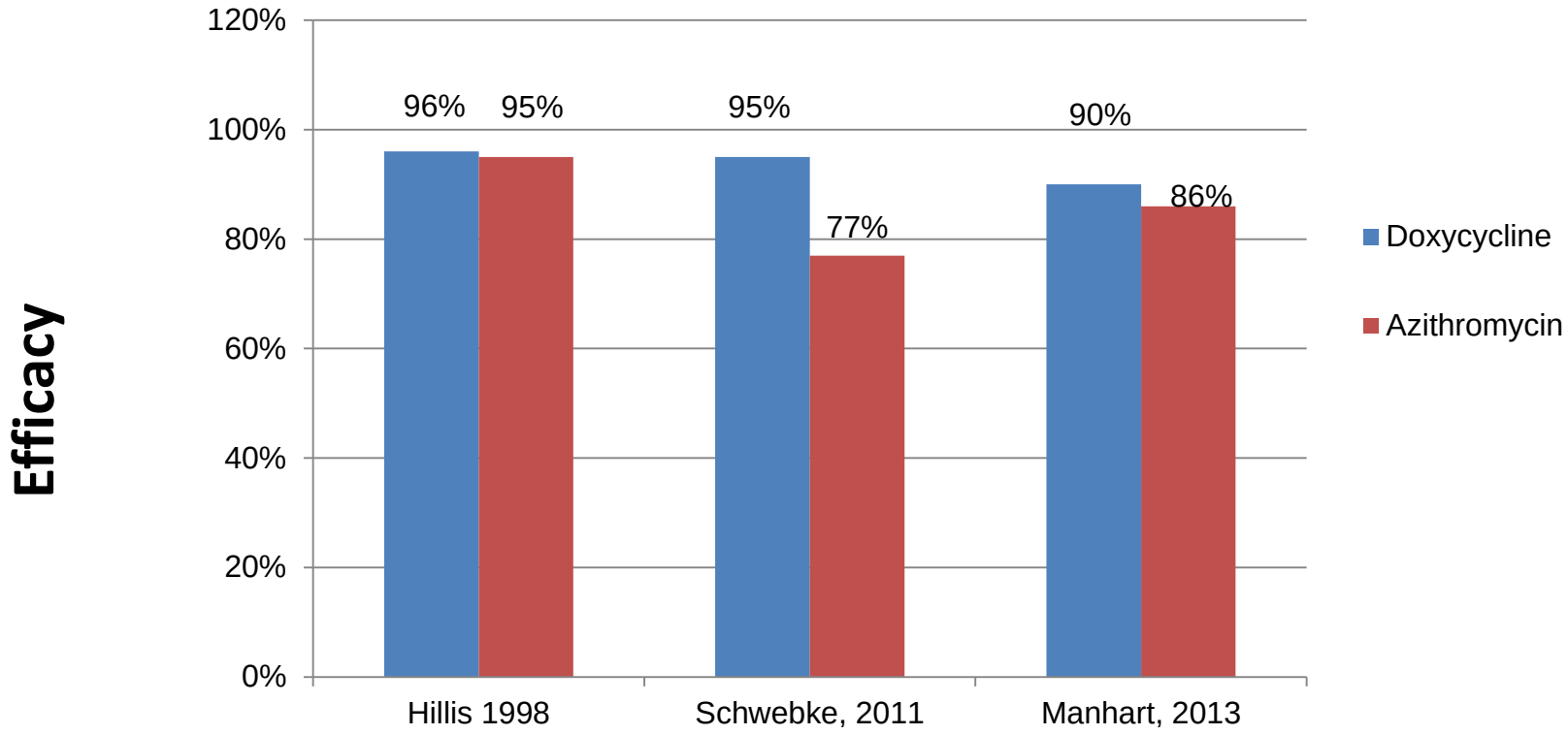
CT Treatment

- **Azithromycin 1gm PO, or**
- **Doxycycline 100mg PO BID X 7 days**
- Alternatives:\Erythromycin base 500mg PO QID x 7 days
  - Erythromycin ethylsuccinate 800mg PO QID x 7d
  - Levofloxacin 500mg PO qday x 7 days
  - Ofloxacin 300mg PO BID x 7 days
- Pregnancy (No tetracyclines!) Azithromycin or Amoxicillin 500mg po tid X 7 days
  - TOC 3-4 weeks after completion and retesting 3 mos after treatment
  - Wait at least 3 weeks or you may get false pos (dead bug) with CT NAAT.

Remember to re-screen at 3 months after treating

MMWR June 5, 2015;64(RR3):1-137

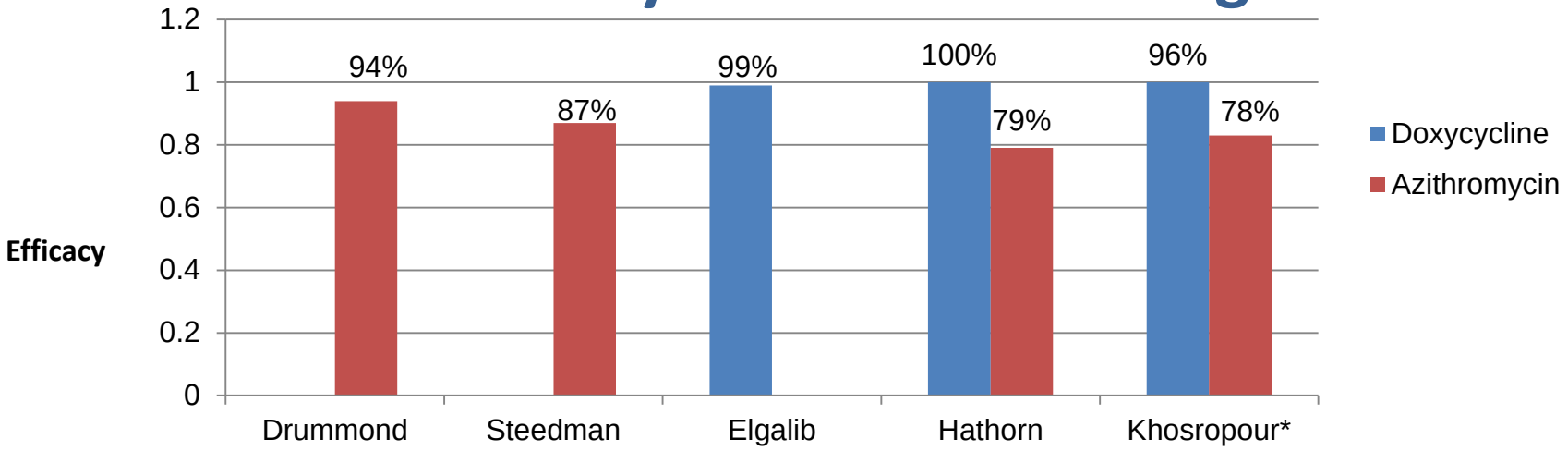
Azithro vs. Doxy RCTs using NAAT



Recent RCT: Geisler et al, NEJM 2015: No treatment failures in doxycycline group, 3.2% treatment failure in azithromycin group.

Metaanalysis: Lau et al., STD 2002: no difference, Kong et al. CID 2014, 3% increased efficacy of doxycycline, 7% inc efficacy in symp urethral infection in men?

Azithro or Doxy for Rectal CT using NAAT



Study, year	Study type	Diagnostic method	Serovar	Males	Females	Symptomatic—rectal[a,b]	HIV positive[b]	STI coinfections[b,c]	Follow-up time when test of cure undertaken	Attrition	Azithromycin efficacy[d]	Doxycycline efficacy[d]
White, 2009[31]	observational	not specified	non-LGV	137	0	0%	not specified	not specified	5 weeks	not specified	10/18 (55.6%)	119/119 (100%)
Steedman, 2009[20]	observational	PCR	non-LGV[e]	78	6	0%	17/97 (17.6%)	38/97 (39.2%) at any site	>3 weeks	10/78 (12.8%)	61/68 (89.7%)[f]	NA
Elgalib, 2010[28]	observational	PCR	non-LGV	252	0	0%	19%	12% (rectal GC)	6 weeks	0/252 (0%)	21/26 (80.8%)	185/186 (99.5%)
Drummond, 2011[21]	observational	PCR	non-LGV[e]	116	0	0%	14/85 (16.5%)	26/85 (30.6%) at any site	median: 11 weeks	31/116 (26.7%)	80/85 (94.1%)[g]	NA
Hathorn, 2012[12]	observational	PCR	non-LGV[h]	94	73	females: 0% males: 5/167 (3.0%)	6/167 (3.6%)	34/167 (20.4%) at any site	6 weeks	85/167 (50.9%)	33/42 (78.6%)	40/40 (100%)
Ding, 2013[32]	observational	PCR	not specified	0	75	1/75 (1.3%)[i]	not specified	1/97 (1.0%) rectal GC	6 weeks	0/75 (0%)	9/11 (81.8%)[j]	NA[k]
Khosropour, 2013[35]	observational[l]	not specified	not specified	338 men and women[m]		not specified	not specified	not specified	6 months	37/338 (10.9%)	41/49 (83.7%)	19/21 (90.5%)
Khosropour, 2014[22]	observational	culture/PCR	not specified	1480	0	92/502 (18.3%)	110/502 (21.9%)	60/502 (12.0%) urethral CT and 91/502 (18.1%) rectal GC	2–13 weeks	978/1480 (66.1%)	180/230 (78.3%)	54/56 (96.4%)

What should ‘Alan’ be treated with?

- Positive CT throat and NG rectal
- ‘Alan’ should get: Cefriaxone 250mg IM X1 PLUS Azithromycin 1g po X1

- Note: the clinical significance of CT pharyngeal infection is unknown, so testing not recommended (but NG/CT tests are bundled, and if you find it you will treat it as there is potential for transmission via oral sex).

Case B: 28 y.o. male with 4 weeks rectal bleeding

- **'Gary' CC**: Slight bloody discharge several times daily
  - Tenesmus; no diarrhea
  - No lightheadedness or pain
  - Similar episode 3 years ago
    - Saw GI doctor, "possible IBD"
    - Rectal steroid didn't help, eventually resolved
- **PMH**: HIV+ but currently off therapy, preserved CD4
- **Social**: MSM: insertive and receptive oral and anal sex w/ ~2-3 partners monthly
- On exam: Moderate rectal tenderness, Some purulent discharge, no ulcers
- What tests do you order?
- **A test was positive**…

Case B: 28 y.o. male with 4 weeks rectal bleeding

- Syphilis treponemal test: Positive, RPR: negative
- Pharyngeal NG/CT: Negative
- Urine NG/CT: Negative
- **Rectal NG/CT NAT: Pos CT**

What should Gary be treated with?

- **Azithromycin 1g po X1?**
- **Doxycycline 100mg po BID X 7 days?**
- **Doxycyline 100mg po BID X 21 days?**

Lymphogranuloma Venereum
LGV

- **D-K serovars** of *Chlamydia trachomatis*: cause the common genital infections that we see.
- **L1-L3 serovars** of *Chlamydia trachomatis*: **Lymphogranuloma venereum (LGV)**
  - **Strains more invasive**
- Rare for many years in US and developed countries
- 2004 seen in the Netherlands
- MMWR→ Michigan: Outbreak amongst HIV+ MSM

Clinical Manifestations

- Primary Lesion 3-21 days after exposure
- The primary lesion of LGV is a small non painful genital papule, which can ulcerate at the site of inoculation – often remains undetected.
- Common lesion sites
  - Coronal sulcus, frenulum, prepuce, penis, urethra, glans and scrotum
  - Posterior vaginal wall, fourchette, posterior lip of the cervix and vulva

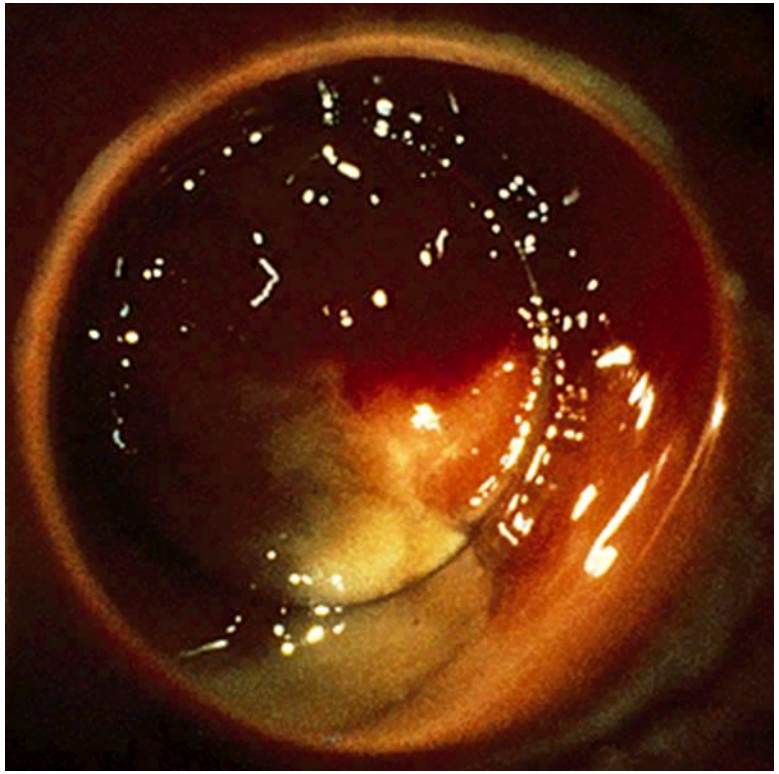
Clinical manifestations

- Secondary lesions 10 days to 6 months
- Tender inguinal/femoral adenopathy (buboes)
  - most often unilateral
  - Coalesce to form stellate abscesses
- Systemic symptoms
- Cutaneous manifestations

Clinical manifestations

- Proctitis: Diarrhea, rectal bleeding, mucous discharge, pain

- Hemorrhagic proctitis/proctocolitis
  - Constipation, spasms, tenesmus
  - Rectal scarring – stricture
  - Severe-can mimic IBD



Diagnosis

- Clinical Findings
- Serologic tests can support diagnosis
- Identification of C. trachomatis from a lesion/bubo/site of infection
- NAAT test will be positive, but need special testing to identify LGV strains—not routinely available.

Treatment

- Doxycycline 100 mg bid x 21 days

- Alternatives
  - Erythromycin base 500 mg qid x 21 days
  - Azithromycin 1 gram orally weekly x 3 weeks

Bottom line: In SYMPTOMATIC MSM with CT+, especially HIV+, would treat empirically for LGV.

‘Gary’ should get Doxycycline X 21 days.

Practical Scenarios-NG/CT

- **Empiric treatment**
  - Urethritis (assuming no POC NG testing): NG therapy (covers CT)
  - Cervicitis: CT therapy + consider NG therapy
- **Post-treatment abstinence: 7 days**
- **Managing sex partners**
  - All sex partners in past 60 days (eval, dx, tx)
  - If no sex in >60 days, then most recent partner
  - **Expedited partner therapy (EPT)** rec'd where legal
    - Heterosexual, provide written educational materials
    - Cefixime 400mg + Azithro 1000mg for NG; Azithro 1000mg for CT
    - www.cdc.gov/std/ept

Questions?

SYPHILIS

Case A: 48 y.o. male with rash and LFT abnormalities

- Presents to office
  - Rash for 5 days
  - Nausea and poor appetite
  - History of chronic HCV and alcohol abuse
- Exam
  - Flat maculo papular rash on trunk, sparing palms & soles
  - Normal mini-mental, no asterixis
- **AST 130** U/L; **ALT 150** U/L
- **Alk Phos 1260 U/L**; T-bili 1.2 mg/dl (baseline 0.5)
- A test was performed…

Case A: 48 y.o. male with rash and LFT abnormalities

- Presents to office
  - Rash for 5 days
  - Nausea and poor appetite
  - History of chronic HCV and alcohol abuse
- Exam
  - Pustular rash on trunk & arms, sparing palms & soles
  - Normal mini-mental, no asterixis
- AST 52 U/L; ALT 58 U/L (baseline)
- **AP 1260 U/L**; T-bili 1.2 mg/dl (baseline 0.5)
- **Serum Treponemal Ab reactive, RPR 1:128**
- Sexual HX: "Maybe a dozen" men & women / year

Case B: 43 male with vision loss

- Progressive vision loss beginning 6 weeks ago
  - First-week R-sided only (blurriness, dark shapes), then left
  - Pain bilaterally, dry eye sensation, mild light sensitivity
  - No longer distinguishing faces – ophthalmologist (2 wk ago)
    - "Uveitis and possible infection"
    - Antibiotic eye drops and prednisone
  - Initial improvement, but now presents with worsening again
  - NO: h/a, neck stiffness, fevers, focal neuro, cognitive probs

- Other history
  - Immigrant from Central America, landscaper
  - Male and female partners, no further disclosure

- Office Exam: barely counting fingers

Case B: 43 male with vision loss

- **Serum Treponemal Ab reactive, RPR 1:256**

- Ophthal Exam
  - Bilateral anterior & intermediate uveitis, vitritis
  - No retinal whitening
- LP
  - WBC 1 / 0; RBC 0 / 0
  - Pro 24, Glucose 63
  - VDRL (resulted 9 days later): Neg

- HIV pos; CD4 85, HIV RNA 731,000

Exposure

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Syphilis
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Secondary Syphilis

Tertiary Syphilis

Cardiovascular Syphilis
10%
(Onset 20-30 Years
Postinfection)

Gummatous Disease
15%
(Onset 1-46 Years
Postinfection)

General Paresis
2%-5%
(Onset 2-30 Years
Postinfection)

2%-9%
(Onset 3-50 Years
Postinfection)

Diagnosing Syphilis

If you see a lesion:

Darkfield microscopy (often not available)
PCR

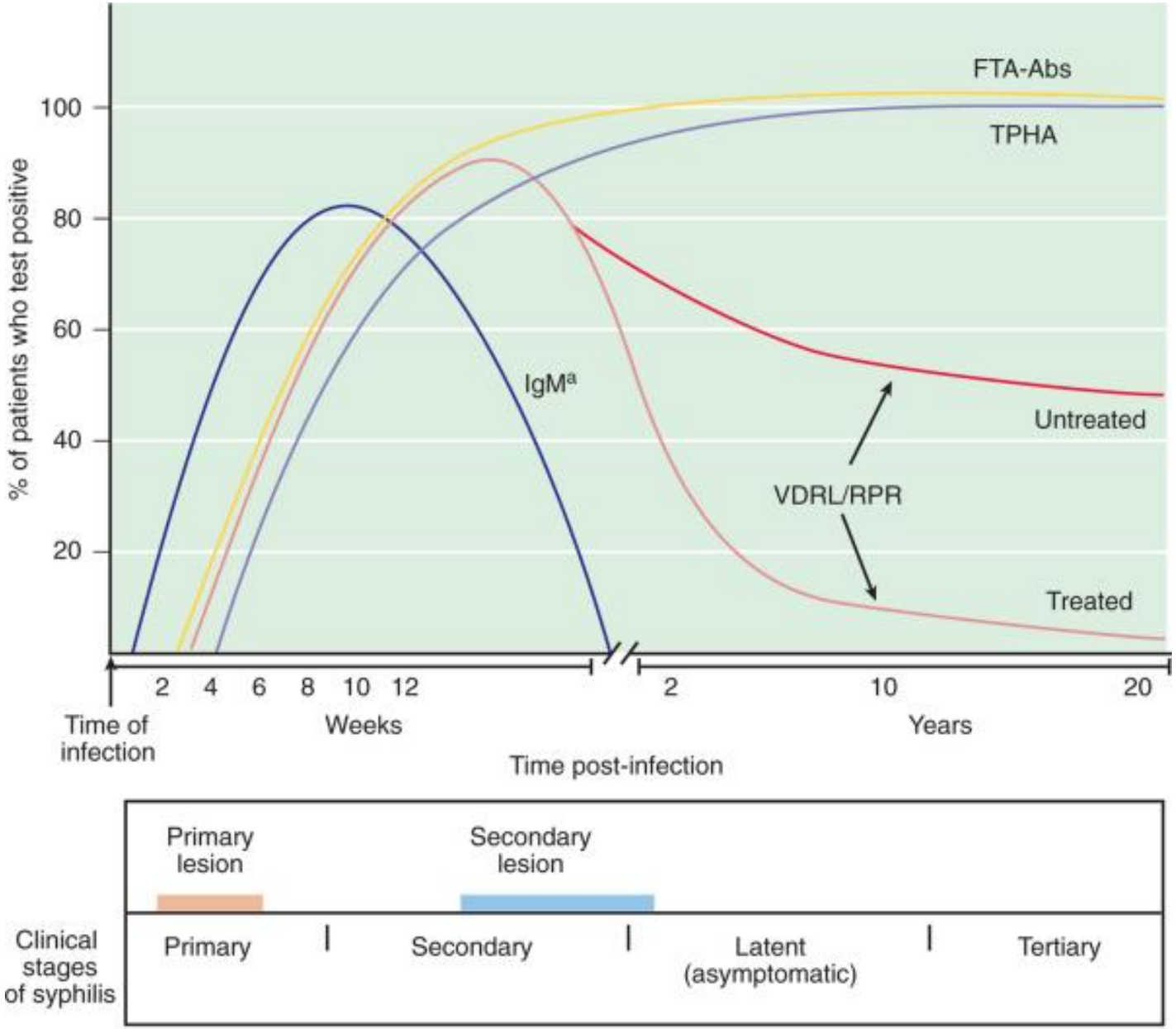
Most diagnosis relies on serology:

Non treponemal tests: (RPR, VDRL)

- nonspecific tests that are very sensitive; This is the first test that you get on anyone you suspect of having syphilis
- If negative (and you don't suspect primary syphilis), then the patient is very unlikely to have syphilis and no more testing is needed
- If positive, then you need to confirm the positive test result by ordering a TREPONEMAL test…
- These go up and down with treatment (and time)

Treponemal Tests (MHA-TP, TPPA, FTA-ABS, EIAs)

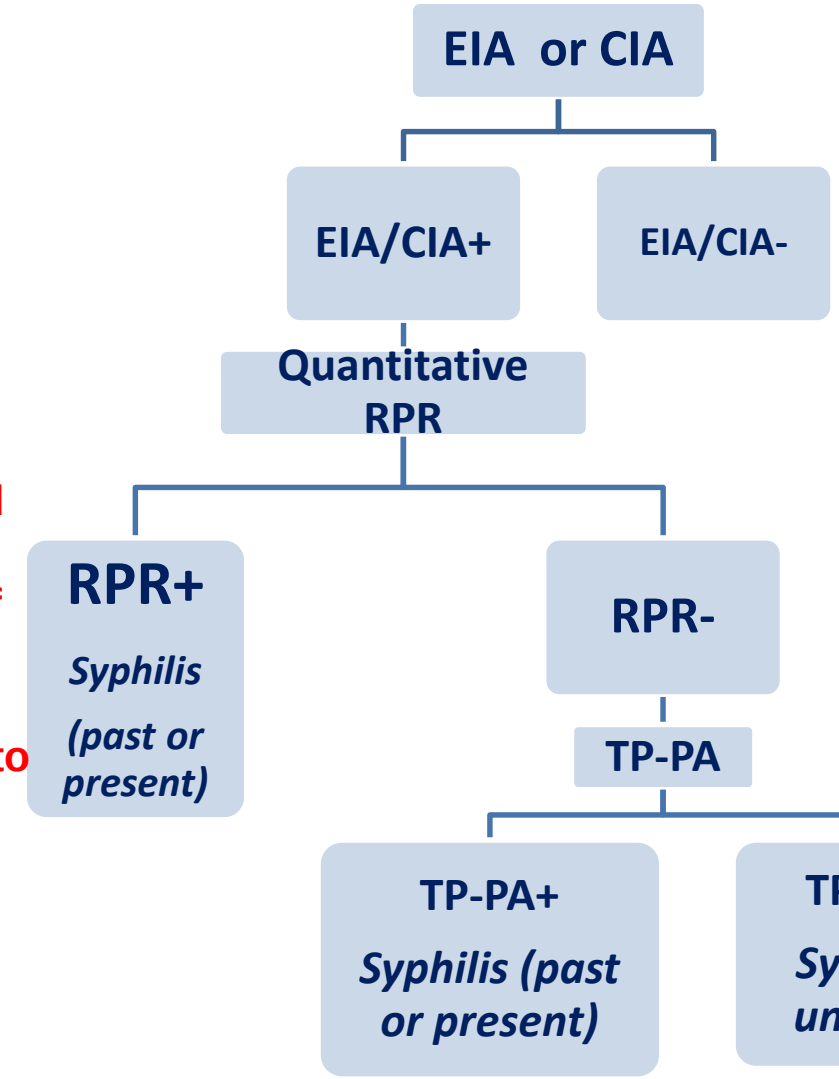
- Test for the presence of antibodies that are treponemal-specific. These tests are very specific for syphilis.
- These tests do NOT provide a titer that we can follow after therapy.
- Once positive ALWAYS positive even after treatment.



Peeling et al. Bulletin of WHO 2004; 82(6):439-46

JOHNS HOPKINS SCHOOL of MEDICINE

Reverse Screening Algorithm



Evaluate clinically, determine if treated for syphilis in the past, assess risk of infection, and administer therapy according to guidelines if not previously treated

If incubating or primary syphilis is suspected, treat with benzathine penicillin G 2.4 million units IM x 1 and/or repeat in 2-4 weeks

If at risk for syphilis, repeat RPR in 2 to 4 weeks

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

Syphilis Therapy: 1°, 2°, Early latent (<1 yr)

- **Benzathine PCN 2.4 million units IM x1**
  - No documented resistance
  - Other PCN forms NOT substitutable
- **Penicillin allergies / reactions**
  - Doxycycline 100mg PO BID x 14 days
  - Ceftriaxone 1-2000mg qday IM or IV x 14 days
  - Azithromycin 2000mg PO x 1
    - NOT in MSM or pregnancy
    - Reports of treatment failures (23s rRNA mutations)
- **Pregnancy**: only use PCN! Desensitize if necessary

Late (>1 yr) latent or latent with unknown duration

- **Benzathine PCN G 2.4 MU x3 doses (1 week intervals)**
  - Careful exam for lesions c/w prim, sec, or tertiary
  - Careful history and exam for neurologic findings
  - PCN-allergy: doxy (or tetra) for 28 days
- **What if they miss a week?**
  - One 10-14 day interval may be acceptable
  - Based on clinical experience, not pharmacology
- **Pregnancy**: only use PCN!
  - MUST be desensitized if true PCN allergy
  - Repeat whole course if miss a 7 day interval

Follow-up Testing

- Follow-up of quantitative non-treponemal titers
  - At least 6, 12, 24 mos
  - Cure=4 fold decline in titers (e.g. 1:32→1:8)
    - 6-12 mos for primary/secondary
    - 6, 12, 24 mos for latent/late
  - Failure of titers to decline?
    - Consider CSF exam
    - Repeat treatment (at least x 1—3 doses BPG)
- HIV-testing after any syphilis diagnosis
- NG/CT screening

Tertiary

- Tertiary (cardiovascular or gummatous lesions, tertiary NS)
  - CSF exam before treatment in all cases
  - If CSF negative, then treat as late latent
  - Some treat cardiovascular disease with CNS regimen

Re: our first patient…Syphilitic Hepatitis

- **Early (primary and secondary) stage**
  - **LFT abnormalities 10-20%** (HIV neg and HIV pos)
  - Mostly asymptomatic
  - Hepatomagaly common
  - Disproportionately elevated AP typical, but not 100%
  - Treponemes identifiable in necrotic liver material
  - **Resolution with treatment (1-4 months)**

- **Late stage:** fibrosis, gummas, and hepar lobatum (pre-antibiotic era)

Lancet. 1975;2(7941):896-9

Int J STD AIDS. 2012;23(8):e4-6

Diagnosis of Neurosyphilis

- Patients with Neurologic signs/sx, ocular or otologic signs /sx during any stage of syphilis need an LP!!

- Dx on Lumbar Puncture by:
  - abnormal CSF cell count (> 5 WBC)
  - abnormal CSF protein
  - Reactive CSF-VDRL with or without symptoms (only about 50% sensitive—so if it's positive it's helpful, but a negative CSF VDRL does not rule out NS.
  - CSF-FTA reactive (More sensitive than CSF-VDRL, but not specific)

Neurosyphilis therapy

- **Recommended:** Aqueous crystalline PCN G 18-24 MU per day, divided 3-4 MU IV q4hr or continuous infusion for 10-14 days
- **Alternative:** Procaine PCN G 2.4 MU IM qday **PLUS** probenecid 500mg PO 4 times daily for 10-14 days
- **Penicillin allergy**
  - Consider ceftriaxone 2000mg qday IM or IV x 10 - 14 days, **OR**
  - Skin test and desensitize
- **Pregnancy**: only use PCN! Desensitize if necessary
- **Practical**: B PCN G in clinic while arranging for LP and IV therapy (if any chance LTFU after leaving clinic
- **Late stage**: consider B PCN G 2.4 MU IM qweek x3 after finishing IV

Follow-up of neurosyphilis

- **Serial CSF exam q6 months**
  - Until cell count normal
  - Also follow protein +/- VDRL
    - Slower to normalize than WBC
    - Significance less clear

- **Consider retreatment**
  - WBC not decreased by 6 months
  - WBC or protein not normal after 2 years

Back to our second patient…

Case B: 43 male with vision loss

- **Serum Treponemal Ab reactive, RPR 1:256**

What is the recommended therapy?

A. Azithromycin 2000mg PO x 1
B. Benzathine PCN-G 2.4 MU IM qweek x 3
C. Aqueous PCN-G 3-4 MU IV q4hr x 10-14 days
D. Ceftriaxone 2000mg IV qday x 10-14 days

CDC MMWR: Ocular syphilis in 8 US Jurisdictions 2014-2015

Review all TP cases*

- 388 / 65,130 (0.6%)
- Range 0.17 – 3.9%
- Male 93%
- Known MSM 69%
- HIV-infected 51%

(Chart review, data not prospectively collected.
CA (partial), FL, IN, MD, NYC, NC, TX, WA

Characteristic	No.	(%)
Total	**388**	**(100.0)**
Stage of syphilis		
Primary	8	(2.1)
Secondary	101	(26.0)
Early latent	79	(20.4)
Late or latent of unknown duration	193	(49.7)
Unknown	7	(1.8)
Additional symptoms of neurosyphilis	87	(22.4)
Reported ocular symptoms (among 326 with symptoms)		
Blurry vision	210	(64.4)
Vision loss	107	(32.8)
Eye pain or red eye	46	(14.1)
CSF VDRL (among 174 with a documented result)		
Reactive	122	(70.1)
Nonreactive	52	(29.9)

MMWR Nov 4, 2016; 65(43): 1185-88

Clinical Advisory: Ocular Syphilis in US. MMWR April 16, 2015

What is it?

- Ocular syphilis is often considered a subset of neurosyphilis, though the syndromes may not overlap
  - 60% of patients with ocular syphilis will have CSF abnormalities (neurosyphilis)
- Decreased visual acuity including permanent blindness

What do I do?

- Screen for visual symptoms in patients at risk for syphilis
- Do a careful neuro exam including all cranial nerves
- If ocular signs or symptoms, send for ophthalmologic evaluation ASAP.
- Do lumbar puncture
- Treat for neurosyphilis
- Report case to state or local health department

Diagnosis of Ocular Syphilis

- **Presumptive diagnosis**
  - **Ocular syphilis can involve any part of the eye at any syphilis stage!**
  - (Ocular signs in a person with syphilis)
  - Most diagnoses are presumptive
  - **Indicates a full treatment course 10-14 Days of IV Penicillin G (like for neurosyphilis even if no abnormalities on CSF)!**

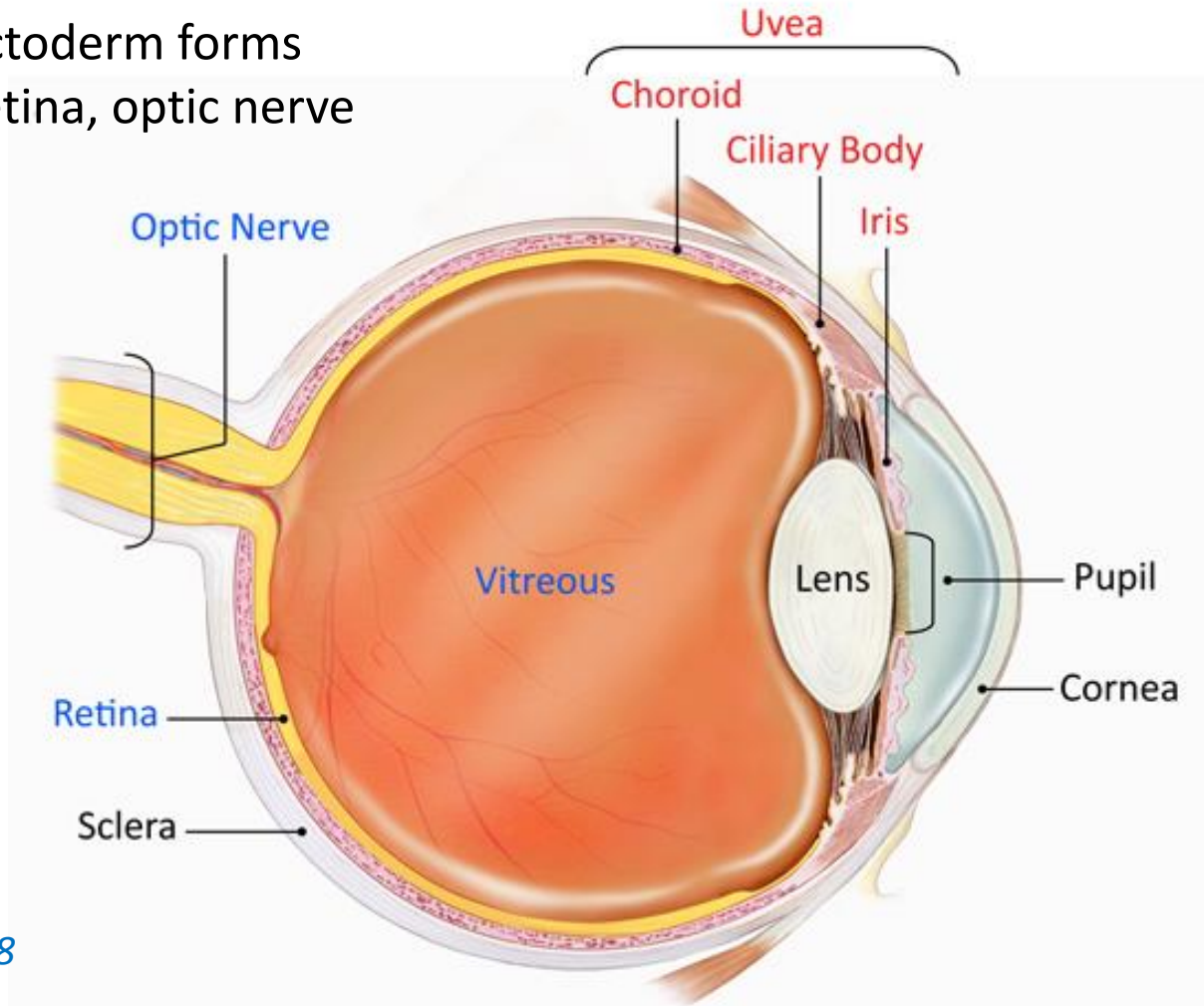
- All patients should have an LP
- Most patients will have positive serum serological tests
  - But serum RPR can be negative in some cases.

Ocular Findings

Are ocular syphilis and neurosyphilis the same entity?

No, but a lot of co-occurrence (~60% have CSF abnormalities)

Embyrologically, neuroectoderm forms posterior layers of iris, retina, optic nerve



Ophthal findings (8 district review)

- Uveitis 46%
- Retinitis 13%
- Optic neuritis 11%
- Ret. detach. 4%

MMWR Nov 4, 2016; 65(43): 1185-88

Do you really need to do an LP in someone who only has eye symptoms and no neurological symptoms if they are going to get IV PCN G for 10-14 days anyway?

- **YES**, and here's why:
  - The guidelines say so.
  - CSF VDRL = DEFINITIVE diagnosis of ocular syphilis
    - Helpful in excluding other causes
    - Abnormal CSF profile with negative VDRL: still consistent with syphilis (but not definitive)
  - Practical
    - While the antibiotic regimen is the same for ocular and neurosyphilis, patients with neurosyphilis (about 60%) need follow-up LP(s)
    - Normalization of the CSF parameters is an objective way to track cure if visual symptoms fail to improve
- **Do not delay antibiotics waiting for the LP!**

Ophthalmology involvement and steroids

- **Ophthalmologist:** recommended in all cases
  - In questionable cases, can help determine if objective eye signs
  - Help manage complications
  - Exam should be right away (24 hours?); in some cases ocular syphilis progresses rapidly to blindness (refer to ED if no urgent ophthalmologist available)
- **Do not delay antibiotics waiting for the ophthalmologist!**
- **Steroids**
  - No clear benefit or harm
  - Topical: adjunct for interstitial keratitis, anterior uveitis
  - Systemic: adjunct for posterior uveitis, scleritis, optic neuritis

Retina 2012; 32:1915–1941

Complications

- Incidence of **visual impairment**
  - 0.29/eye year for HIV uninfected
  - 0.21/eye year for HIV infected
- Incidence of **permanent blindness**
  - 0.07/eye year for HIV uninfected
  - 0.06/eye year for HIV infected

- **Risk factors for poor visual outcomes**: longer duration of untreated infection; macular chorioretinitis
- **Long-term complications**: glaucoma, cataract, epiretinal membrane and macular edema, choroidal neovascularization, widespread chorioretinal scarring

Am J Ophthalmol 2015; 159:334-43
Lancet Infect Dis 2004; 4(7):456-66

Some interesting ideas…

- PEP for syphilis?
- CROI 2017: ON DEMAND POST EXPOSURE PROPHYLAXIS WITH DOXYCYCLINE FOR MSM ENROLLED IN A PREP TRIAL
  - Molina et al
  - High risk adult MSM in PrEP trial randomized to take 200mg of doxycycline within 72 h after condomless sexual intercourse (not more than 600mg per week) or none
  - Decrease in incidence of chlamydia and syphilis infection in those PEP.

- PrEP for syphilis?
  - Daily 100mg doxycycline

Doxycycline Prophylaxis to Reduce Incident Syphilis among HIV-Infected Men who have Sex with Men who Continue to Engage in High Risk Sex: A Randomized, Controlled Pilot Study

Recap

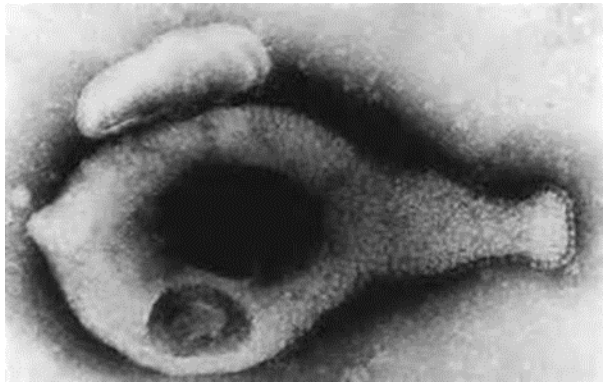
- Rates of gonorrhea, chlamydia and syphilis are going up in the US
- Congenital syphilis and Ocular syphilis are on the rise
- Extragenital screening for Gonorrhea and Chlamydia is important-ask about sites of exposure and test accordingly!
- Gonorrhea drug resistance is an increasing problem

And by the way…a "New" STI…

- *Mycoplasma genitalium*
- NGU: non-gonococcal urethritis
  - Non-specific diagnosis, many infectious etiologies possible
  - (Chlamydia, Ureaplasma? Trichomonas vaginalis (in MSW), HSV, Adenovirus, M. genitalium)
  - M. genitalium causes 15-25% of NGU, 30-40% of persistent NGU…

Mycoplasma genitalium

- Recognized cause of urethritis
- Role in cervicitis increasingly clear, ? PID
- NO diagnostic test FDA cleared for use
  - NAATs available in some large medical centers and commercial laboratories
- Suspect in persistent or recurrent urethritis and consider in persistent cervicitis and PID
- Treatment implications
  - Azithromycin > doxycycline
  - Increasing resistance to azithromycin
  - Moxifloxacin for recurrence, but now reports of fluoroquinolone resistance as well…



NGU Treatment

Recommended

- Azithromycin 1 gm PO x 1 dose

OR

- Doxycycline 100 mg PO BID x 7 days

Alternative

- Erythromycin base 500 mg PO QID x 7 days
- Erythromycin ethylsuccinate 800 mg QID x 7 days
- Levofloxacin 500 mg QD x 7 days
- Ofloxacin 300 mg PO BID x 7 days

Efficacy of AZ for *M. genitalium* declining
Manhart et al, CID 2013

Persistent NGU Treatment

Objective signs should be present before repeat therapy given

- Gram stain

If azithromycin NOT given for 1st episode:

- Azithromycin 1 g orally in a single dose **PLUS**
- Metronidazole 2 g orally in a single dose* OR
- Tinidazole 2 g orally in a single dose*

If azithromycin given for 1st episode:

- Moxifloxacin 400 mg orally qd x 7d

PLUS

- Metronidazole 2 g orally in a single dose* OR
- Tinidazole 2 g orally in a single dose*

*In men who have sex with women and where TV is highly prevalent