

STD Hot Topics:

Extra-genital testing, antibiotic resistance, and anal cancer screening

Rosalyn Plotzker, MD, MPH

Sexually Transmitted Diseases Fellow, California Prevention Training Center/ CA Dept. Public Health

> 2018 LOS ANGELES COUNTY STD SUMMIT IMPROVING PREVENTION AND CARE



DISCLOSURE

Rosalyn Plotzker, MD, MPH has no relevant financial relationships with an entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on patients.

This presentation contains several puns.



WHAT'S NEW?

- Extra-genital screening for gonorrhea and chlamydia
- Antibiotic resistant gonorrhea update
- Anal cytology for anal cancer screening

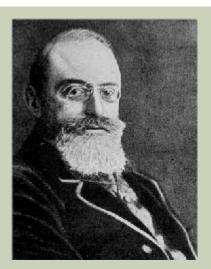
WHAT'S OLD? A LITTLE MEDICAL HISTORY...

What's in a Name?

- Galen ~ 160 A.D
 - "gon"=semen/seed + "rhea"=flow; → 'flow of seed'
- "The Clap"
 - 'Clapiers', or French public brothels

Eureka! Discovery!

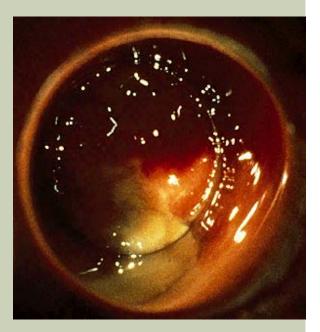
- 1879 Albert Ludwig Sigesmund <u>Neisser</u> discovers the 'micrococcus'
- 1907 Halberstaedter and von Prowazek describes CT in epithelial scrapings from orangutans inoculated with material from trachoma patients



CLINICAL MANIFESTATIONS: Pharyngitis, epididymitis, and proctitis



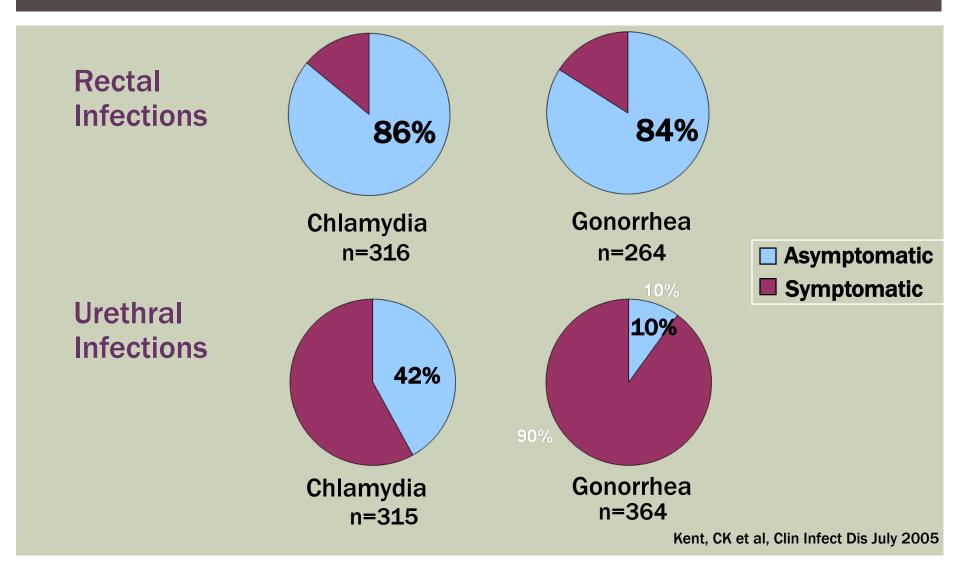




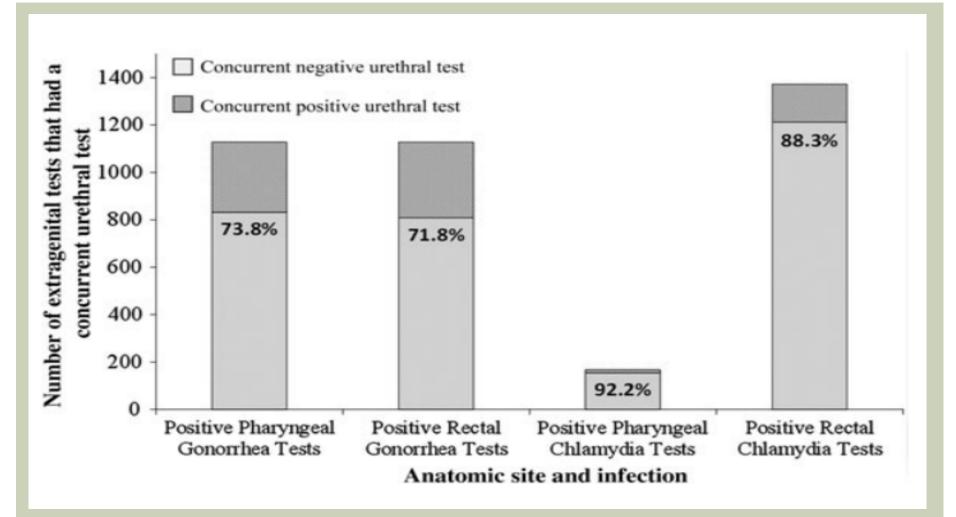




MAJORITY OF RECTAL INFECTIONS IN MSM ARE ASYMPTOMATIC

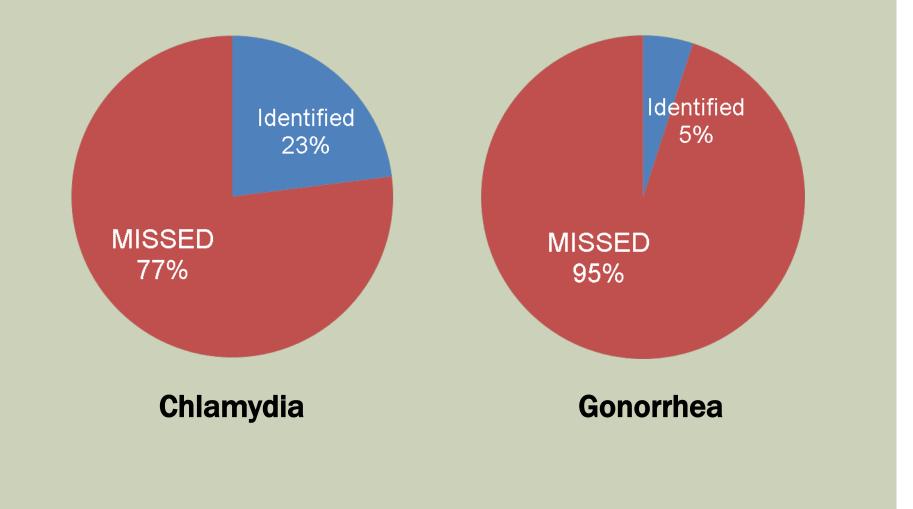


HIGH PROPORTION OF EXTRA-GENITAL CT/GC ASSOCIATED WITH NEGATIVE URINE TEST, STD SURVEILLANCE NETWORK (SSUN) (N=21,994)



Patton et al CID 2014

PROPORTION OF CT/GC INFECTIONS <u>MISSED</u> AMONG 3398 ASYMPTOMATIC MSM IF SCREENING ONLY URINE/URETHRAL SITES, SAN FRANCISCO, 2008-2009





GC/CT NAATS: RECTAL AND PHARYNGEAL SITES

- NAATs have not been cleared by FDA for these indications
- NAATs can be used by laboratories that have undergone validation procedures and met all regulatory requirements for an off-label procedure
- Large commercial labs accept these specimens
- Opportunity for self-collection (may require validation)

https://www.cdph.ca.gov/Programs/CIDa/DCDC/Pages/STD-MSMToolkit.aspx

CDC. MMWR 2014 / 63(RR02);1-19 Van der helm, 2009, STD; Sexton, 2013 J Fam Pract; Dodge, 2012 Sex Health Freeman 2011, STD; Alexander 2008, STI; Moncada 2009, STD



RECTAL GC: NAAT OR CULTURE?

		Rectal NAAT		
		Positive	Negative	Total
Rectal Culture	Positive	39	0	39
	Negative	28	635	663
	Total	67	635	702

Sensitivity of culture: 58.2%



PHARYNGEAL GC: NAAT OR CULTURE?

		Pharyngeal NAAT		
		Positive	Negative	Total
Rectal Culture	Positive	18	0	18
	Negative	50	695	745
	Total	68	695	763

Sensitivity of culture: 26.5%



NAAT LABORATORY ORDERING AND BILLING CODES

	Company-Specific Ordering Codes for Combined GC/CT Nucleic Acid Amplified Tests (NAATs)		Company-Specific Ordering Codes for CT test only
	LabCorp*	Quest*	LabCorp
Rectal	188672	16506	188706
Pharyngeal	188698	70051	188714
NAATs are offered at (or from) any location in the country with these two codes.			

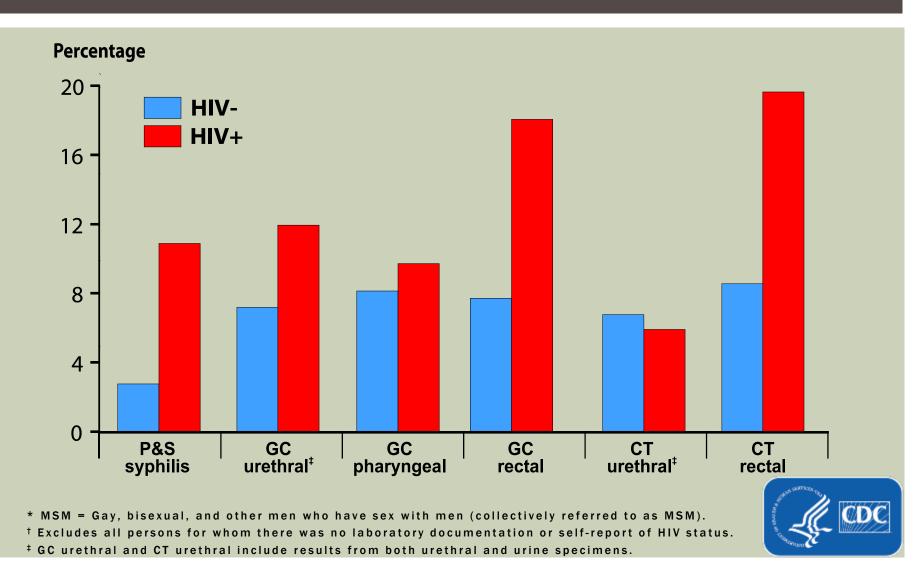
For information on specimen collection and transportation, clinicians should contact the local reference laboratory representative.

CPT Billing Codes		
CT detection by NAAT	87491	
GC detection by NAAT	87591	

*CDC does not endorse these laboratories, however, they represent the largest laboratories nationally. There may be other private laboratories that have verified rectal and pharyngeal testing with NAATs. Many PHLs have also verified rectal and pharyngeal testing.



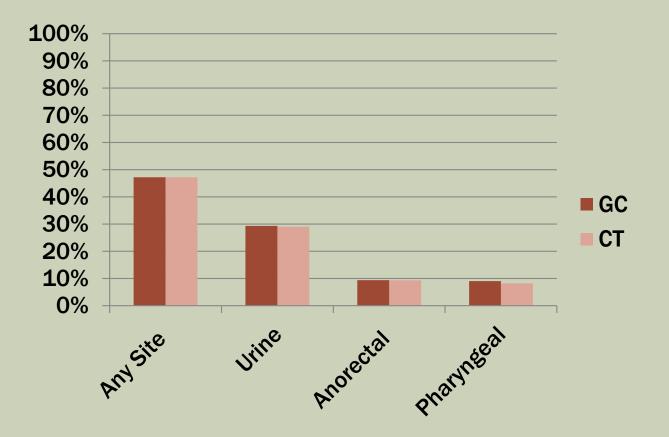
MSM* ATTENDING STD CLINICS: P&S SYPHILIS, GC, OR CT BY HIV STATUS[†] (SSUN), 2015





GC/CT SCREENING AMONG MSM IN HIV CARE

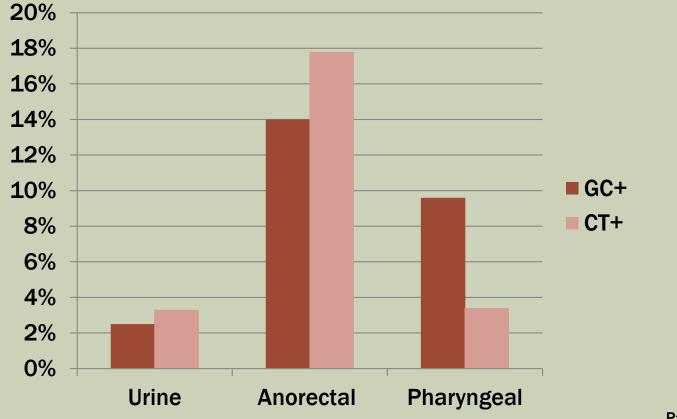
N=3118 (2013-2014) interviews and chart reviews from MMP, testing by anatomical site





EXTRAGENITAL GC/CT SCREENING AMONG MSM IN HIV CARE

N=3118 (2013-2014) interviews and chart reviews from MMP, positivity rate by anatomical site and infection



Patel et al., 2017



BARRIERS TO SCREENING

- Discomfort with sexual history taking or genital examination
- Lack of knowledge about need for testing
- Patient reluctance
- Lack of time



SELF-COLLECTED RECTAL/PHARYNGEAL SPECIMENS

Highly acceptable, similar performance compared to clinician-collected specimens

Self-collection can be performed at laboratory along with blood draw/urine collection or in the exam room before/after the provider visit

May save patient an office visit

May save the provider time

Van der helm, 2009, STD; Sexton, 2013 J Fam Pract; Dodge, 2012 Sex Health Freeman 2011, STD; Alexander 2008, STI; Moncada 2009, STD, Park 2017



PATIENT SELF COLLECTION INSTRUCTIONS



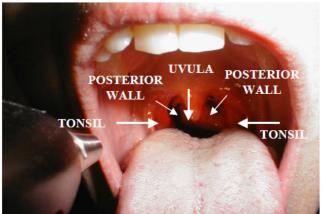
Pharyngeal Swab Collection Instructions



Open kit and remove tube and package with green writing. Remove the swab with the BLUE shaft. USE BLUE SHAFT SWAB ONLY.

Step 2.

Instruct patient to open mouth widely. Be sure to make good contact with 5 key areas of the throat (See below).





Step 3.

Remove cap from test tube. Place swab in test tube. Do not puncture the foil cap.

Break swab shaft at the score mark.

Step 4.

SNAP !

Put cap back tightly on test tube to prevent any leaking. Try not to splash the liquid out the tube.

Step 5.

Discard wrapper and unused swab. Wash your hands.





CHLAMYDIA TREATMENT ADOLESCENTS AND ADULTS

Recommended regimens (non-pregnant):

- Azithromycin 1 g orally in a single dose
- Doxycycline 100 mg orally twice daily for 7 days

Recommended regimens (pregnant*):

- Azithromycin 1 g orally in a single dose
- Amoxicillin 500 mg po TID x 7 days

* Test of cure at 3-4 weeks only in pregnancy



CHLAMYDIA TREATMENT: Alternative regimen

Alternative Regimen (non-pregnant):

- Doxycycline (delayed release) 200 mg QD x 7 d
- Equally efficacious to doxycycline BID,
 GI side effects
- More \$\$\$

Moved to Alternative Regimen (pregnant*):

Amoxicillin 500 mg po TID x 7 days

- CT persistence documented in vitro after treatment prompted removal from recommended to alternate

Is azithro adequate treatment for rectal chlamydia infection?

Population	Treatment	Repeat positive
MSM in Australia (N=85)	Azithro 1 g	13%
MSM in Seattle (N=407)	Azithro 1 g	22%
(N=95)	Doxy 100 BID x 7	8%

Retrospective uncontrolled observational clinical data: Dummond, Int J STD AIDS 2011; 22:478 and Khosropour, STD 2014; 41:79



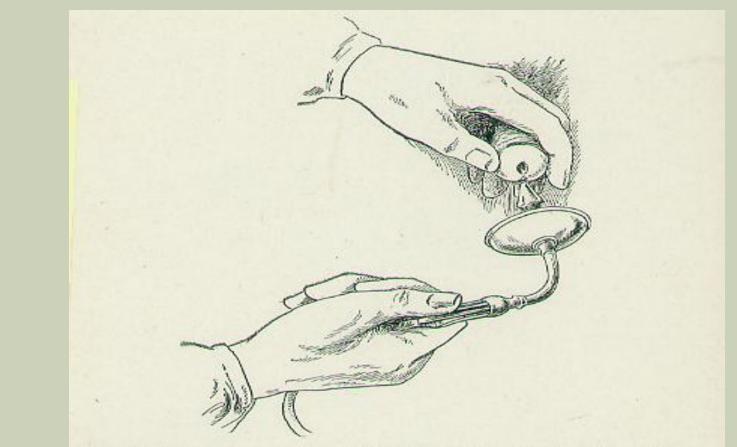


Fig. 39.—The compression of the middle and ring fingers is then released and the entire *anterior* urethra is irrigated.



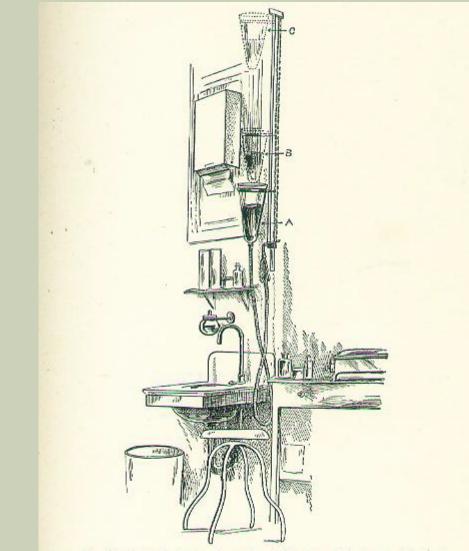


Fig. 37.—Author's treatment outfit. Patient stands in front of the basin, which is placed lower than the average basin height: A, Position of jar for anterior irrigations; B, position of jar for posterior irrigations; C, dangerous pressure for gonococcal urethritis.



GONORRHEA DUAL THERAPY UNCOMPLICATED GENITAL, RECTAL, OR PHARYNGEAL INFECTIONS

PLUS*

Ceftriaxone 250 mg IM in a single dose

Azithromycin 1 g PO or Doxycycline 100 mg BID x 7 days

*Regardless of CT test result



Gonorrhea Treatment Alternatives Anogenital Infections

ALTERNATIVE CEPHALOSPORINS:

Cefixime 400 mg orally once *PLUS*Azithromycin 1 g (preferred)

IN CASE OF SEVERE ALLERGY:

Gentamicin 240 mg IM + azithromycin 2 g PO OR Gemifloxacin 320 mg orally + azithromycin 2 g PO

CDC 2015 STD Treatment Guidelines www.cdc.gov/std/treatment



	Gentamicin Regimen	Gemifloxacin Regimen
Route	IM or IV	Oral
Nausea	27%	37%
Vomiting (<1 hour)	3%	7%
Availability	OK	FDA reported shortage in May 2015
Volume	Need 6 cc (40mg/cc)	



Who needs a test of cure for GC?

- Patients with pharyngeal GC treated with an <u>alternative</u> regimen
 - Obtain test of cure 14 days after treatment, using either culture or NAAT
- Cases of suspected treatment failure
 - (culture and NAAT)
- Consider if using non-standard or monotherapy
- All positive cultures for test-of cure should undergo antimicrobial susceptibility testing.



Test of cure for anogenital GC: prospective cohort study

- Limited evidence for timing of test of cure using modern NAATs
- Of 77 patients:
 - 5 self-cleared GC before treatment
 - 10 lost to follow up
 - 62 remaining patients all cleared. Median time to clearance: 2 days
 - Range 1-7 days for RNA-based NAAT
 - Range 1-15 days for DNA-based NAAT

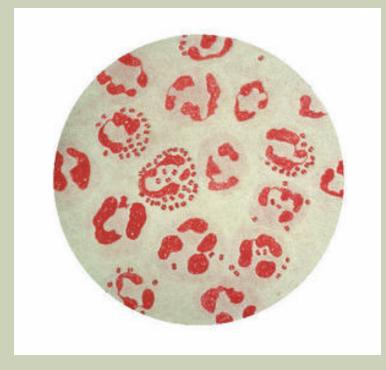




https://www.youtube.com/watch?v=8UtqT2sVBxg



ANTIBIOTIC-RESISTANT GONORRHEA





GLOBAL PRIORITY LIST OF ANTIBIOTIC-RESISTANT BACTERIA TO GUIDE RESEARCH, DISCOVERY, AND DEVELOPMENT OF NEW ANTIBIOTICS

Publication: February 27, 2017

Priority 1: CRITICAL[#]

Acinetobacter baumannii, carbapenem-resistant

Pseudomonas aeruginosa, carbapenem-resistant

*Enterobacteriaceae**, carbapenem-resistant, 3rd generation cephalosporin-resistant

Priority 2: HIGH

Enterococcus faecium, vancomycin-resistant

Staphylococcus aureus, methicillin-resistant, vancomycin intermediate and resistant

Helicobacter pylori, clarithromycin-resistant

Campylobacter, fluoroquinolone-resistant

Salmonella spp., fluoroquinolone-resistant

Neisseria gonorrhoeae, 3rd generation cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM

Streptococcus pneumoniae, penicillin-non-susceptible

Haemophilus influenzae, ampicillin-resistant

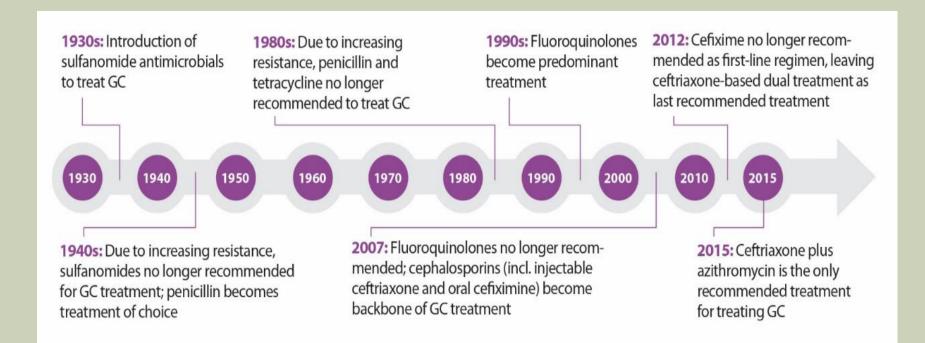
Shigella spp., fluoroquinolone-resistant



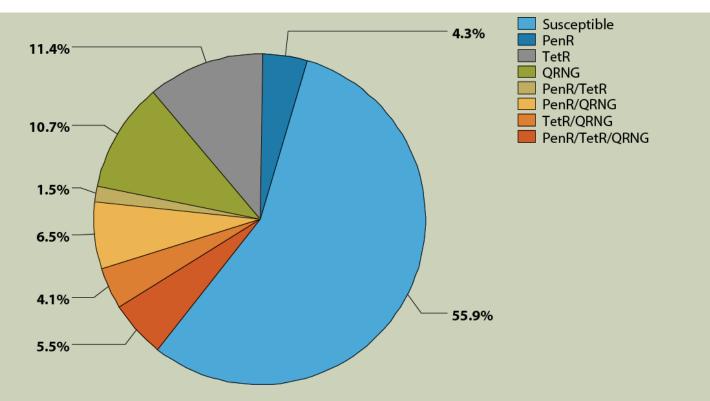




GC antibiotic resistance over time



ISOLATES WITH PENICILLIN, TETRACYCLINE, AND/OR CIPROFLOXACIN RESISTANCE, GONOCOCCAL ISOLATE SURVEILLANCE PROJECT (GISP), 2016

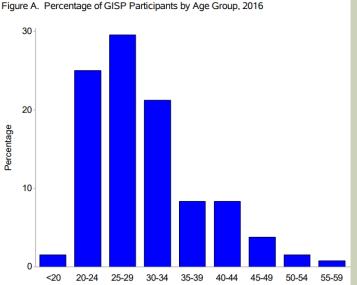


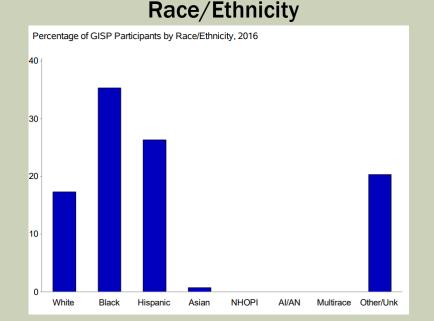
PenR = penicillinase-producing *Neisseria gonorrhoeae* and chromosomally-mediated penicillin-resistant *N. gonorrhoeae*; TetR = chromosomally- and plasmid-mediated tetracycline-resistant *N. gonorrhoeae*; QRNG = quinolone-resistant *N. gonorrhoeae*.



GISP PARTICIPANTS LOS ANGELES, CA 2016, N=133

Age



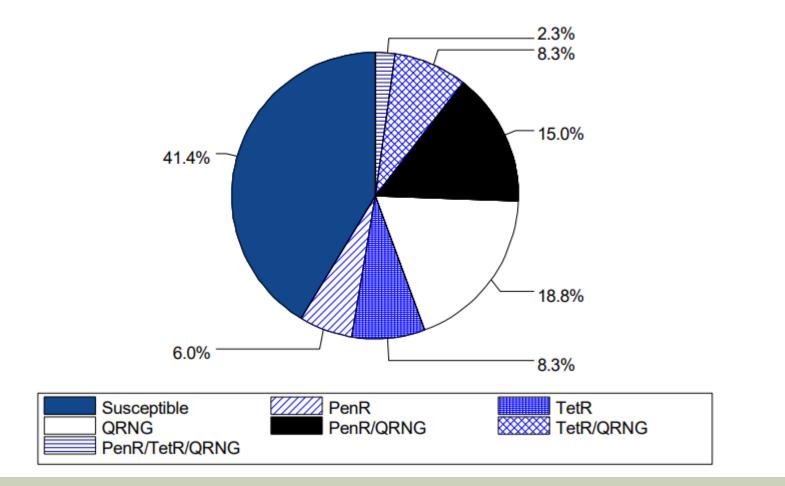


Approximately 67% MSM



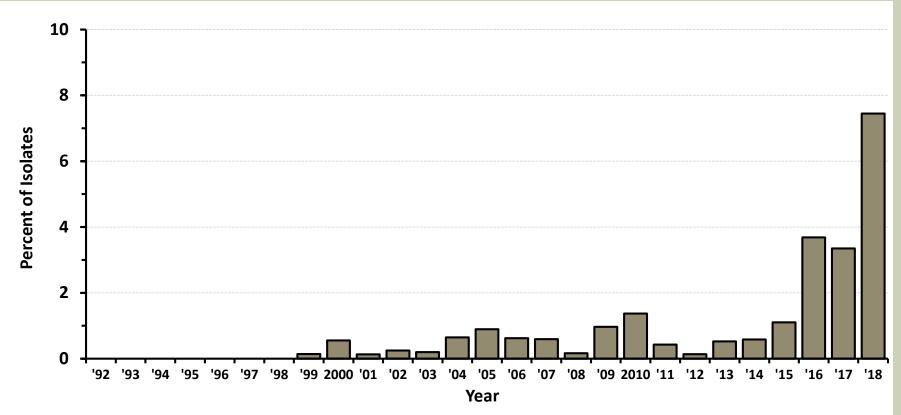
Los Angeles, California (N=133)

Figure F. Percentage of GISP Isolates with Penicillin, Tetracycline, and/or Ciprofloxacin Resistance, 2016





PERCENT OF NEISSERIA GONORRHOEAE ISOLATES WITH CDC "ALERT" VALUES FOR AZITHROMYCIN IN CALIFORNIA GISP STD CLINIC SITES, 1992-AUG. 2018



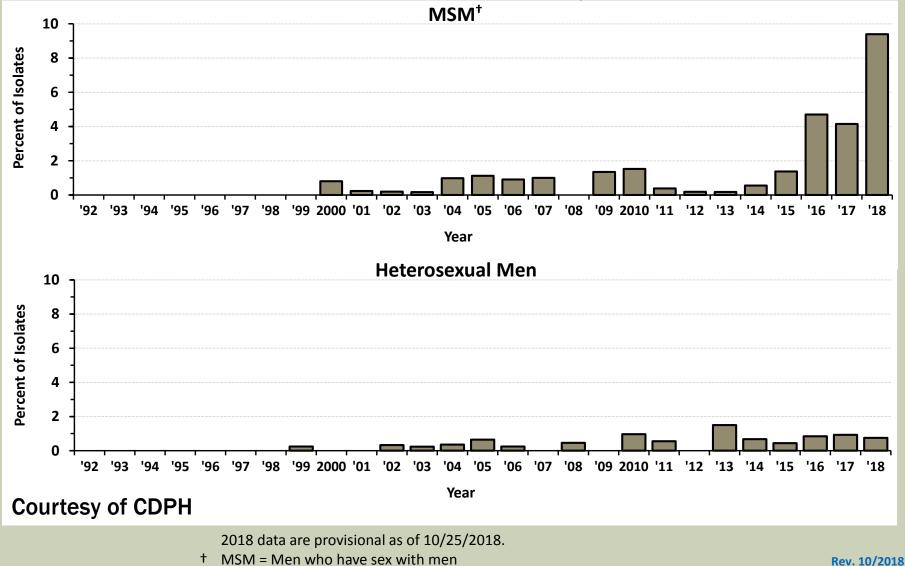
Courtesy of CDPH

Note: "Alert" values are set by CDC as markers to look at possible decreased susceptibility. Azithromycin alerts have MICs ≥ 2.0 µg/mL. No data before 1992. 2018 data are provisional as of 10/25/2018.

STD Clinic Sites:Long Beach (ended participation in 2007), Los Angeles (added in 2003), Orange,
San Diego, San FranciscoRev. 10/2018

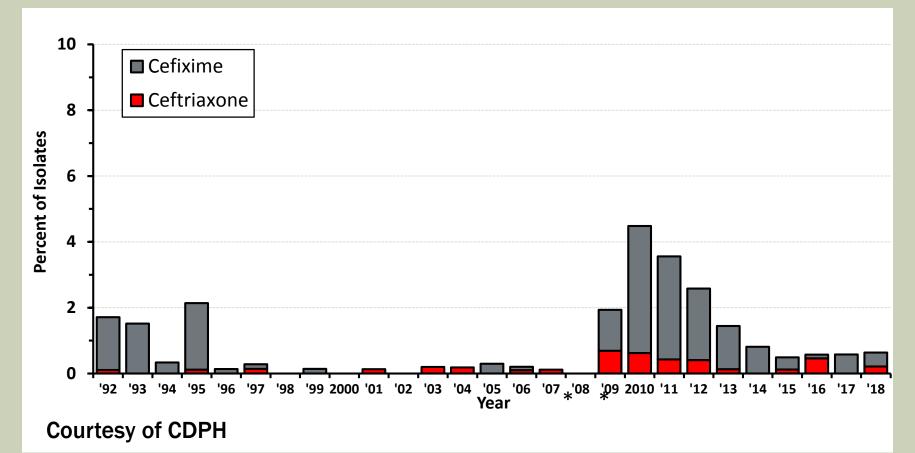
CAPTC

PERCENT OF *N. GONORRHOEAE* ISOLATES WITH CDC "ALERT" VALUES FOR AZITHROMYCIN, BY SEXUAL ORIENTATION, IN CALIFORNIA GISP STD CLINIC SITES, 1992-AUG. 2018





PERCENT OF *N. GONORRHOEAE* ISOLATES WITH CDC "ALERT" VALUES FOR SELECTED **CEPHALOSPORINS** IN CALIFORNIA GISP STD CLINIC SITES, 1992-AUG. 2018



*Cefixime susceptibility was not run in 2007-2008.

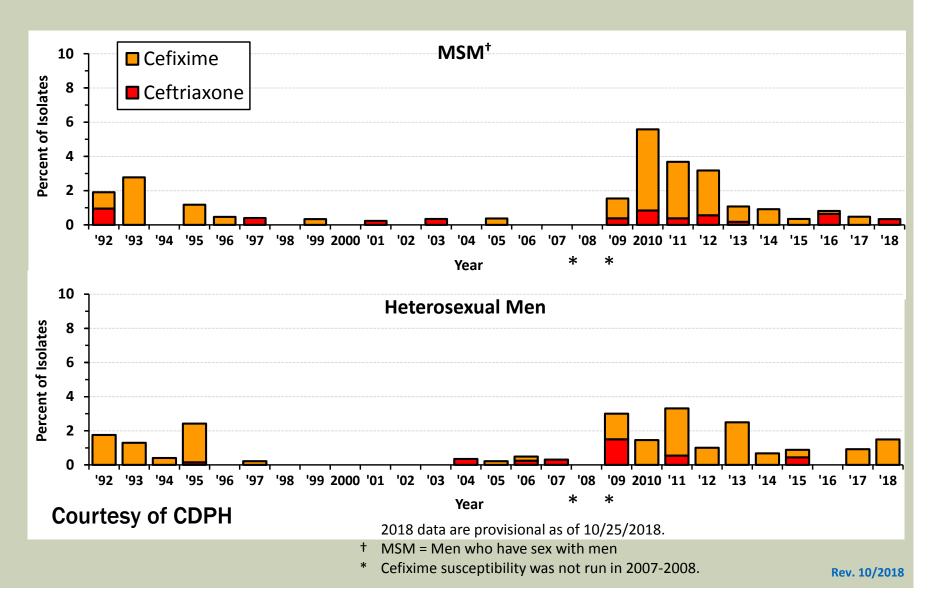
Note: "Alert" values are set by CDC as markers to look at possible decreased susceptibility. Cefixime alerts have MICs $\geq 0.25 \ \mu g/mL$. Ceftriaxone alerts have MICs $\geq 0.125 \ \mu g/mL$. 2018 data are provisional as of 10/25/2018.

Rev. 10/2018

STD Clinic Sites: Long Beach (ended participation in 2007), Los Angeles (added in 2003), Orange, San Diego, San Francisco

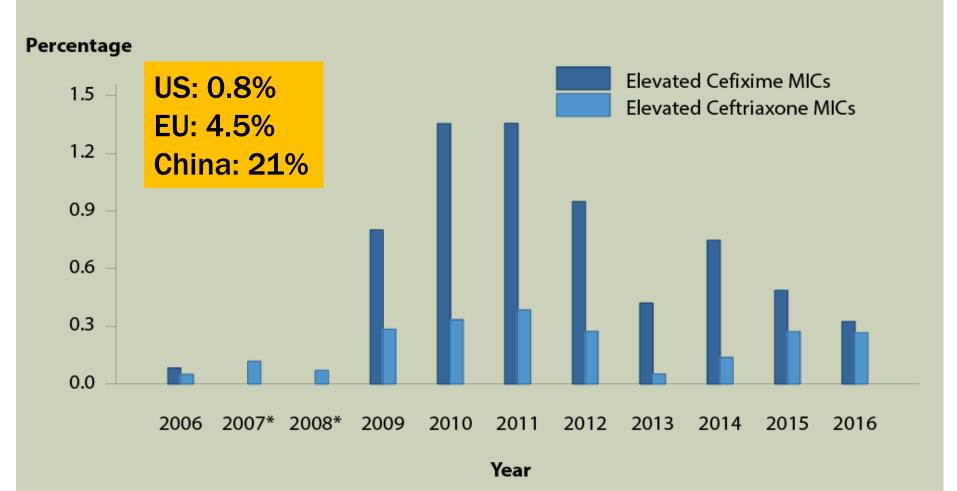


N. GONORRHOEAE ISOLATES WITH CDC "ALERT" VALUES FOR SELECTED CEPHALOSPORINS, BY SEXUAL ORIENTATION, IN CALIFORNIA GISP STD CLINIC SITES, 1992-AUG. 2018





Isolates with elevated <u>ceftriaxone</u> mics (\geq 0.125 µg/ml) and elevated <u>cefixime</u> mics (\geq 0.25 µg/ml), GISP, 2006–2016



* Isolates not tested for cefixime susceptibility in 2007 and 2008.



Doctors fear spread of 'super-gonorrhoea' across Britain

Drug-resistant strain of sexually transmitted superbug at risk of becoming untreatable, say health experts

Isolated from a the oropharyngeal specimen of a heterosexual man who attended sexual health services in England.

- One regular female partner, UK
- One female sexual contact, south-east Asia, a month prior to symptom onset.



Public Health England

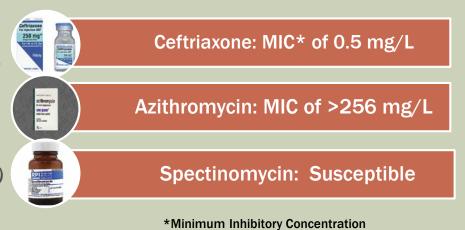
Protecting and improving the nation's health

UK case of *Neisseria gonorrhoeae* with high-level resistance to azithromycin and resistance to ceftriaxone acquired abroad

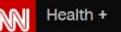
> Health Protection Report Advanced Access Report Volume 12 Number 11

"A multi-drug-resistant isolate of Neisseria gonorrhoeae confirmed by the Public Health England Reference Laboratory as resistant to the current recommended dual first-line therapy...

This is the first global report of High Level Azithromycin Resistant (HLAziR) N. gonorrhoeae which is also resistant to ceftriaxone. "



- Treated empirically with ceftriaxone (1 g), and subsequently with spectinomycin.
 - Test of Cure: Urine NAAT, negative. Throat swab culture positive.
 - Reinfection was excluded, indicating treatment failure.
- Ultimately treated with IV ertapenem.
 - Ertapenem MIC was low (0.032 mg/L) suggesting this may be an effective therapy.





Gonorrhea outbreak in Hawaii shows increased antibiotic resistance

By Susan Scutti, CNN Updated 10:50 AM ET, Thu September 22, 2016







CEFTRIAXONE-RESISTANT GONORRHEA HAS REACHED NORTH AMERICA

REALTH

Rare strain of gonorrhea identified in Canada, compounding fears of drug resistance

#2 HELEN BRANDWELL Distantionant 2 NOVEMBER 18, 201



Notisiarlo generations besteria, which cause generates.

Ceftriaxone-Resistant Neisseria gonorrhoeae, Canada, 2017

Emerging Infectious Diseases, Vol 24 (2), February 2018



CASE: I'M NOT ANY BETTER

- 25 yr old MSM on PrEP presents with discharge x 2 days, + urine GC/CT negative
- Treated with ceftriaxone 250 mg IM and azithromycin 1g (directly observed therapy)
- Returns 1 week later, with persistent discharge visible on exam.
- He denies any interim sexual contact



POLL: WHAT DO YOU DO NEXT?

A) Panic

- B) Call the health department
- C) Repeat treatment with gentamicin 240 mg IM and azithromycin 2 g orally
- D) Get a culture of the discharge
- E) Get a urine NAAT for GC
- F) All of the above except choice A



SUSPECTED GC TREATMENT FAILURE

TEST WITH CULTURE AND NAAT:

REPEAT TREATMENT:

- Gentamicin* 240 mg IM + AZ 2g (OR Gemifloxacin 320 mg PO + AZ 2g if available)
- If reinfection suspected, repeat treatment with CTX 250 + AZ 1g

REPORT:

• To Local Health Department within 24 hours

TEST AND TREAT PARTNERS:

• Treat all partners in last 60 days with same regimen as patient.

TEST OF CURE (TOC):

• TOC 7-14 days with culture (preferred) and NAAT



ANTIBIOTICS IN THE PIPELINE

- Solithromycin: novel oral fluoroketolide
- Phase 2 trial (1200 mg vs. 1000 mg) GC treatment
 - 100% cured (neg culture) with either dose
 - GI side effects common and dose-related
- Phase 3 trial underway

Zoliflodacin (ETX0914/AZD0914)

- Topoisomerase II inhibitor (spiropyrimidinetrione)
 - Non-beta-lactam, good for PCN allergy
- Phase II trial promising, but still needs 5-10 more years...
- Global Antibiotic Research and Development Partnership

Hook, EW et al, CID 2015. Fernandez, P et al, Bioorg Med Chem 2016 Alm RA, Antimicrob Agents Chem. 2015



ANAL CYTOLOGY

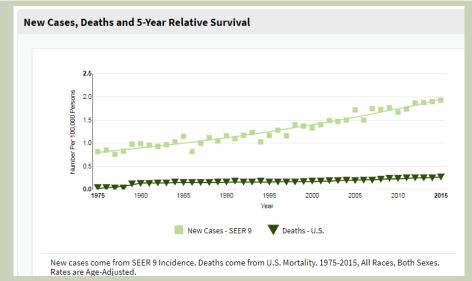


What do You mean? I'm not supposed to go in the ears?!? Where in the hell am i Supposed to go, then ??





ANAL CANCER FAST FACTS



- 8,580 new U.S. cases in 2018
 - 2,960 men
 - 5,620 women
- Median age at diagnosis: 62
- 1,160 deaths in 2018
- Median age at death 65
- 67% survive 5 years or more
- The incidence of anal cancer is rising worldwide at about 2% per year
- Morphologically analogous to cervical cancer
- Strongly associated with high risk HPV infection, e.g. 16 and 18
- Rates of anal Ca << Rates of cervical Ca
 - Anal epithelium less susceptible to oncogenic transformation?
 - Hormonal influences? Microenvironment? pH?

Amer Cancer Society Fast Facts Wang, C.J., et al Surg Oncol Clin N Am, 2017. **26**(1): p. 17-31.

RATES OF ANAL CA VARY BY POPULATION

Population	Rate per 100,000
Overall	1.8*
All men	1.5*
All women	2.1*
HIV-infected women	Up to 30**
MSM, prior to HIV epidemic	Up to 36.9^
HIV-infected MSM on HAART	Up to 131^^

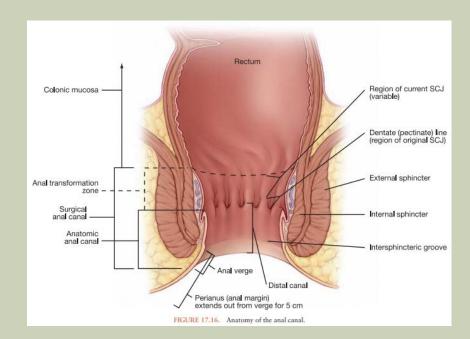
* SEER data, 2011-2015 ** J.M. Berry, Chapter Communication ^ Dahling, JAMA 1982 ^^ Silverberg, CID 2012



ANAL CYTOLOGY: WHAT'S THE BOTTOM LINE?

- Screens for anal cancer
 - Analogous to cervical pap smears
- Often incorporated into routine HIV care as an annual screening test
- No universal screening guidelines
 - Who?
 - How often?

Research is ongoing...





ANAL CANCER SCREENING ALGORITHM

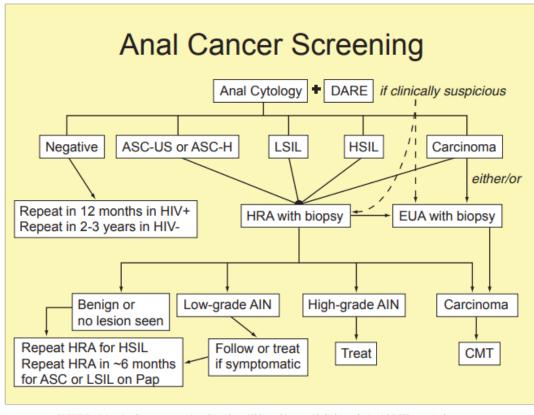


FIGURE 17.3. Anal cancer screening algorithm. AIN, anal intraepithelial neoplasia; ASC-US, atypical squamous cells of undetermined significance; ASC-H, atypical squamous cells cannot exclude high-grade SIL; CMT, combined modality therapy; DARE, digital anorectal examination; EUA, examination under anesthesia; HRA, high-resolution anoscopy; HSIL, high-grade intraepithelial lesions; LSIL, low-grade squamous intraepithelial lesions. (Adapted from Park IU, Palefsky JM. Evaluation and management of anal intraepithelial neoplasia in HIV-negative and HIV-positive men who have sex with men. *Curr Infect Dis Rep* 2010;12(2):126–33.)



ANAL PAP SMEARS: HOW TO

- Patient in lateral recumbent position, women can be in dorsal lithotomy
- Pre-moisten polyester swab (not cotton or cytobrush) with tap
- Gently insert into the anal canal until it bypasses the internal sphincter and abuts the distal wall of the rectum.
 - Usually 2 to 3 inches (\sim 5 to 7 cm).
- Rotate the swab 360 degrees in a circular fashion, with firm lateral pressure against the canal walls, while slowly retracting the swab over the course of 10-20 seconds
- Place the swab in the liquid medium and agitate vigorously to transfer cells.





ANAL PAP SMEARS: CYTOLOGY

Normal



HSIL

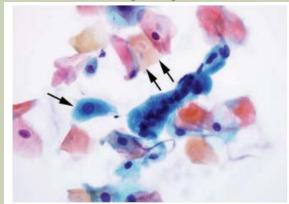


FIGURE 17.4. Normal cellular components on anal cytology. Note the nucleated squamous cells, squamous metaplastic cell (*single arrow*), anucleate squames (*double arrow*), and cluster of rectal columnar cells (Anal ThinPrep[®], high magnification). columnar cells (Anal ThinPrep[®], high magnification).

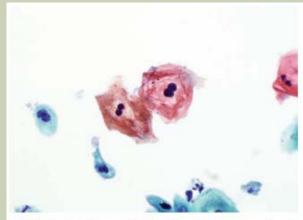


FIGURE 17.7. LSIL on anal cytology. Binucleate squamous cells with HPV-cytopathic effect or koilocytosis are present (Anal ThinPrep[®], high magnification).

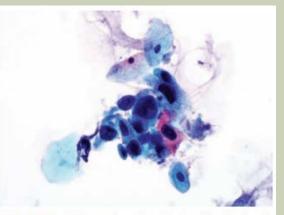
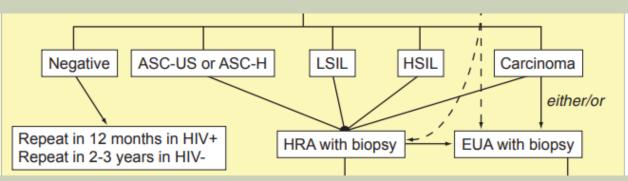


FIGURE 17.8. HSIL on anal cytology. Note the cells with enlarged, hyperchromatic nuclei and scant, dense cytoplasm characteristic of HSIL arising in immature squamous metaplasia of the AnTZ (Anal ThinPrep^a, high magnification).





Epidemiology of anal high-grade squamous intraepithelial lesions (HSIL) and anal human papillomavirus (HPV) infection.

	HIV-positive MSM	HIV-negative MSM	HIV- positive Women	Women	Men
Anal HPV infection prevalence	80-95%	60%	66-80%	32-42%	18%
HSIL prevalence	29.1-52%	21.5-24.7%	9-27%	4-9 %	NA



REGRESSION OF ANAL HSIL?



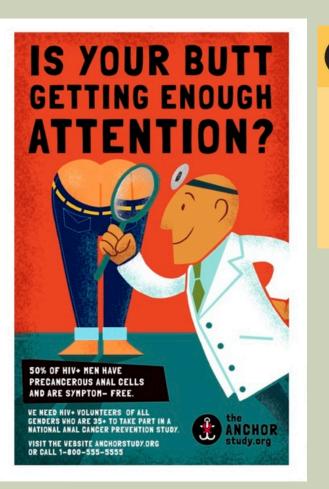
- N=616 MSM (HIV+ and HIV-)
- Prevalence: 47% HIV+, vs 32%HIV- (<p<0.001)</p>

After 36 months	Clearance per 100 py	95% CI	p value
Overall	22.2	(18.5-25.9)	<0.001
Prevalent HSIL	24.7	(20.5-29.8)	
Incident HSIL	45.6	(33.9-61.3)	

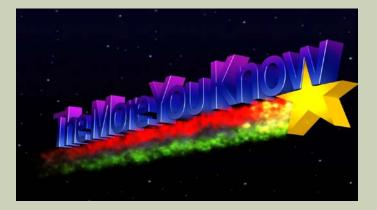
- 60% who cleared HSIL remained HSIL free after 2 yrs
- Younger age, lower grade of AIN associated with clearance



ONGOING RESEARCH...









THANK YOU Any burning questions?

Acknowledgments: Drs. Heidi Bauer, Ina Park, Sharon Adler, Naomi Jay, & J. Michael Berry