STIs 102:
Mycoplasma genitalium, HSV, Epididymitis/orchitis

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Disclosures

- The author and their spouses/partners wish to disclose they have no financial interests or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters.

PTC Disclaimer

Some terms in this presentation may have been modified to align with executive order requirements that this CDC-funded grant has received.

Objectives

- Revisit the differential diagnosis of non-gonococcal urethritis
- Touch briefly on workup for NGU
- Describe Mycoplasma genitalium (Mgen) presentation and testing
- Discuss treatment for Mgen, including rationale, resistance concerns, and options for treatment failure
- Briefly review the differential and workup for genital ulcer disease
- Describe genital herpes presentation and epidemiology
- Discuss HSV diagnosis, treatment strategies, and transmission prevention
- Describe the presentation, etiology, and treatment of epididymitis and orchitis

Burning Questions

- Jeremy is a 35 year old man who presents to sexual health clinic where he is seen regularly for PrEP
- C/o 5 days of dysuria and mucopurulent penile discharge
- Sexual hx: chlamydia urethritis 3 months ago treated at outside clinic with 1 gram azithromycin x 1. 5 male and 2 female sex partners in the last 3 months, reports condomless anal (receptive and insertive), vaginal, and oral sex
- Exam: no active discharge, trace meatal irritation
- You order comprehensive STI/HIV testing including urine GC/CT, and prescribe empiric CTX 500 mg IM x 1 + doxycycline 100 mg BID x 7 days
- Urine G/C is negative, and symptoms continue…

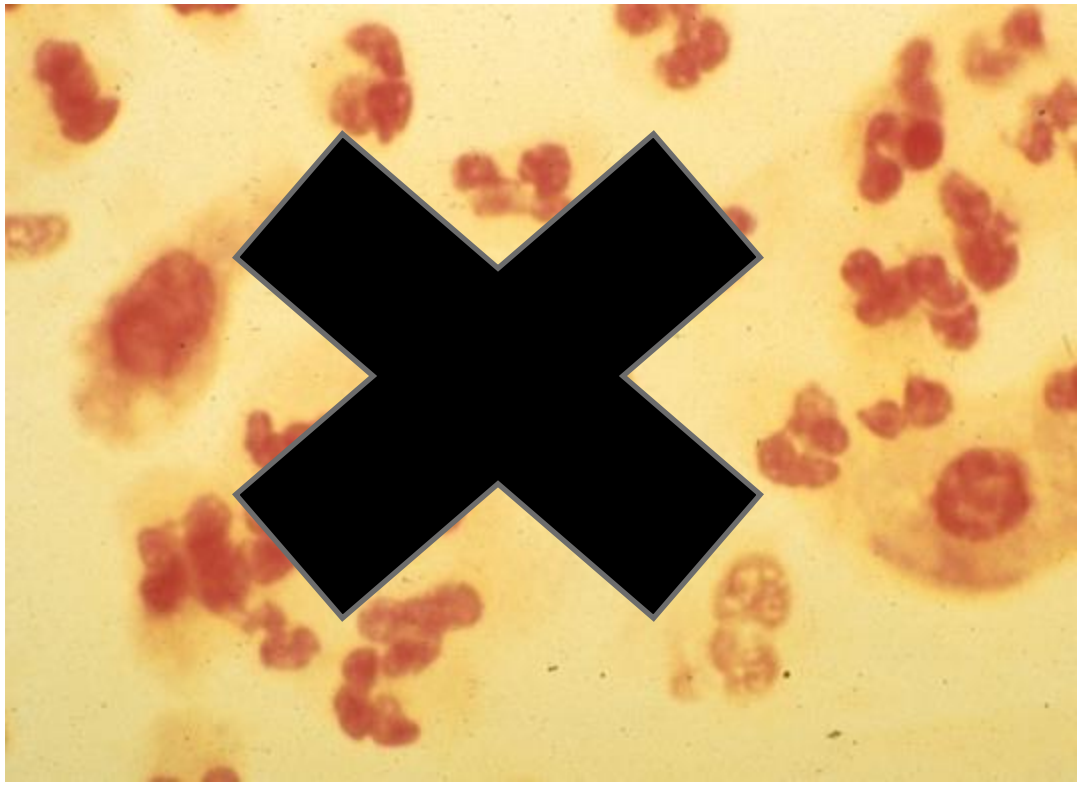
What workup would you send?

Choose all that apply:

- A: RPR with reflex to FTA-ABS
- B: HSV-1/HSV-2 PCR (urine)
- C: Repeat gonorrhea/chlamydia NAAT
- D: Urinalysis with microscopy
- E: Trichomonas NAAT
- F: Mycoplasma genitalium NAAT
- G: Urine bacterial culture
- H: PET-CT of the entire body

Non-Gonococcal Urethritis

Non-chlamydial ^



Etiology

- ~~*C. trachomatis* (15-40%)~~
- *M. genitalium* (15-25%)
- T. vaginalis (1-8%)
- HSV (3%)
- N. meningitidis
- Other bacteria (i.e. *H. influenzae*)
- Other viruses (i.e. adenovirus, EBV)
- UNKNOWN (~50%)!

Non-GC, non-CT urethritis workup

- Trichomonas urine NAAT (if MSW)
- Mycoplasma genitalium NAAT
- Consider HSV PCR

Less likely cause of isolated urethritis in females. Consider pelvic exam

NOT M hominis, Ureaplasma spp

- Confirm urethritis!
  - Mucoid/purulent urethral discharge on exam
  - First-void urine : +LE or >10 WBC/HPF

- If neither: consider e.g. chronic prostatitis/CPP, interstitial cystitis

What workup would you send?

- A: RPR with reflex to FTA-ABS
- B: HSV-1/HSV-2 PCR (urine)
- C: Repeat gonorrhea/chlamydia NAAT
- D: Urinalysis with microscopy
- E: Trichomonas NAAT
- F: Mycoplasma genitalium NAAT
- G: Urine bacterial culture
- H: PET-CT of the entire body

Jeremy's results

Work-up:

UA: 20 WBCs

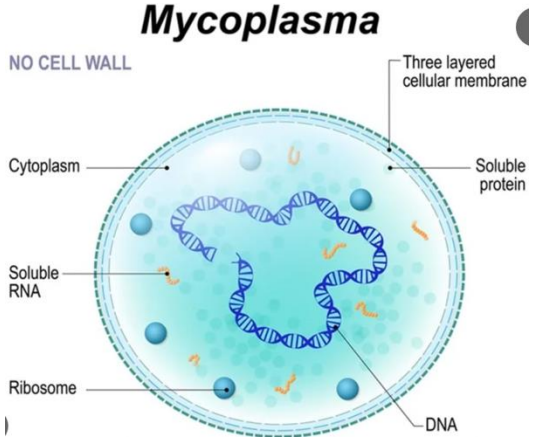
Trichomonas urine NAAT: neg

M. genitalium NAAT: positive

HSV urine PCR: neg

Molli-not-so-cute

- Mollicutes: class of bacteria distinguished by lack of a peptidoglycan cell wall
  - medically significant genera include Mycoplasma and Ureaplasma
- Largely parasitic and intracellular, very small genome size—some of the smallest and simplest living things
- Difficult to culture, diagnosis depends on molecular testing
- Simplicity confers intrinsic resistance to many antibiotics
  - No peptidoglycan – no beta lactams, glycopeptides, or fosfomycin
  - No enzymes for folic acid metabolism – no TMP-SMX
  - Intracellular – poor activity of most aminoglycosides
  - Mutations in RNA polymerase – no rifampin



Vladislav M Chernov, Olga A Chernova, Alexey A Mouzykantov, Elena S Medvedeva, Natalia B Baranova, Tatiana Y Malygina, Rustam I Aminov, Maxim V Trushin, Antimicrobial resistance in mollicutes: known and newly emerging mechanisms, *FEMS Microbiology Letters*, Volume 365, Issue 18, September 2018, fny185, https://doi.org/10.1093/femsle/fny185

M genitalium (Mgen) epidemiology

- 2017-2018 NHANES: overall prevalence about 1.7% among people in the US aged 14-59
  - Other series with prevalence in the general population closer to 5%
  - In series from US STI clinics, prevalence 26% among women, 28.7% among men
  - Higher prevalence among people with HIV
  - Prevalence not increased among MSM
    - In this group, M genitalium detected in rectal >urine >> pharyngeal specimens
  - Concordance among couples is high, approximately 40-50% in heterosexual couples. One Australian study showed concordance among MSM of 27%

Mycoplasma Genitalium - CDC Detailed Fact Sheet. Centers for Disease Control and Prevention. https://www.cdc.gov/std/mgen/stdfact-Mgen-detailed.htm#_edn4

Cina M, Baumann L, Egli-Gany D, Halbeisen FS, Ali H, Scott P, Low N. *Mycoplasma genitalium* incidence, persistence, concordance between partners and progression: systematic review and meta-analysis. Sex Transm Infect. 2019 Aug;95(5):328-335. doi: 10.1136/sextrans-2018-053823. Epub 2019 May 4. PMID: 31055469; PMCID: PMC6678058.

Syndromes associated with Mgen

Male:

- Urethritis: 20-25% of non-gonococcal, non-chlamydial urethritis, and 40% of persistent or recurrent urethritis
- Proctitis: conflicting association in MSM between rectal Mgen detection and symptoms; weak or not present
- Pharyngitis: Mgen has not been demonstrated as a cause
- No clear association with chornic complications e.g. prostatitis

- Female:
  - Cervicitis – Mgen detected in 10-30% of women with clinical cervicitis. Co-infection common, but also studies showing cytokine normalization after treatment
  - PID – multiple studies demonstrate greater frequency of Mgen in women with PID, but generally cross-sectional. No clear prospective evidence of cause, or trial data showing that treatment of Mgen cervicitis prevents PID.
  - Pregnancy/fertility-related complications– separate discussion!

Dehon PM, McGowin CL. The Immunopathogenesis of Mycoplasma genitalium Infections in Women: A Narrative Review. Sex Transm Dis. 2017 Jul;44(7):428-432. doi: 10.1097/OLQ.0000000000000621. PMID: 28608793; PMCID: PMC5470585.

Back to Jeremy. What's our treatment?

- A: Minocycline 100 mg BID x 14 days
- B: Doxycycline 100 mg BID x 7 days, followed by azithromycin 1 gram x 1, then 500 mg daily x 3 days
- C: Azithromycin 1 gram x 1
- D: Doxycycline 100 mg BID x 7 days followed by moxifloxacin 400 mg daily x 7 days
- E: Moxifloxacin 400 mg daily x 14 days
- F: Bloodletting to rebalance his humours

Treatment – why so complicated?

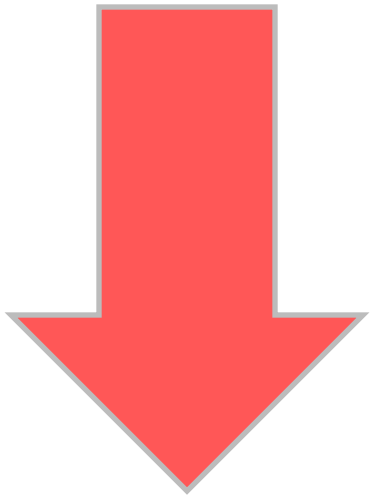
- Intrinsic resistance leading to reliance on ribosomal agents with good intracellular activity
  - primary classes with activity include **macrolides, tetracyclines, and quinolones**

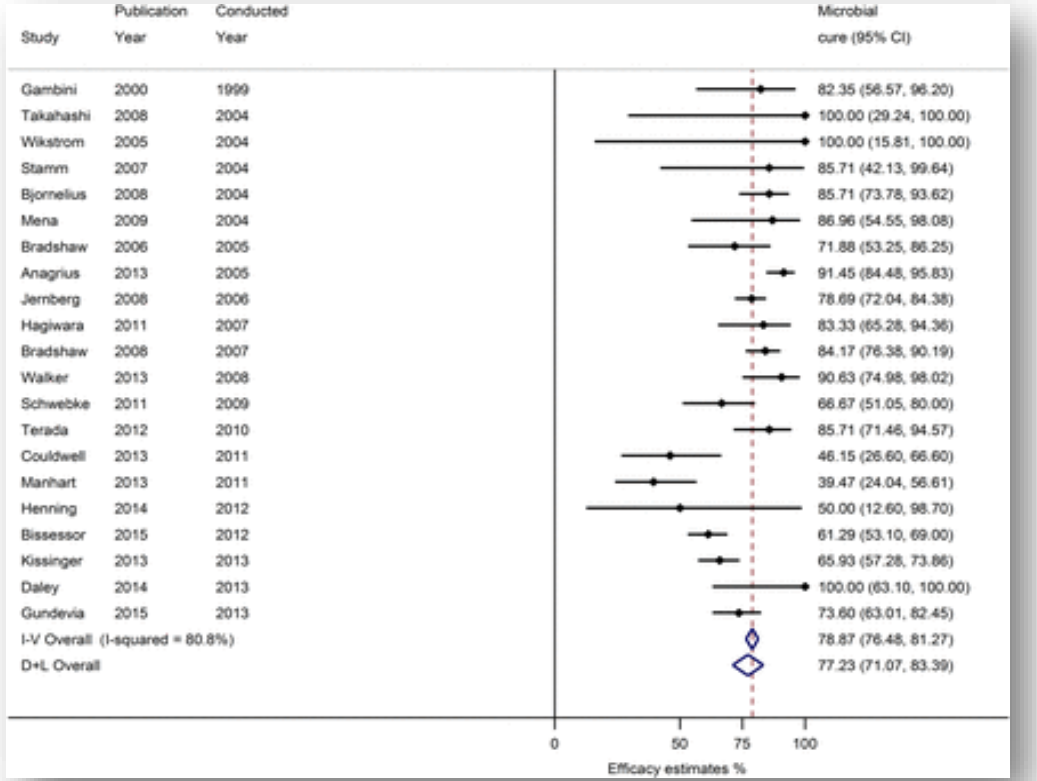
- Azithromycin 1 gram x 1 was previously the standard for syndromic treatment of non-gonococcal urethritis, and had good efficacy against M genitalium, but…

Macrolide Resistance in M. genitalium

Driven by 5 SNP mutations in the 23S rRNA gene

- Pooled microbial cure rate 77.2%
  - Prior to 2009 – 85.3%
  - Since 2009 – 67%





- Lau A, Bradshaw CS, Lewis D, Fairley CK, Chen MY, Kong FY, Hocking JS. The Efficacy of Azithromycin for the Treatment of Genital Mycoplasma genitalium: A Systematic Review and Meta-analysis. Clin Infect Dis. 2015 Nov 1;61(9):1389-99. doi: 10.1093/cid/civ644. Epub 2015 Aug 3. PMID: 26240201.

Macrolide Resistance in M. genitalium

7 cities
48% (clinic attendees)[5]

Seattle, WA
62% (hetero men)[1]
69% (men w/urethritis)[2]
90% (MSM)[3]

Pittsburgh, PA
58% (men w/urethritis)[2]

Durham & Greensboro, NC
61% & 64%
(men w/urethritis)[2]

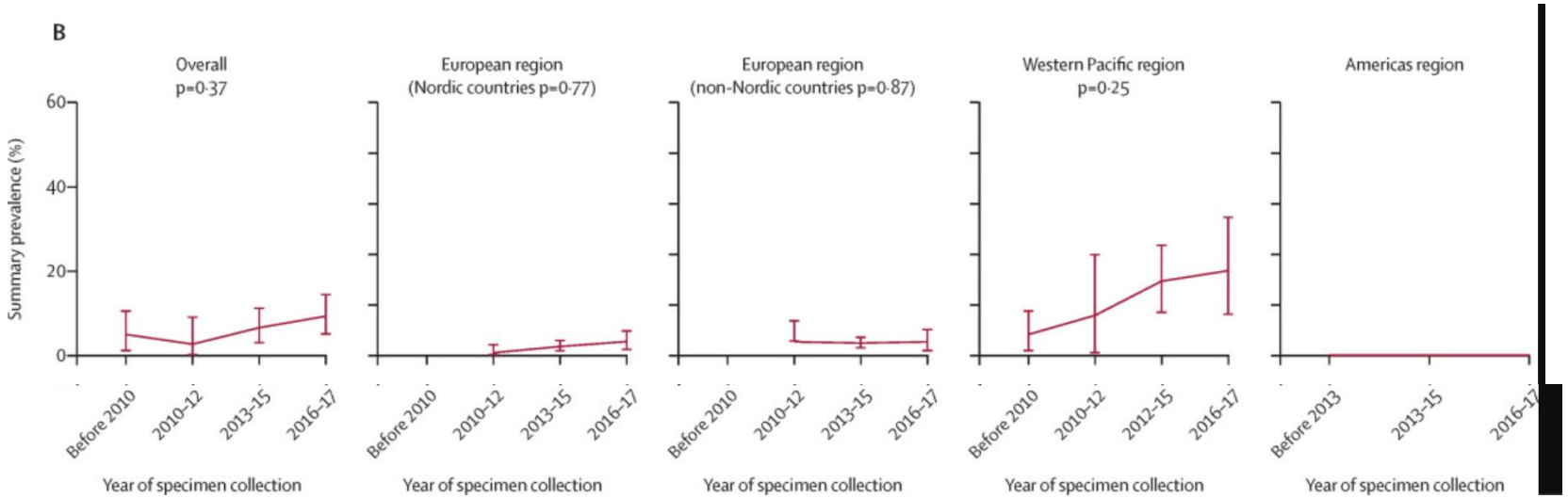
Los Angeles, CA
80% (clinic attendees)[4]

Birmingham, AL
44% (STD Clinic)[6]
61% (hetero couples)[7]
61% (men w/urethritis)[2]
74% (HIV+ MSM)[8]

New Orleans, LA
60% (men w/urethritis)[2]

- Romano 2018; [2]Bachmann 2019; [3]Cham [7]Xiao 2019; [8]Dionne-Odom 2018
- Slide credit: Lisa Manhart

Quinolone resistance in M genitalium



- Meta-analysis included 25 studies reporting SNPs associated with quinolone resistance
- Global rate 2016-2017: 9.3%
- Americas region rate: 10.1% (insufficient data for temporal trend)

Dorothy A Machalek et al. Prevalence of mutations associated with resistance to macrolides and fluoroquinolones in Mycoplasma genitalium: a systematic review and meta-analysis,The Lancet Infectious Diseases,Volume 20, Issue 11, 2020, Pages 1302-1314

Doxycycline treatment failures in M. Gen

Gossé et al. BMC Infectious Diseases (2021) 21:1225
https://doi.org/10.1186/s12879-021-06910-1

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Evaluation of treatment with two weeks of doxycycline on macrolide-resistant strains of *Mycoplasma genitalium*: a retrospective observational study

M. Gossé[1*], S. A. Nordbø[1,2] and B. Pukstad[1,3]

- 59% had a negative test of cure following treatment
- An additional 35% of symptomatic patients without negative test of cure experienced resolution of symptoms

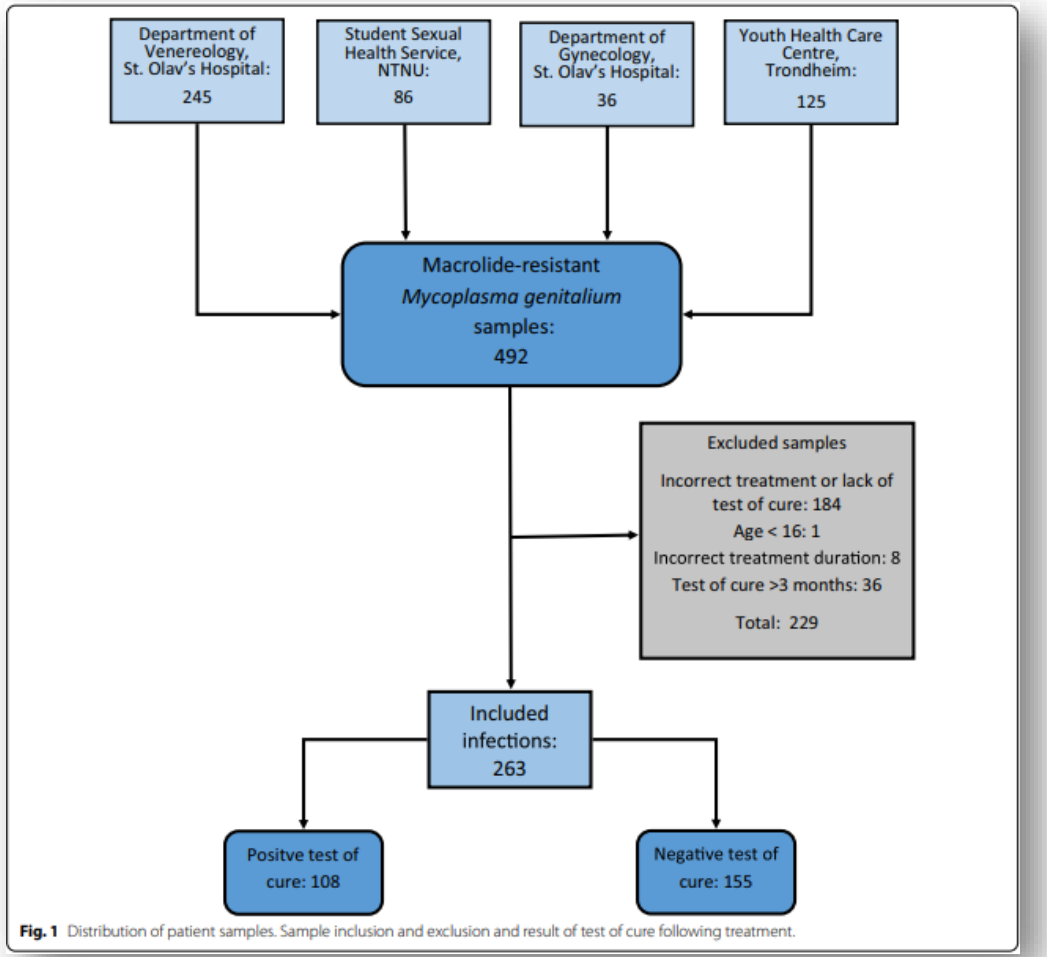


Fig. 1 Distribution of patient samples. Sample inclusion and exclusion and result of test of cure following treatment.

Slide credit: Jason Zucker

- Gossé, M., Nordbø, S.A. & Pukstad, B. Evaluation of treatment with two weeks of doxycycline on macrolide-resistant strains of Mycoplasma genitalium: a retrospective observational study. BMC Infect Dis 21, 1225 (2021).

But doxy has its advantages

JOURNAL ARTICLE

Identification of 16S rRNA mutations in *Mycoplasma genitalium* potentially associated with tetracycline resistance *in vivo* but not selected *in vitro* in *M. genitalium* and *Chlamydia trachomatis* FREE

Chloé Le Roy, Arabella Touati, Carla Balcon, Justine Garraud, Jean-Michel Molina, Béatrice Berçot, Bertille de Barbeyrac, Sabine Pereyre, Olivia Peuchant, Cécile Bébéar ✉
Author Notes

Journal of Antimicrobial Chemotherapy, Volume 76, Issue 5, May 2021, Pages 1150–1154,
https://doi.org/10.1093/jac/dkab016
Published: 04 February 2021 **Article history** ▾

- 106 specimens of M. genitalium collected at the French National Reference Centre for Bacterial STIs from 2017-2019
- Samples passaged for 30 generations in subinhibitory concentrations of doxycycline or tetracycline
- No isolates developed elevated MICs to doxycycline at the end of the experiment
- 6 specimens had 16S rRNA mutations associated with doxy resistance in other organisms, but were still in vitro susceptible

Resistance-guided sequential therapy

Clinical Infectious Diseases

MAJOR ARTICLE

Outcomes of Resistance-guided Sequential Treatment of *Mycoplasma genitalium* Infections: A Prospective Evaluation

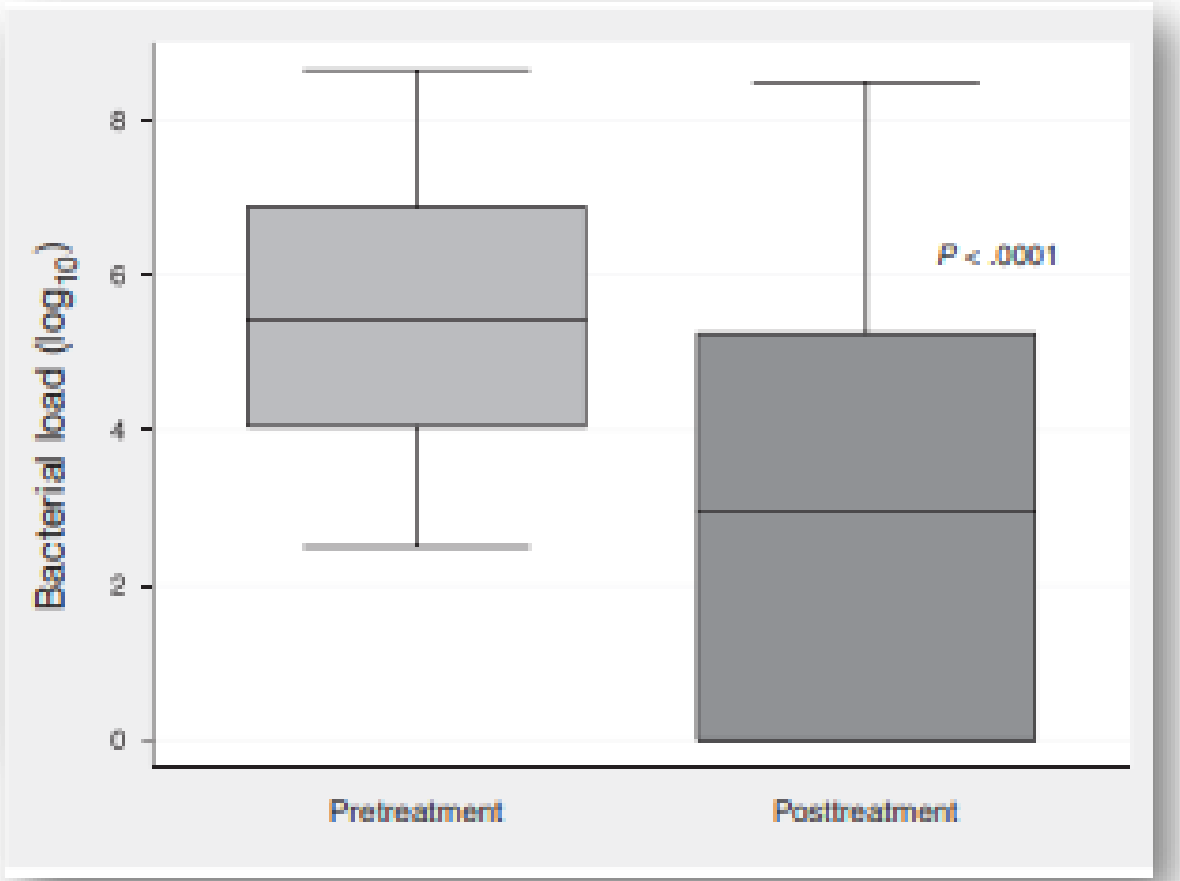
Tim R. H. Read,[1,2] Christopher K. Fairley,[1,2] Gerald L. Murray,[3,4,5,6] Jorgen S. Jensen,[7] Jennifer Danielewski,[3,4] Karen Worthington,[2] Michelle Doyle,[2] Elisa Mokany,[8] Litty Tan,[8] Eric P. F. Chow,[1,2] Suzanne M. Garland,[3,4,6,9] and Catriona S. Bradshaw[1,2]

[1]Central Clinical School, Faculty of Medicine, Nursing and Health Sciences, Monash University, Melbourne, [2]Melbourne Sexual Health Centre, Alfred Health, Carlton, [3]Murdoch Children's Research Institute, Parkville, [4]Department of Microbiology and Infectious Diseases, Royal Women's Hospital, Melbourne, [5]Infection and Immunity Program, Monash Biomedicine Discovery Institute, and [6]Royal Children's Hospital, Melbourne, Victoria, Australia; [7]Statens Serum Institut, Copenhagen, Denmark; [8]SpeeDx Pty Ltd, Eveleigh, New South Wales, and [9]Department of Obstetrics and Gynaecology, University of Melbourne, Victoria, Australia

(See the Major Article by Braun et al on pages 569-76 and Editorial commentary by Sulkowski on pages 577-9.)

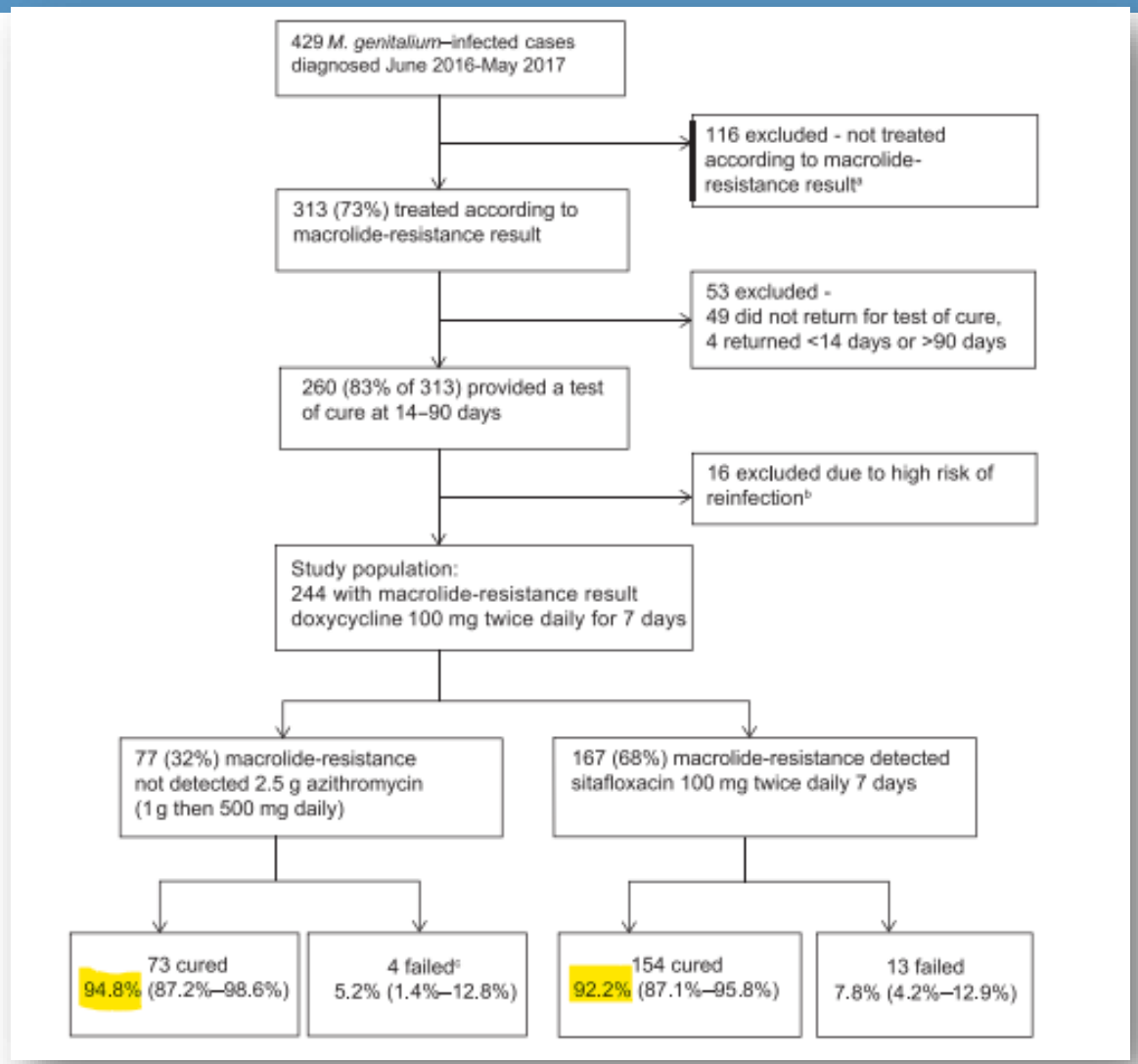
Background. Rising macrolide and quinolone resistance in *Mycoplasma genitalium* necessitate new treatment approaches. We evaluated outcomes of sequential antimicrobial therapy for *M. genitalium* guided by a macrolide-resistance assay.

Methods. In mid-2016, Melbourne Sexual Health Centre switched from azithromycin to doxycycline (100 mg twice daily for 7 days) for nongonococcal urethritis, cervicitis, and proctitis. Cases were tested for *M. genitalium* and macrolide-resistance mutations (MRMs) by polymerase chain reaction. Directly after doxycycline, MRM-negative infections received 2.5 g azithromycin (1 g, then 500 mg daily for 3 days), and MRM-positive infections received sitafloxacin (100 mg twice daily for 7 days). Assessment of test of cure and reinfection risk occurred 14–90 days after the second antibiotic.



Resistance Guided, sequential therapy (cont.)

- Success rates of 92-95% with this strategy
- Similar rates (92%) demonstrated by the same group when moxifloxacin was used in place of sitafloxacin
- Low (~5%) treatment-associated macrolide resistance



Sounds good, but…

- Molecular tests with detection of macrolide resistance not yet cleared by FDA
- Testing from commercial labs (e.g. LabCorp and ARUP) may be available in your area
- Another option is sending specimens out to University of Alabama at Birmingham
  - Now with quinolone RAM testing!

Test Menu	Acceptable Specimens	Transport/Processing Details	Turnaround Time	CPT Code
PCR- Mycoplasma genitalium Includes detection of macrolide resistance	• Cervical swab • Throat • Urine • Urogenital swab • Vaginal swab	**Collection Device:** Sterile container (can also be used as transport if received with 48 hours of collection and kept 2-8C) **Transport Media:** Mycoplasma Ureaplasma transport media (examples: M4, M5, UTM, UVTM, eSwab)	1-4 days	87581

Jeremy at Last

A: Minocycline 100 mg BID x 14 days

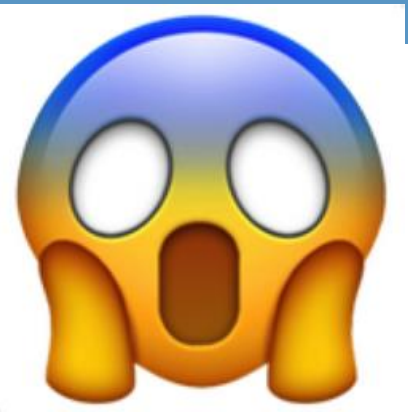
B: Doxycycline 100 mg BID x 7 days, followed by azithromycin 1 gram x 1, then 500 mg daily x 3 days

C: Azithromycin 1 gram x 1

D: Doxycycline 100 mg BID x 7 days followed by moxifloxacin 400 mg daily x 7 days
- default treatment for most US M gen cases at this time

E: Moxifloxacin 400 mg daily x 14 days

Treatment failure



- **Minocycline**
  - Slightly lower MICs than doxycycline observed
  - Largest case series of 90 patients with macrolide resistant M gen – 66.7% cure rate [1]
    - 100 mg BID x 14 days
    - 62 had failed tx with moxifloxacin

- **Pristinamycin**
  - 85/114 (75%) of patients with macrolide resistant M gen cured with 10 days treatment
  - Not available in the USA

Clarke EJ, Vodstrcil LA, Plummer EL, Aguirre I, Samra RS, Fairley CK, Chow EPF, Bradshaw CS. Efficacy of Minocycline for the Treatment of *Mycoplasma genitalium*. Open Forum Infect Dis. 2023 Aug 11;10(8):ofad427.

Read TRH, Jensen JS, Fairley CK, Grant M, Danielewski JA, Su J, Murray GL, Chow EPF, Worthington K, Garland SM, Tabrizi SN, Bradshaw CS. Use of Pristinamycin for Macrolide-Resistant Mycoplasma genitalium Infection. Emerg Infect Dis. 2018 Feb;24(2):328-335.

Mycoplasma genitalium Treatment Failure Registry

The purpose of this form is to collect clinical information on cases of *Mycoplasma genitalium* that fail antimicrobial therapy. All reported information will be maintained in the strictest confidence.

Wasn't there something about pregnancy?

- 2022 meta-analysis assessed risk of adverse pregnancy and peri-natal outcomes
  - Pre-term birth: strongest evidence, OR of approximately 2
    - Oddly greater than OR for this outcome with gonorrhea/chlamydia/trichomonas
    - Unable to assess confounding due to lack of adjustment for variables other than age
  - Spontaneous abortion: OR = 1
  - PROM, low birth weight, perinatal death: minimal data

- Authors conclude that there is insufficient evidence to recommend screening for Mgen in asymptomatic pregnant patients

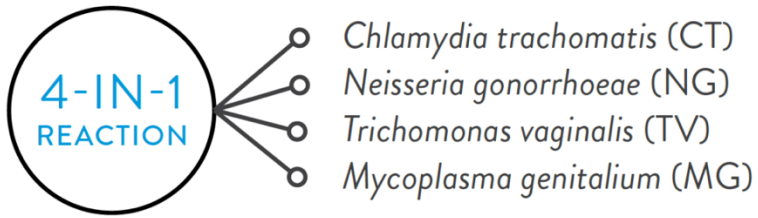
Frenzer C, Egli-Gany D, Vallely LM, Vallely AJ, Low N. Adverse pregnancy and perinatal outcomes associated with *Mycoplasma genitalium:* systematic review and meta-analysis. Sex Transm Infect. 2022 May;98(3):222-227

Mgen in the pregnant patient

- Moxifloxacin and doxycycline not routinely recommended for use during pregnancy
- Given lack of clear evidence for harms, reasonable to defer therapy if no sxs
- For patients with symptoms, azithromycin is the only drug routinely recommended for use
  - In this group, reasonable to send resistance testing to UAB
    - If macrolide-susceptible, can treat with azithromycin 4-day course
    - If resistant, risk-benefit conversation with patient, then potential treatment after delivery

And yet…

ONE ASSAY, MULTIPLE POSSIBILITIES REDEFINING THE FUTURE OF STI TESTING WITH OPERATIONAL EFFICIENCY

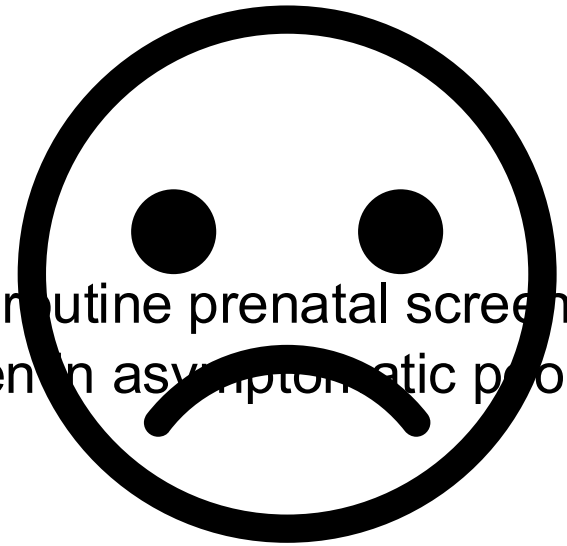


Alinity m STI assay is a 4-in-1 multiplex assay to detect and differentiate CT, TV, MG, and NG to aid in the diagnosis of infection from these organisms.

ANALYTES

Anyplex™ II
STI-7e Detection

- *Chlamydia trachomatis* (CT)
- *Mycoplasma genitalium* (MG)
- *Mycoplasma hominis* (MH)
- *Neisseria gonorrhoeae* (NG)
- *Trichomonas vaginalis* (TV)
- *Ureaplasma parvum* (UP)
- *Ureaplasma urealyticum* (UU)
- Exogenous Internal Control



- Enter the multiplex PCR
- Used at some sites as part of routine prenatal screening rather than G/C alone
- Can result in detection of Mgen in asymptomatic people, especially pregnant patients!

Take Home

- Mycoplasma genitalium is a relatively common inhabitant of the male and female GU tract

- Clinical syndromes include urethritis in males, possibly proctitis. In females: cervicitis and PID—data are not adequate to demonstrate Mgen causality for preterm birth, spontaneous abortion, perinatal death

- Mgen cell makeup confers intrinsic resistance to many antibiotics
  - Macrolide resistance is prevalent, and fluoroquinolone resistance rising

Take home (cont.)

- Treatment relies on sequential therapy with doxycycline followed by moxifloxacin (unless resistance testing available)
- Options for treatment failure in the US include minocycline, potentially checking for macrolide susceptibility
- Options for treatment of pregnant patients are extremely limited—no indication for screening in the absence of symptoms

The rest of the gang

- Mollicutes class includes some other names that may be familiar:
  - Mycoplasma hominis
  - Ureaplasma urealyticum
  - Ureaplasma parvum

- No clear causal association with cervicitis—testing is not recommended
- Inconsistent association with NGU—at present testing for these organisms is not recommended for urethritis
- No role for screening in any population

• Horner P el al. Should we be testing for urogenital Mycoplasma hominis, Ureaplasma parvum and Ureaplasma urealyticum in men and women? - a position statement from the European STI Guidelines Editorial Board. J Eur Acad Dermatol Venereol. 2018 Nov;32(11):1845-1851

Questions?

Eyes for a Sore Site

- Jasmine is a 29 year old woman who presents to her PCP for an urgent visit
- Complains of painful genital lesions x 5 days. Mild fever at symptom onset - resolved. Also dysuria, which is improving. No vaginal discharge, pelvic pain.
- No history of anything similar, no new cleansing products/detergents. Has 1 new male sexual partner x 6 months, reports oral sex (gives and receives), and vaginal sex. Stopped using condoms 4 months ago after negative STI screening. Has not seen genital lesions on her partner.
- Exam: many small erythematous erosions of the labia majora and minora as well as surrounding skin, a few have started to crust. Bilateral tender inguinal lymphadenopathy.

Physical Exam

- CDC Public Health Image Library. Stock photo. Posed by model.

What workup would you send for Jasmine?

Choose all that apply

- A: RPR with reflex to FTA-ABS
- B: HIV ab/ag
- C: HSV-1/HSV-2 IgG/IgM
- D: HSV-2 lesion PCR
- E: HSV-1/HSV-2 lesion PCR
- F: Urine gonorrhea/chlamydia NAAT
- G: Multiplex PCR panel with ALL STIs

Genital ulcer disease ddx

Syndrome	Differential	Distinguishing features
Genital ulcer		
	HSV	History of prior outbreaks, systemic symptoms are rare in non-primary infection.
	Primary syphilis	Ulcer is typically painless. Rectal ulcers , however, may be painful.
	Mpox	Systemic symptoms present at some time during course, papular-stage lesions often umbilicated
	LGV	Ulcer typically painless, often resolved at time of presentation. Inguinal LAD pronounced in men. Proctocolitis for rectal infection.
	Chancroid/Granuloma Inguinale	Rare in the USA.
Rash (localized or general)		
	VZV	Dermatomal distribution (shingles), isolated anogenital involvement less common
	Molluscum contagiosum	Lesions typically painless, systemic symptoms and mucosal involvement less common

What workup would you send for Jasmine?

Choose all that apply

- A: RPR with reflex to FTA-ABS
- B: HIV ab/ag
- C: HSV-1/HSV-2 IgG/IgM
- D: HSV-2 only lesion PCR
- E: HSV-1/HSV-2 lesion PCR
- F: Urine gonorrhea/chlamydia NAAT
- G: Multiplex PCR panel with ALL STIs

Jasmine's results

Work-up:

HSV-1 PCR: positive

HSV-2 PCR: negative

HIV ab/ag: neg

RPR neg

3-site G/C NAAT neg

HSV virology/epidemiology

- Transmission via direct contact with lesions or saliva
- Primary infection with higher incidence of systemic sxs, higher severity
- Latency in sensory nerves, followed by episodes of reactivation
  - HSV-1 reactivates more efficiently from trigeminal ganglia (orolabial herpes)
  - HSV-2 reactivates more efficiently from sacral dorsal root ganglia (anogenital herpes)
  - EITHER HSV can cause genital herpes. Rates of HSV-1 genital herpes are rising
  - Recurrence and asymptomatic shedding more common with HSV-2
- From 2015-2016, 11.9% of US adults aged 14-49 were HSV-2+, and 47.8% HSV-1+
- Rate of clinical genital herpes 2019-2021: 236-280 per 100,000 person/years

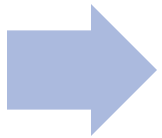
Margolis TP, Imai Y, Yang L, Vallas V, Krause PR. Herpes simplex virus type 2 (HSV-2) establishes latent infection in a different population of ganglionic neurons than HSV-1: role of latency-associated transcripts. J Virol. 2007 Feb;81(4):1872-8.

McQuillan G, Kruszon-Moran D, Flagg EW, Paulose-Ram R. Prevalence of herpes simplex virus type 1 and type 2 in persons aged 14–49: United States, 2015–2016. NCHS Data Brief, no 304. Hyattsville, MD: National Center for Health Statistics. 2018.

Jain, Purva PhD, MPH[+]; Embry, Alan PhD[†]; Arakaki, Brent BS[+]; Estevez, Irisdaly MPH[+]; Marcum, Zachary A. PharmD, PhD[+]; Viscidi, Emma PhD, MHS[†]. Prevalence of Genital Herpes and Antiviral Treatment. Sexually Transmitted Diseases 51(10):p 686-693, October 2024.

Diagnosis: Virologic Tests (when lesions are present)

Detection of HSV from genital ulcers or mucocutaneous lesions (PCR or viral culture)



HSV PCR is the preferred diagnostic test

- FDA cleared PCR based HSV tests
  - Sensitive and specific
  - Can distinguish HSV-1 from HSV-2

- Viral culture
  - Low sensitivity (especially for recurrent lesions and in healing lesions)
  - Only way to detect acyclovir resistant HSV

Guideline updates – serologic HSV testing

- Useful
  - Recurrent or atypical genital symptoms or lesions with a negative HSV PCR or culture result
  - Clinical diagnosis of genital herpes without laboratory confirmation
  - 12 weeks after suspected recent acquisition
  - Patient's partner has genital herpes

- Might be useful
  - Persons at higher risk for infection (presenting for STI evaluation—10 or more lifetime sex partners)
  - Persons with HIV

- Not useful
  - Screening of the general population

Two-Step Serologic Testing

Step 1: EIA Assay (IgG)* (often falsely positive at low index value (<3.0)

Positive EIA

Step 2: Confirm with a second test that uses a different antigen (Biokit/Western blot)

*IgM is not recommended for serologic testing

What treatment would you offer Jasmine?

- A: Valacyclovir 1 g PO twice daily x 7-10 days
- B: Valacyclovir 1 gram PO daily x 5 days
- C: Valacylovir 2 grams PO twice daily x 1 day
- D: Acyclovir 10 mg/kg IV q 8 hours
- E: Valacyclovir 1 gram daily indefinitely
- F: Transplant of the spinal dorsal nerve root ganglia

Treatment Options

All patients with <u>first episodes</u> of genital herpes should receive antiviral therapy

1. Acyclovir 400 mg orally 3 times/day for 7–10 days
2. Famciclovir 250 mg orally 3 times/day for 7–10 days
3. Valacyclovir 1 gm orally 2 times/day for 7–10 days

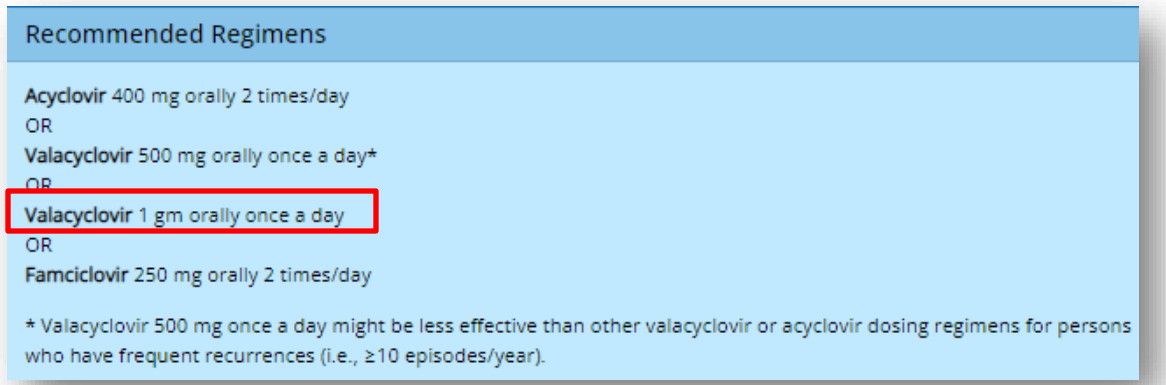
- Treatment can be extended if healing is incomplete after 10 days of therapy.

Treating/Preventing Recurrences

- **Episodic/Intermittent therapy** - ameliorate or shorten the duration of lesions
  - Recurrences are less frequent after the first episode of HSV-1 genital herpes, and genital shedding rapidly decreases during the first year of infection
- **Suppressive therapy** - reduce the frequency of recurrences
  - Almost all persons with symptomatic first-episode HSV-2 genital herpes subsequently experience recurrent episodes of genital lesions
  - Suppressive therapy can decrease recurrence rate by 70-80% in those with frequent episodes
  - May confer benefits for preventing transmission (more later)

Antiviral Options

Suppressive

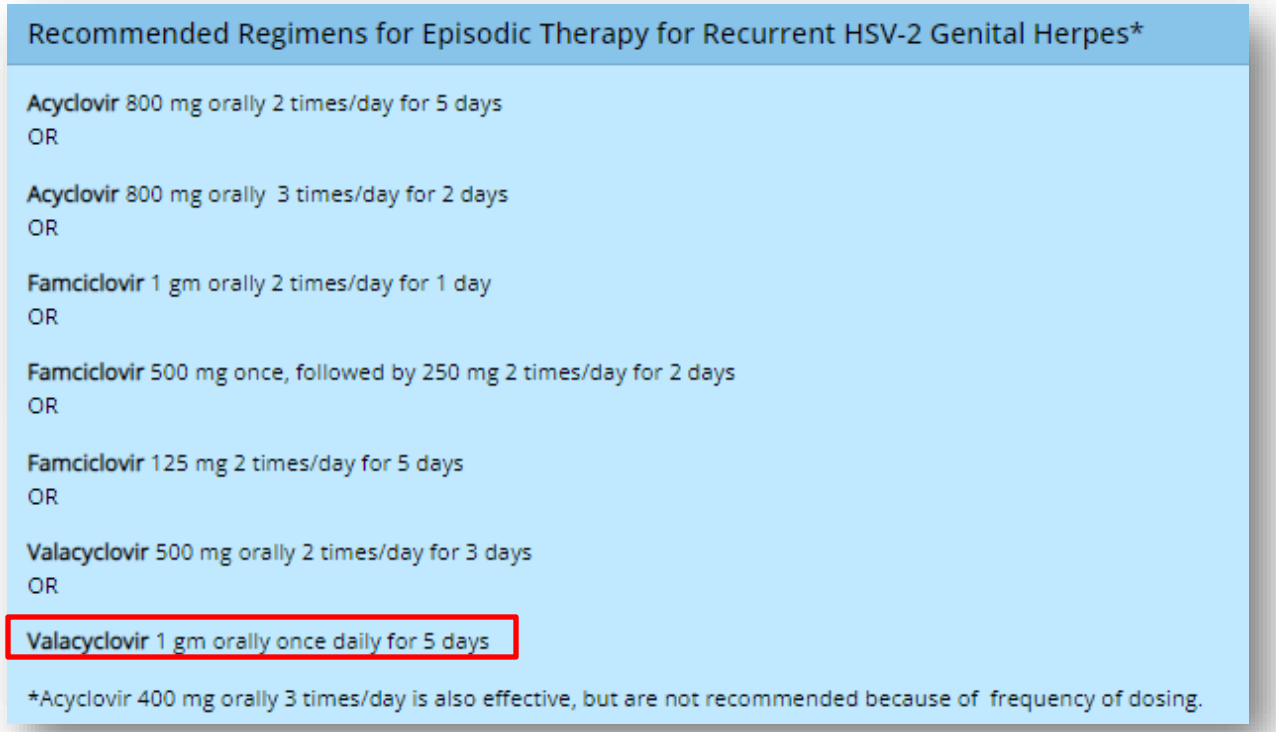


Recommended Regimens

Acyclovir 400 mg orally 2 times/day
OR
Valacyclovir 500 mg orally once a day*
OR
Valacyclovir 1 gm orally once a day
OR
Famciclovir 250 mg orally 2 times/day

* Valacyclovir 500 mg once a day might be less effective than other valacyclovir or acyclovir dosing regimens for persons who have frequent recurrences (i.e., ≥10 episodes/year).

Intermittent



Recommended Regimens for Episodic Therapy for Recurrent HSV-2 Genital Herpes*

Acyclovir 800 mg orally 2 times/day for 5 days
OR

Acyclovir 800 mg orally 3 times/day for 2 days
OR

Famciclovir 1 gm orally 2 times/day for 1 day
OR

Famciclovir 500 mg once, followed by 250 mg 2 times/day for 2 days
OR

Famciclovir 125 mg 2 times/day for 5 days
OR

Valacyclovir 500 mg orally 2 times/day for 3 days
OR

Valacyclovir 1 gm orally once daily for 5 days

*Acyclovir 400 mg orally 3 times/day is also effective, but are not recommended because of frequency of dosing.

Dose and/or duration are increased for immunosuppressed people: e.g. valacyclovir 1 gram BID x 7-10 days (intermittent), valacyclovir 500 mg BID for suppression

What treatment would you offer Jasmine?

- A: Valacyclovir 1 g PO twice daily x 7-10 days
- B: Valacyclovir 1 gram PO daily x 5 days
- C: Valacylovir 2 grams PO twice daily x 1 day
- D: Acyclovir 10 mg/kg IV q 8 hours
- E: Valacyclovir 1 gram daily indefinitely
- F: Transplant of the spinal dorsal nerve root ganglia

Preventing Transmission

- Daily valacyclovir lowers risk of HSV-2 transmission from HIV-negative people with symptomatic genital herpes (approx. 50%)
  - Unknown if true for those without a history of symptoms. Not effective/recommended for people with HIV not on ART
- Condoms decrease, but don't eliminate, risk for HSV-2 transmission
- Male medical circumcision
- Caution against HSV acquisition during pregnancy – avoid genital and/or oral sex with partners who have history of orolabial or genital herpes in 3rd trimester, monitor closely peri-delivery
- Pregnant patients with a history of genital herpes should be offered suppression starting at 36 weeks to decrease risk of recurrence during delivery, c-section rate, and asymptomatic shedding

Corey L, Wald A, Patel R, Sacks SL, Tyring SK, Warren T, Douglas JM Jr, Paavonen J, Morrow RA, Beutner KR, Stratchounsky LS, Mertz G, Keene ON, Watson HA, Tait D, Vargas-Cortes M; Valacyclovir HSV Transmission Study Group. Once-daily valacyclovir to reduce the risk of transmission of genital herpes. N Engl J Med. 2004 Jan 1;350(1):11-20

Urato AC. ACOG Practice Bulletin No. 220: Management of Genital Herpes in Pregnancy.Obstet Gynecol. 2020 Oct;136(4):850-851

HSV patient counseling

- People with a history of genital herpes are recommended to disclose to prospective sex partners
- Transmission more likely with active lesions, but can occur during asymptomatic periods of viral shedding
- Serology cannot determine whether someone is infected orally, genitally, or both
  - HSV-1 is an increasing cause of genital herpes among young women and MSM
- HSV-2 transmission reduced, but not eliminated, by male condom use and valacyclovir suppression (among people without HIV only)
- Suppression not proven to reduce risk of transmission of HSV-1
- People with HSV-2 are at increased risk of acquiring HIV when exposed via sexual contact

HSV takeaway points

- When possible, HSV diagnosis should be confirmed with PCR testing from an active lesion
- Serology may help support the diagnosis w/o active lesions, but is not conclusive
- All patients with a first episode of HSV should get antiviral treatment
- Subsequent outbreaks can be treated with episodic or suppressive therapy
  - Suppressive typically used for those with frequent outbreaks

HSV takeaway points

- HSV 1 is an increasingly common cause of genital herpes, especially among younger people, but typically causes fewer outbreaks and less viral shedding
- HSV 2 causes more frequent outbreaks and increases the risk of HIV transmission.
- Suppressive therapy can reduce outbreak frequency in all patients, and reduce the chances of HSV-2 transmission among people without HIV

Resources

- American Society for Sexual Health patient education materials
  - Patient handouts in English and Spanish for most STIs, including Mgen and HSV
  - https://www.ashapublications.org/patient-education-materials

- CDC STI 2021 guidelines include patient counseling points for genital herpes
  - https://www.cdc.gov/std/treatment-guidelines/herpes.htm

Testy business

Josh is a 54M presenting with 3 days of testicular pain and swelling

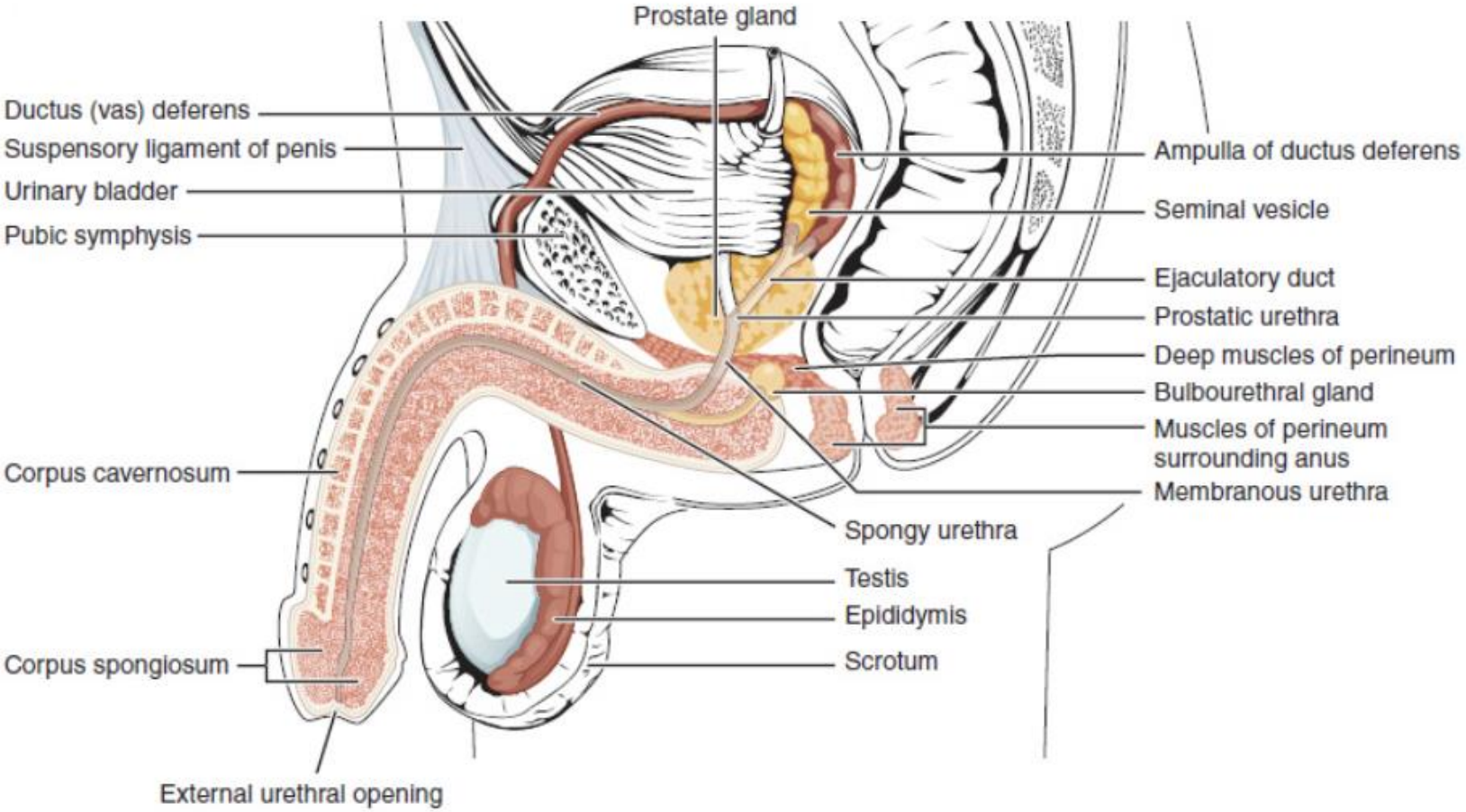
- Onset over the course of a day, no preceding trauma
- + dysuria, no urethral discharge
- PMH: HTN, DM2 on metformin and empagliflozin, PrEP. No allergies
- MSM, insertive and receptive anal sex, gives and receives oral sex. 2 partners in last 6 months, uses condoms with new partners, not primary partner

Physical Exam

- R-sided scrotal erythema and swelling
- R testicle in normal vertical position
- Exquisitely tender with palpable localized swelling along posterior aspect and in spermatic cord
- Cremasteric reflex intact

What Is Our **Differential Diagnosis**?

Epididymo-orchitis



Epididymitis/epididymo-orchitis - Presentation

- Symptoms:
  - Unilateral testicular pain/swelling.
  - Onset typically acute, sometimes chronic, but not sudden.
  - Concurrent dysuria is typical
- Exam: hydrocele, swelling and tenderness of epididymis/testis (tail -> head -> testicle) and spermatic cord
  - Testicle in normal position (not horizontal)

What Is Our **Differential Diagnosis**?

- **Acute (<6 weeks)**
  - STI: N. gonorrhea, chlamydia, Mgen
    - Younger***, sexually active
  - Enteric pathogens: E coli, etc
    - Older***, urinary obstruction or instrumentation, insertive anal sex
- **Chronic**
  - Infections: MTB
  - Post-infectious pain
  - Drug-induced: amiodarone
  - Inflammatory: Behcet's

Hyperacute/sudden onset: don't forget to consider testicular torsion!

What **Diagnostics** Do We Want To Send?

Work-up:

Urine gonorrhea/chlamydia NAAT

UA with microscopy and reflex culture

Comprehensive STI testing

What treatment should we start for Josh?

A. CTX 500 mg x 1 + doxycycline 100 mg BID x 7 days

B. CTX 500 mg x 1 + levofloxacin 500 mg daily x 10 days

C. Levofloxacin 500 mg daily x 10 days

D. CTX 500 mg + doxycycline 100 mg BID x 7d + levofloxacin 500 mg daily x 10d

E. No treatment, wait for results of testing

What treatment should we start for Josh?

A. CTX 500 mg x 1 + doxycycline 100 mg BID x 7 days

- Sexually active, no risk for enteric pathogens (no insertive anal sex, no history or suspicion of urinary tract obstruction/instrumentation)

B. CTX 500 mg x 1 + levofloxacin 500 mg daily x 10 days

- Sexually active ***with*** risk for enteric pathogen

C. Levofloxacin 500 mg daily x 10 days

- Not sexually active (alt TMP-SMX 1 DS tab BID)

D. CTX 500 mg + doxycycline 100 mg BID x 7d + levofloxacin 500 mg daily x 10d

- Duplicates therapy for chlamydia

E. No treatment, wait for results of testing

- Empiric treatment recommended while awaiting results

Josh's test results

Work-up:

Urine gonorrhea/chlamydia NAAT (-)

UA with microscopy and reflex culture: Proteus vulgaris, pan-susceptible

Comprehensive STI testing (-)

Follow up/supportive care

- Tailor antibiotics to urine culture/NAATs
- Scrotal elevation, NSAIDs
- Counsel regarding potential for prolonged time to resolution of discomfort (up to weeks)
- Follow up testing for negative results with persistent symptoms (e.g. Mgen NAAT, urology referral)

What's new in epididymitis?

Treatment of Acute Epididymitis: A Systematic Review and Discussion of the Implications for Treatment Based on Etiology

Louette, Aaron[*]; Krahn, Jessica[*]; Caine, Vera PhD[*]; Ha, Shalane MSc[†]; Lau, Tim T. Y. PharmD[‡]; Singh, Ameeta E. BMBS, MSc[§] Author Information

Sexually Transmitted Diseases

December 2018 , Volume 45 (12), p e104 – e108

- Systematic review of evidence around treatment of epididymitis from 2006-2017
- Included all experimental and observational studies that described etiology and treatment (French/English)
- **1 study met inclusion criteria**
- Retrospective review from 2 STI clinics in Ottowa of epididymitis due to G/C
- 57 patients, 42 chlamydia, 9 gonorrhea, 6 co-infection
- 2 NG treatment failure, no elevated MIC

Digging into etiology

ELSEVIER

European Urology

Volume 68, Issue 3, September 2015, Pages 428-435

Platinum Priority – Infections

Editorial by Jean-Nicolas Cornu and Franck Bruyère on pp. 436–437 of this issue

Acute Epididymitis Revisited: Impact of Molecular Diagnostics on Etiology and Contemporary Guideline Recommendations

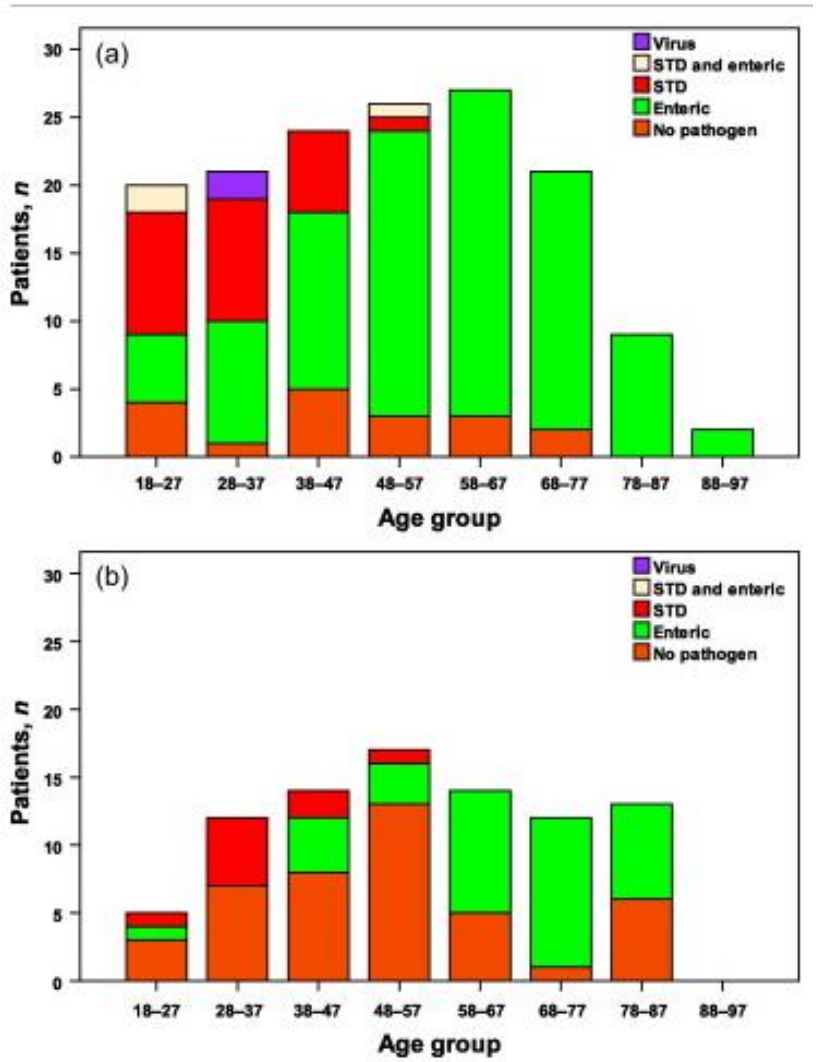
EU ★ ACME ☆

Adrian Pilatz [a], Hamid Hossain [b], Rolf Kaiser [c], Annette Mankertz [d], Christian G. Schüttler [e], Eugen Domann [b], Hans-Christian Schuppe [a], Trinad Chakraborty [b], Wolfgang Weidner [a], Florian Wagenlehner [a]

- 2007-2013 237 patients with acute epididymitis
  - Compared 150 antibiotic-naïve, 87 pre-treated
- All with cultures, STI testing (if sexually active), 16s rDNA analysis if cx neg, and multiplex viral PCR if no other +
- Median age 50s, 55 vs 59% sexually active

Digging into etiology (cont.)

STI-PCR in all sexually active patients	$n = 89$	$n = 48$
Chlamydia trachomatis, *n*	20	5
Mycoplasma spp, *n*	7	1
Neisseria gonorrhoeae, *n*	2	4
Sexually active patients with positive STI, *n*	28	9†
Patients with negative culture and negative STI-PCR, *n*	29	57
16S rDNA analysis in culture- and STI-negative patients	$n = 29$	$n = 57$
Escherichia coli, *n*	0	8
Proteus spp, *n*	0	2
Staphylococcus epidermidis, *n*	0	1
Aerococcus spp, *n*	0	1
Propionibacterium spp, *n*	0	1
Haemophilus spp, *n*	5	1
Lactobacillus spp, *n*	2	0
Bacteroides spp, *n*	1	0
Eubacterium spp, *n*	1	0
Patients with positive 16S rDNA analysis, *n*	9	14‡



Epididymitis/epididymo-orchitis take-home

- Onset is acute, but not sudden (don't forget torsion!)
- Unilateral, often (but not always) with dysuria. Pain/swelling of epididymis +/- testicle
- DDx:
  - STI: GC, CT, Mgen
  - Enteric: E coli, Klebsiella, etc.
  - Others: H flu, enteroviruses?
- Testing: Urine G/C NAAT +/- Mgen NAAT, UA with microscopy and culture
- Treatment: add levofloxacin instead of doxy to CTX if suspicion for enteric + STI
- NSAIDs/scrotal elevation -- symptom resolution may be slow

Questions?