

Update on the Epidemiology, Diagnosis, and Management of Mycoplasma genitalium Infection

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Disclosures

- Research Support
 - Hologic, Inc.

- Consulting/Speaking
 - Hologic, Inc.
 - Sanofi
 - Abbott
 - Visby

Case 1

History: 18yo heterosexual male in Alabama presents with urethral “discomfort” and intermittent urethral discharge for 7 days. He began a new sexual relationship 6 weeks ago

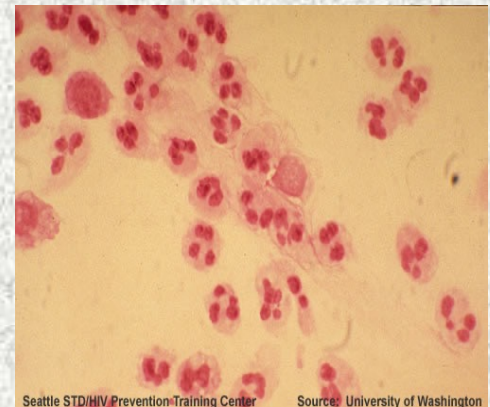
Examination: cloudy urethral discharge

Lab: urethral Gram stain with ~15 PMNs/oil field, no Gram-negative diplococci seen

Diagnosis: nongonococcal urethritis (NGU)



Photo courtesy of William Geisler



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

Case 1 continued

- Urethral swab tested for *Chlamydia trachomatis* (chlamydia), *Neisseria gonorrhoeae* (gonorrhea), and *Trichomonas vaginalis* (trichomoniasis)
- Empirically treated with doxycycline 100 mg BID (twice daily) x 7d
- Counseled about:
 - sexually acquired nature of infection
 - abstinence until treatment complete
 - need to arrange for exam and treatment of partner
 - return if symptoms do not resolve or they recur
 - return in approximately 3 months after treatment for repeat chlamydia gonorrhea, or trichomoniasis testing if he tests positive for one of these

Case 1 Continued

- Chlamydia test returned positive. Gonorrhea and trichomoniasis tests were negative
- He completed his 7-day doxycycline treatment course
- He returned to clinic 2 weeks after completing treatment with persisting urethral discomfort and intermittent clear urethral discharge
- Repeat exam and urethral Gram stain showed NGU findings

Question

Should he be tested for *Mycoplasma genitalium* (MG) at this time?

A. Yes

B. No

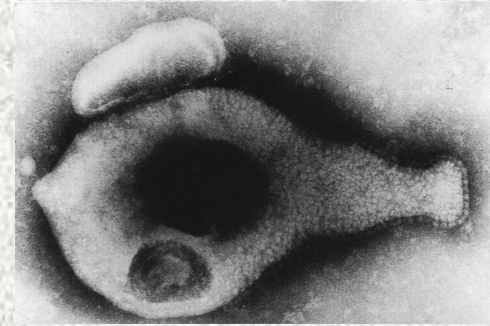
Question

Would you give him any treatment now?

- A. Yes, azithromycin 1 g PO single dose (directly observed)
- B. Yes, moxifloxacin 400 mg PO daily X 7 days
- C. Yes, doxycycline 100 mg PO BID X 7 days, followed by moxifloxacin 400 mg PO daily X 7 days
- D. No, would not give any treatment at this time; would wait for test results to come back

What is *Mycoplasma genitalium* (MG)?

- Small pathogenic bacteria lacking a cell wall
 - Has a terminal organelle facilitating attachment
- Sexually transmitted
- 1st isolated in 1980 in culture
 - Classified as new species in 1983 – Strain G37
- Genome sequenced in 1995
 - size 0.58 Mbp, 475 genes
 - Differs from other *Mycoplasma* species in energy generating pathways



MG infection is low in general populations

Site	Males			Females		
	<u>MG</u>	<u>CT</u>	<u>NG</u>	<u>MG</u>	<u>CT</u>	<u>NG</u>
U.S. (Add Health; 18-27yo) ^{1,2}	1.1%	3.7%	0.4%	0.8%	4.7%	0.4%
U.K. (Natsal-3; 16-44yo) ^{3,4}	1.2%	1.1%	<0.1%	1.3%	1.5%	<0.1%
Denmark (21-23yo) ⁵	1.1%	5.6%	---	2.3%	8.4%	---

¹Manhart LE, et al. *Am J Public Health*. 2007

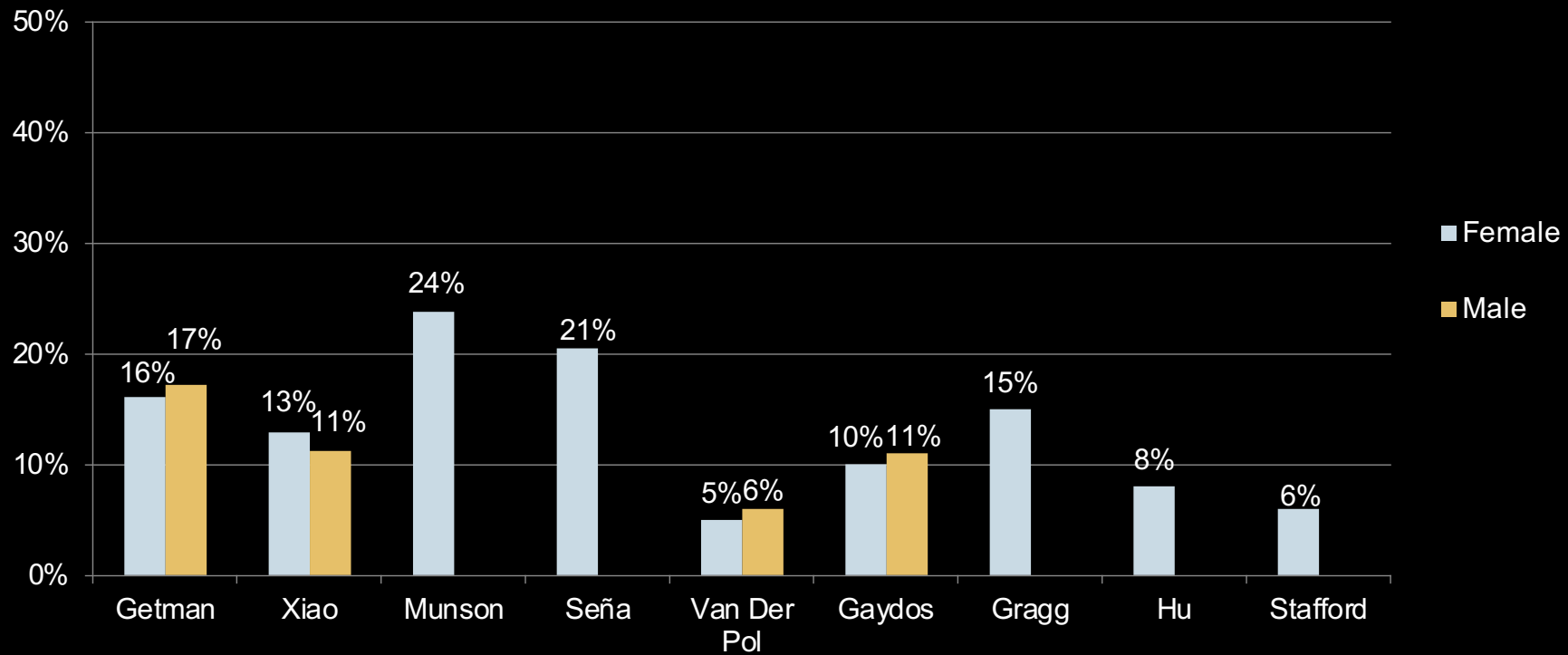
²Miller, et al. *JAMA* 2004

³Sonnenberg, et al. *Int J Epidemiol*. 2015

⁴Sonnenberg, et al. *Lancet*. 2013

⁵Andersen, et al. *Sex Transm Infect*. 2006

MG is common in U.S. Clinics



MG prevalence ranged from 5%-24% in U.S. clinics

(including STD, OB-GYN, ED, family medicine/care, family planning, public health, and research clinics)

Getman, et al. *J Clin Microbiol* 2016 Sep;54(9):2278-83.

Xiao, et al. *Sex Transm Dis*. 2019 Jan;46(1):18-24.

Munson, et al. *J Clin Microbiol*. 2016 Dec 28;55(1):321-325.

Seña, et al. *Clin Infect Dis*. 2018 Jun 18;67(1):73-79.

Stafford, et al. *BMJ Open*. 2021;11(6):e050475.

Van Der Pol, et al. *J Clin Microbiol*. 2020;58(6):e02124-19.

Gaydos, et al. *J Clin Microbiol*. 2019;57(11):e01125-19.

Gragg, et al. *Sex Transm Dis*. 2021;48(2):e27-e29.

Hu, et al. *Int J Gynaecol Obstet*. 2023; 160(1):341-344

What about MG prevalence in pregnant women?

- 4 studies before 2015¹ → ~1%
- 4 studies after 2015²⁻⁵ → 6%-17%



Adobe Stock

1. Baumann et al. *Sex Transm Infect* 2018
2. Smullin et al. *Sex Transm Infect* 2020
3. Trent et al. *Sex Transm Infect* 2018
4. Stafford, et al. *BMJ Open* 2021
5. Hu, et al. *Int J Gynaecol Obstet* 2023

What are reported predictors of MG infection?

- **Similar to predictors associated with chlamydia**
 - Younger age (adolescents, young adults)¹⁻³
 - Black race^{2,4}
 - Multiple sexual partners¹

1. Manhart et al. *J Infect Dis.* 2003;187(4):650.

2. Hancock et al. *Sex Transm Dis.* 2010;37(12):777.

3. Mobley et al. *Sex Transm Dis.* 2012;39(9):706.

4. Manhart et al. *Am J Public Health.* 2007;97(6):1118.

Clinical Manifestations of MG Infection

Majority of infections are asymptomatic



- **Urethritis**^{1,2} - common
- **Epididymitis**¹ - rare
- **Proctitis**³ - uncommon

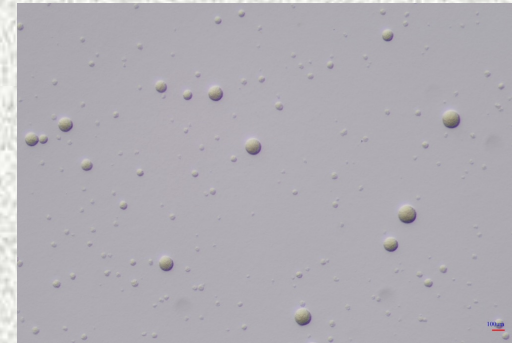


- **Cervicitis**⁴ - common
- **PID**⁴ - moderate evidence of significant association
- **Infertility**⁴ - limited evidence of significant association
- **Perinatal Complications**⁴ - limited evidence and not consistent
- **Vaginal Discharge** - inconsistent association

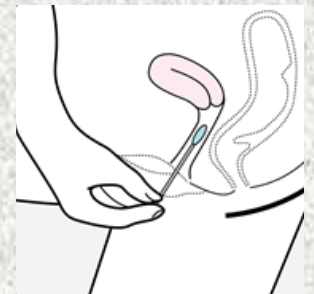
1. Taylor-Robinson D et al. Clin Microbiol Rev 2011; 24:498-514.
2. Bachmann LH, et al. Clin Infect Dis 2020; 71: e624–e632
3. Ong JJ, et al. Sex Transm Dis. 2018;45:522-526.
4. Lis, et al. Clin Infect Dis 61:418-426, 2015.

MG Detection

- Culture not useful for detecting *M. genitalium* in clinical care
- Nucleic acid amplification test (NAAT) is recommended for *M. genitalium* detection¹
 - Three MG NAATs are FDA approved in the U.S., none which test for resistance markers
- Optimal specimens for *M. genitalium* NAAT are first-catch urine in men and vaginal swab in women²



freepik



<https://www.sh.uk/self-sampling/vaginal-swab>

1. CDC. 2021 Sexually Transmitted Infections Treatment Guidelines

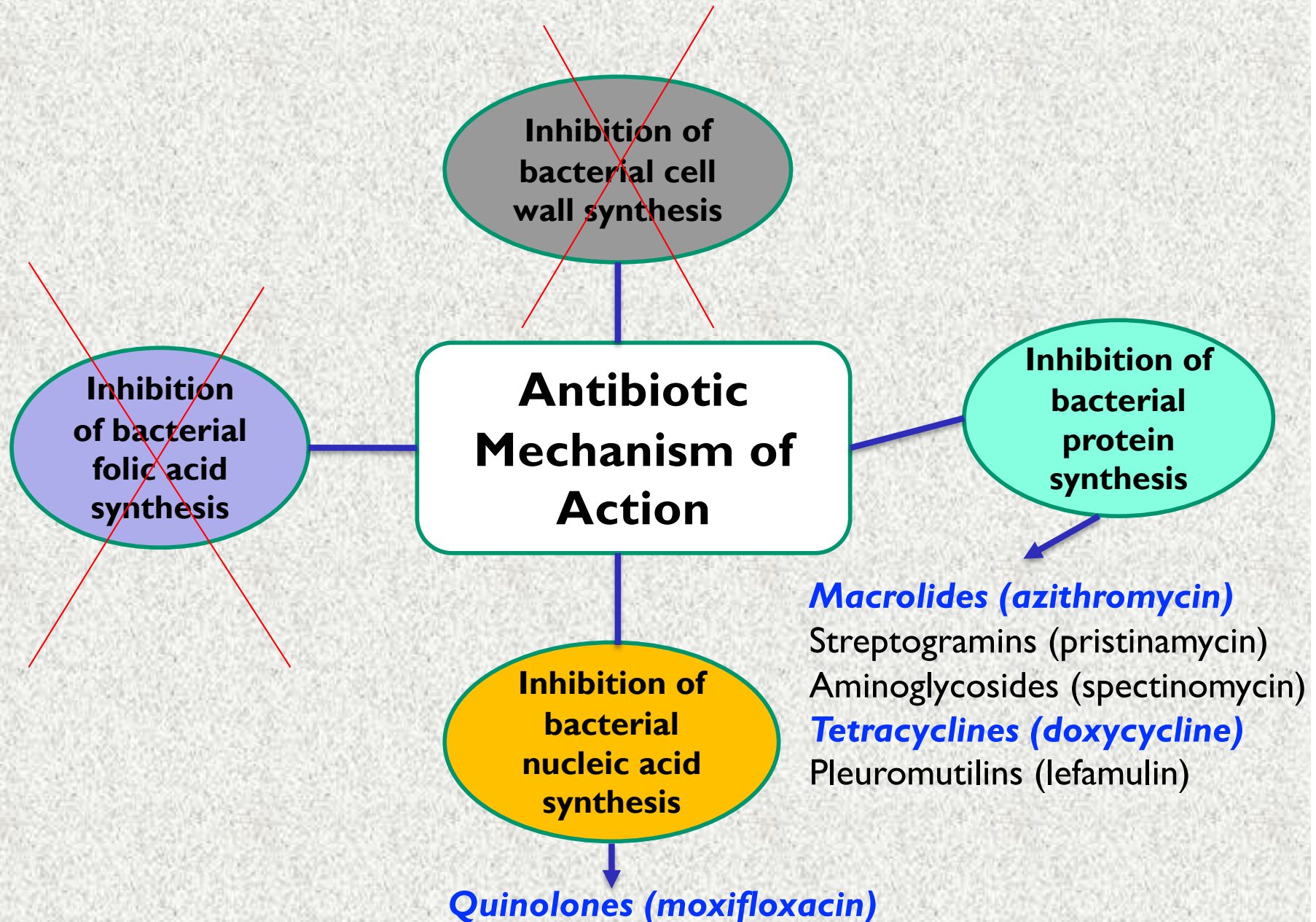
2. Van Der Pol B, et al. J Clin Microbiol. 2020;58:e02124-19.

CDC MG Testing Recommendations

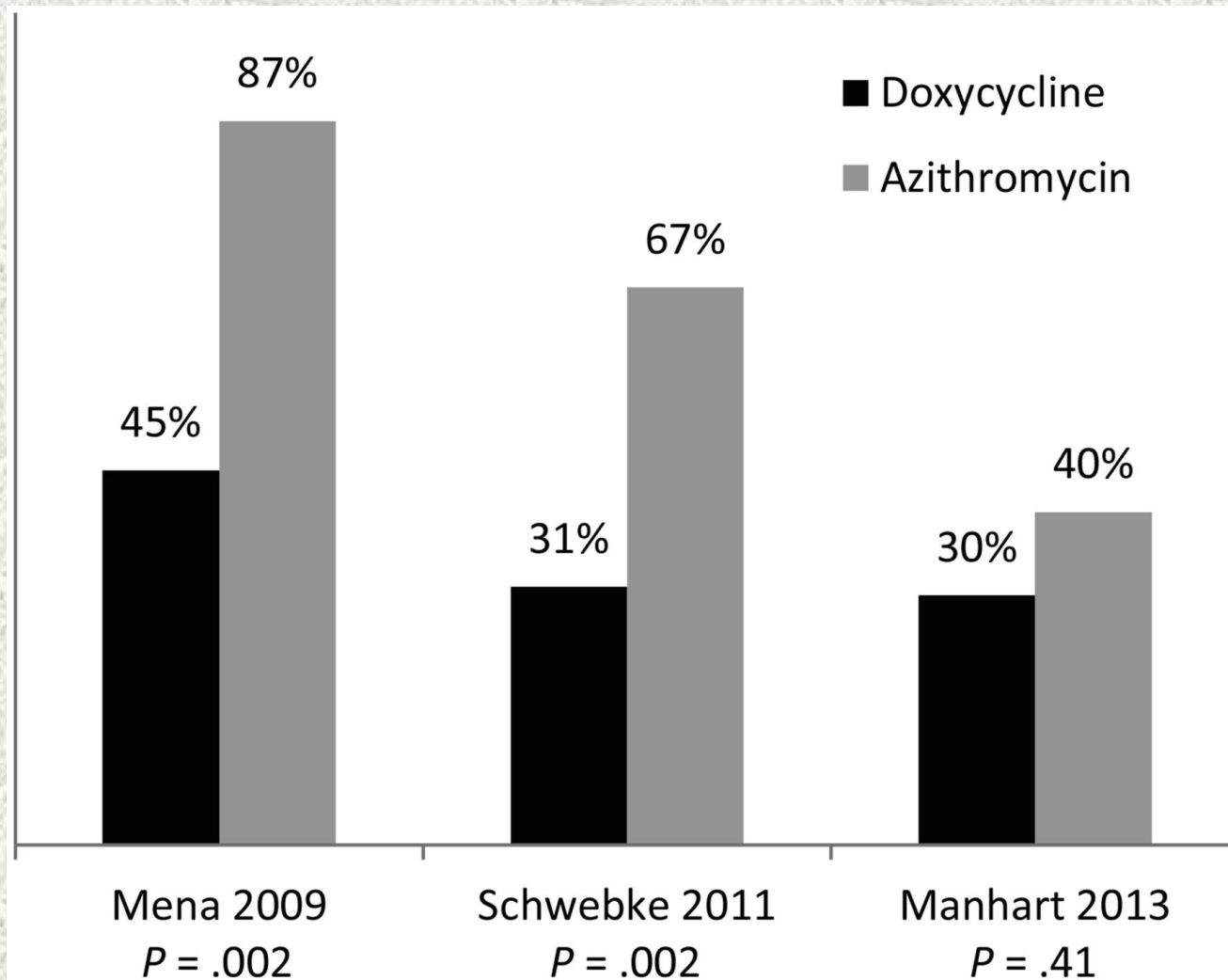
- MG testing should be done in *persisting or recurrent* cases of urethritis or cervicitis
- MG testing should be considered for PID
- There is no discussion about whether MG testing should be done with persisting or recurrent vaginal discharge
- Routine MG screening (in asymptomatic persons) is not recommended
 - ***Insufficient evidence on natural history of untreated MG infection***

MG Treatment

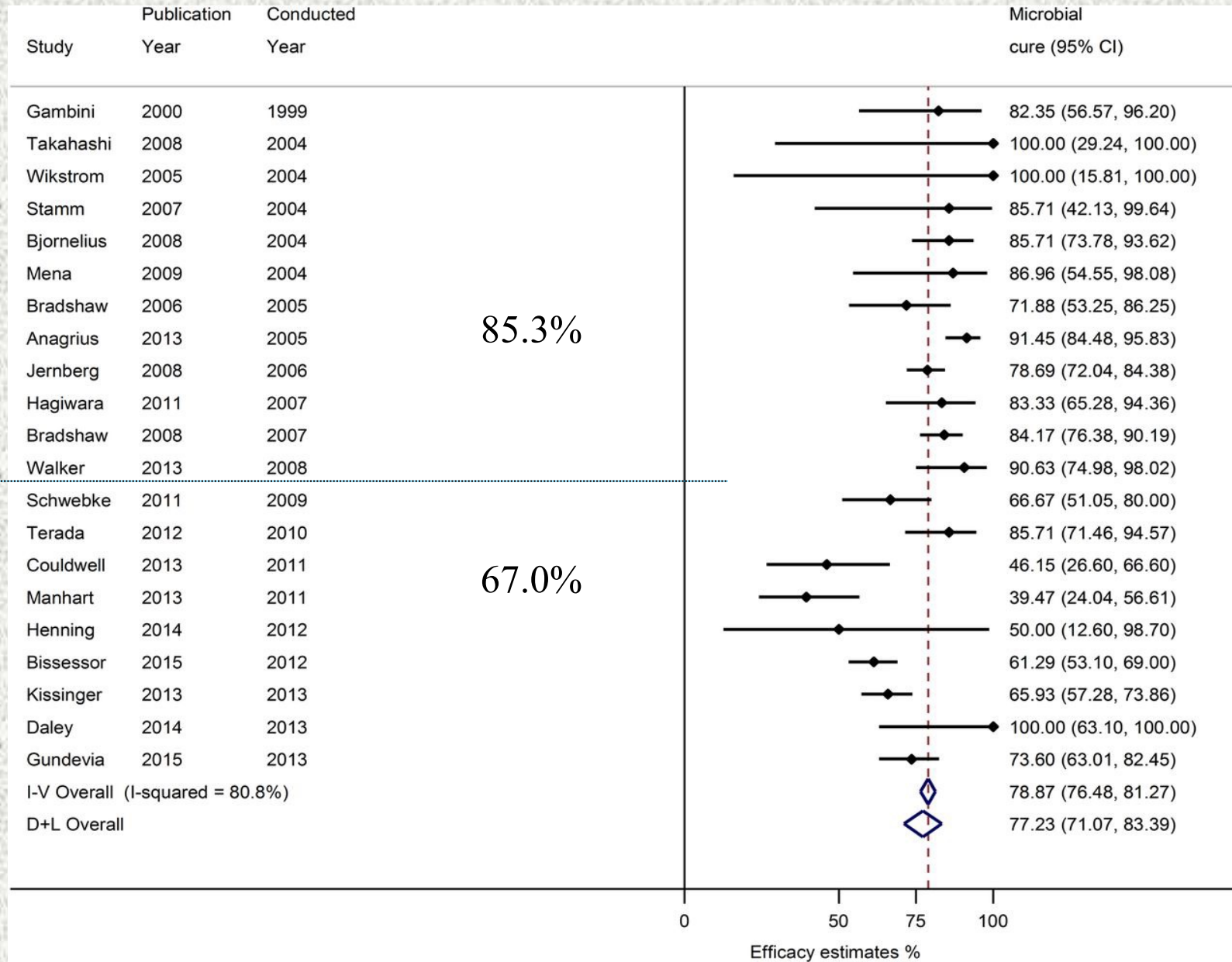
Antibiotic Classes Active Against Mycoplasmas



MG Urethritis Treatment Trials Show Declining Cure Rates For Main MG Treatments

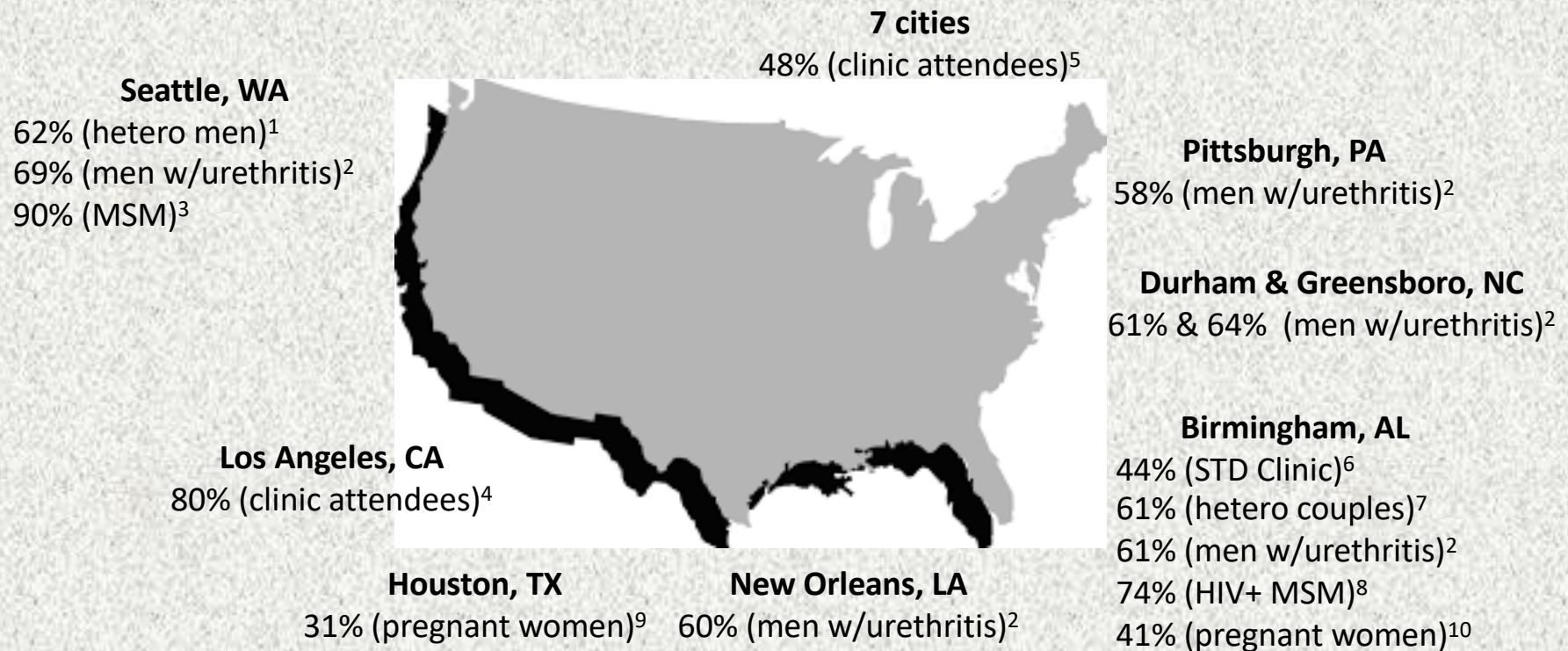


Microbial cure rates with azithromycin 1 g for urogenital MG infection



MG Macrolide Resistance Mutations (MRMs)* in the U.S.

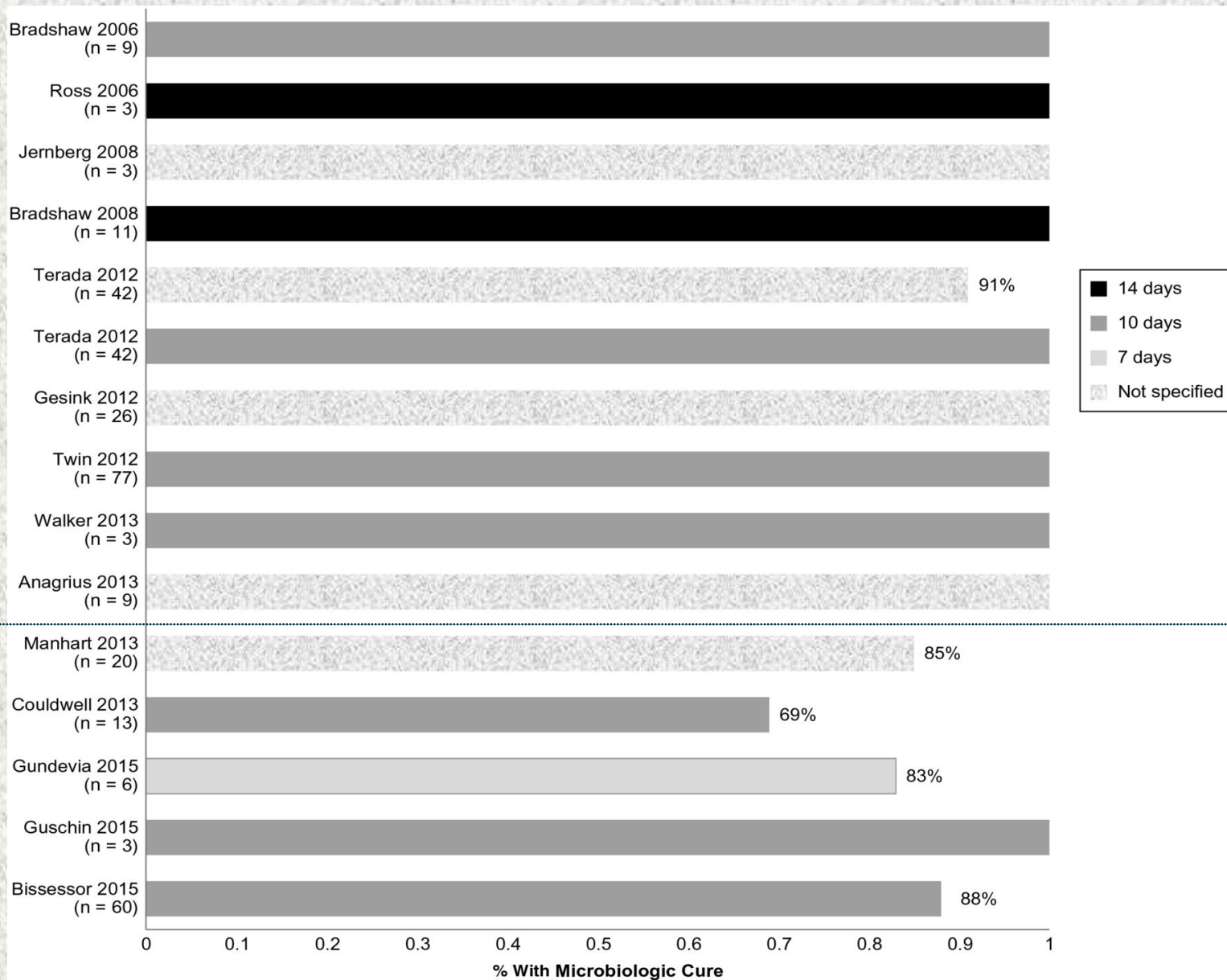
MG MRM prevalence range from 31%-90% across U.S. sites



*MRMs in the 23S rRNA gene, typically A2071 and A2072 (*E.coli* numbering 2058 and 2059)

1. Romano 2018, 2. Bachmann 2020, 3. Chambers 2019, 4. Allan-Blitz 2018, 5. Getman 2016,
6. Xiao 2018, 7. Xiao 2019, 8. Dionne-Odom 2018, 9. Stafford 2021, 10. Hu 2023

MG Treatment Outcomes Have Also Been Declining with Moxifloxacin



MG Quinolone Resistance Mutations (QRMs) in the U.S.

- Not all mutations in the MG quinolone resistance-determining regions are associated with treatment failure
 - S83I mutation in *parC* is the MG QRM most strongly associated with moxifloxacin treatment failure¹ (~59%²)
 - Treatment failure may be higher in patients with *parC* S83I/*gyrA* dual mutations (mostly *gyrA* M95I) when compared with infections with single S83I SNP alone³
- Prevalence of the *parC* S83I mutation in the U.S. ranges from 5.7%-29.6%⁴⁻⁶
 - Higher prevalence of *parC* 83I among MSM^{4,5}
 - MG strains with *parC* S83I usually have MRMs^{4,5}

1. Fookes, et al. BMC Genomics. 2017;18 2. Murray, et al. Antimicrob Agents Chemother. 2022;66
3. Murray, et al. Clin Infect Dis. 2023;76. 4. Dionne Odom, et al. Clin Infect Dis. 2018;66
5. Xiao, et al. Sex Transm Dis. 2019;46. 6. Bachmann, et al. Clin Infect Dis. 2020; 71

Sequential MG Treatment Strategy is Now Recommended for MG Infection

Recommended Regimens if *M. genitalium* Resistance Testing Is Available

If macrolide sensitive: Doxycycline 100 mg orally 2 times/day for 7 days, followed by azithromycin 1 g orally initial dose, followed by 500 mg orally once daily for 3 additional days (2.5 g total)

If macrolide resistant: Doxycycline 100 mg orally 2 times/day for 7 days followed by moxifloxacin 400 mg orally once daily for 7 days

Recommended Regimen if *M. genitalium* Resistance Testing Is Not Available

If *M. genitalium* is detected by an FDA-cleared NAAT: Doxycycline 100 mg orally 2 times/day for 7 days, followed by moxifloxacin 400 mg orally once daily for 7 days

There are no FDA-cleared MG NAAT that detect resistance markers

Other MG Management Considerations

- Test partners of MG-infected patients and treat if positive
- Test of cure is not recommended by CDC for asymptomatic patients or in those whose clinical signs/symptoms resolve (i.e., those who are clinically cured)

Case 1 Continued

- He completed sequential therapy with a 7-day doxycycline course followed by a 7-day moxifloxacin course
- Her returns 2 weeks later with persisting urethral discomfort and intermittent clear urethral discharge
- He reports complete adherence with treatment and no sexual activity since his initial treatment
- Repeat exam and urethral Gram stain shows NGU findings

Question

What treatment would you prescribe for him now?

- A. Azithromycin 1 g PO day 1, then 500mg daily for 3 more days
- B. Moxifloxacin 400 mg PO daily X 14 more days
- C. Minocycline 100 mg PO BID X 14 days
- D. Tinidazole 2 g daily X 7 days

Salvage MG Treatment Regimens in the U.S.

- **Minocycline (100mg PO twice daily for 14 days)**
 - Old tetracycline class antibiotic
 - Cure rate of 71% in one observational study;¹ case reports also reporting cure^{2,3}
- **Omadacycline (two 150mg tabs PO daily x ? days)**
 - New tetracycline class antibiotic FDA approved for SSTI and CABP
 - Best in vitro activity of tetracyclines against tetracycline-resistant MG strain⁴
 - No published clinical efficacy data; very expensive
- **Lefamulin (two 150mg tabs PO daily x ? days)**
 - From the drug class pleuromutilin and FDA approved for CABP
 - Good in vitro activity against multidrug-resistant MG strains⁵
 - No published clinical efficacy data; very expensive
- **Tinidazole (2g daily x ? days)**
 - Nitroimidazole class antibiotic mostly used to treat protozoa
 - Best in vitro activity of nitroimidazoles against MG⁶
 - No published clinical efficacy data

1) Doyle, Open Forum Infect Dis. 2020, 2) Glaser, Int J STD AIDS. 2019, 3) Deguchi. J Infect Chemother. 2017,
4) Waites, *Microbiology Spectrum*, 2022, 5) Paukner, Antimicrob Agents Chemother. 2018; 6) Wood, Antimicrob Agents Chemother. 2023

Case 2

- A 19-year-old pregnant woman who is at ~13 weeks gestation presents for her first prenatal visit.
- She reports having vaginal intercourse with a single male partner for the last 12 months and not using condoms
- She denies any urogenital or pelvic symptoms and her genital examination is normal
- Her OB physician tells her that routine STI testing will be performed per standard of care

Case 2 continued

- **STI test results:**
 - *Chlamydia trachomatis*: negative
 - *Neisseria gonorrhoeae*: negative
 - *Trichomonas vaginalis*: negative
 - MG: positive

Case 2 continued

Would you treat the positive MG result?

A. Yes

B. No

MG Treatment in Pregnancy

- **Macrolides (e.g., azithromycin)** are the only antibiotic class available in the U.S. to treat MG that are considered safe in pregnancy and have efficacy data
 - Tetracyclines, quinolones, and lefamulin not considered safe in pregnancy
 - No clinical efficacy data for nitroimidazoles against MG
- **Pristinamycin** is available in select countries outside the U.S.
 - From the antibiotic class streptogramin
 - Pregnancy category B
 - Active against macrolide-resistant MG
 - Cures majority of MG infections¹
 - Importing to the U.S. for treatment requires approval from the FDA (patient expanded access IND) and is a complicated, labor-intensive process

1. Read, et al. Emerg Infect Dis. 2018;24

Case 2 continued

- After a shared decision approach that included a patient-provider discussion about potential benefits and risks of treating MG in pregnancy with azithromycin, the patient was given an extended azithromycin regimen (1g Day 1, 500mg daily Days 2-4)
- A repeat MG test was done 4 weeks later and was positive. No further treatment was given during pregnancy
- She had a normal term delivery and was then treated with doxycycline for 7 days followed by moxifloxacin for 7 days

Questions / Comments?

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