Mycoplasma genitalium Treatment Failure Registry

Purpose

The purpose of this information collection is to determine which second-line antibiotics are in use for *Mycoplasma genitalium* treatment failure and monitor genetic markers of antibiotic resistance among treatment failure cases throughout the United States.

Background

Mycoplasma genitalium is a sexually transmitted bacterium that was first identified in the early 1980s. According to the National Longitudinal Study of Adolescent Health, *M. genitalium* is more common than gonorrhea but less common than chlamydia. (Manhart 2007, *Am J Public Health*, Mena 2002, *Clin Infect Dis*) *Mycoplasma* and chlamydia coinfections may also occur. (Huppert 2008, *Sex Transm Dis*) *M. genitalium* is strongly associated with urethritis in males, accounting for approximately 15-20% of all cases of non-gonococcal urethritis (NGU) and 30% of persistent or recurrent urethritis (Taylor-Robinson 2011 *Clin Microbiol Rev*). Despite a clear association with urethritis, it is unknown whether *M. genitalium* causes male infertility or upper urogenital tract disease. *M. genitalium* can be detected in the rectum but its relationship with clinical proctitis is also unclear. In females, *M. genitalium* has been associated with 1.6-1.9-fold increased odds of cervicitis, pelvic inflammatory disease, preterm birth, and spontaneous abortion. It may also be associated with tubal factor infertility (Lis 2015, *Clin Infect Dis*)

Until recently in the United States, suspected *M. genitalium* was managed on a syndromic basis, as there were previously no FDA-approved tests for clinical diagnostic use. As of 2019, the FDA approved the first nucleic acid amplification testing (NAAT) for *M. genitalium*, (Aptima, Hologic Inc., Marlborough, MA), which will greatly expand access to testing and identification of *M. genitalium* infections. There are no national guidelines for use of *M. genitalium* NAAT for asymptomatic screening. However, the 2020 CDC STD Treatment Guidelines will address use of M. genitalium NAAT testing for patients with genital or urinary symptoms.

Previously in the 2015 CDC STD Treatment Guidelines, the recommended treatment for *M. genitalium* was the macrolide antibiotic azithromycin followed by a course of moxifloxacin in cases of azithromycin treatment failure. The cure rate for moxifloxacin was previously thought to be 100%, however, reports of antibiotic resistance or treatment failure have been reported from Australia, Japan, South Africa, Europe, and the US (Murray 2017, *Emerg Infect Dis*; Deguchi 2018, *J Infect Chemother*, Muller 2019, *BMC Infect Dis*, Unemo 2018, *Clin Microbiol Infect*, Glaser 2019 *Int J STD AIDS*). In the United States, there are currently no national guidelines for treatment in cases of moxifloxacin treatment failure, and data are needed to provide evidence for future treatment recommendations.

Objectives

1) Describe the number of treatment failure cases reported annually
2) Describe which second-line antibiotic therapies currently in use in patients experiencing treatment failure
3) Describe demographic and behavioral factors among patients with treatment failure
4) Describe the proportion of specimens from treatment failure patients with molecular markers of macrolide, tetracycline, and fluoroquinolone resistance

Methods

Study design: Cross-sectional

Sampling: Convenience sample of US health care providers.

Sample size: up to 100 per year. It is unknown how many patients in the US will experience treatment failure annually, as case reports up until this point have been uncommon.

Study population: The respondent universe consists of clinicians who care for patients with *Mycoplasma genitalium*. Clinicians may come from private health care practices, publicly funded health care facilities, hospitals, universities, medical centers, federal agency clinics (e.g. Indian Health Service), and state and local health departments.

The population eligible for surveillance through the *Mycoplasma genitalium* Treatment Failure Registry ("the Registry") include persons of any gender who are infected with anogenital *Mycoplasma genitalium*.

The following patients are eligible to be included in the Registry:

1) Adult patients (age 18 or older) with recurrent urethritis, cervicitis or proctitis (see Case Report Form**)** and laboratory confirmation of *Mycoplasma genitalium* using a nucleic acid amplification test (NAAT) AND
2) Received CDC-recommended treatment (at least seven days of moxifloxacin for antibiotic therapy) AND
3) Remain persistently symptomatic (subjective) and have either
    a. Elevations in urine WBC or persistent discharge AND/OR
    b. Have a persist positive NAAT test for *M. genitalium*.

The following patients will be excluded from the Registry:

1) Pregnant patients
2) Minors and children

Case Report Form: Respondent clinicians will be asked to complete the Case Report Form for the *Mycoplasma genitalium* Treatment Failure Registry (see attached) which will be made available on the CDC DSTDP website and by request from the Registry Project Officer. The Case

Report Form will collect categories of information in identifiable format from respondent clinicians such as: clinician's name, work mailing address, work phone numbers, work email address. The case report from includes patient sociodemographic and medical history information which may be relevant to a history of treatment failure.

- Age, sex, race/ethnicity, gender identity, gender of sex partners
- Testing history, including any history of prior testing for genetic markers of antibioitic resistance
- Dates of diagnosis, treatment and treatment rendered
- HIV status

Case deidentification: The responding provider will generate a unique identifier for the case report form. This will allow linking of patient data with laboratory testing data, if specimens are sent to CDC for testing. This will also allow linkage of data internally in case a patient experiences multiple episodes of treatment failure. The unique identifier will consist of the patients first and last initial, 2-digit year of birth, and last 4 digits of the Medical Record Number. (e.g., John Smith, born 1973, MRN 1234567 = JS73-4567). There will be no links to personally identifiable information.

Reporting procedures: Reporting providers will be asked to submit the two-page case report form (either by fax or email) to CDC DSTDP. Upon receipt, Case Report Form data will be entered into an electronic database at CDC. Future analysis of provider-level data will be limited to the reporting providers' state, to determine if there is regional clustering of treatment failure cases. Patient level characteristics will be analyzed in aggregate. No identifying information will be sent to the CDC, other than the dates of antibiotic treatment.

Laboratory specimen collection:

If specimens are available, remnant specimens from patients with *M. genitalium* treatment failure will be sent to the DSTDP laboratory to be tested for genetic mutations associated with antibiotic resistance to macrolides, fluroquinolones, and tetracyclines. Testing performed at DSTDP's laboratories will be performed according to the laboratory's Standard Operating Procedures. Results will not be used for immediate clinical management.

The submitting laboratory will be asked to remove labels with PHI and replace them with a label containing the CDC unique identifier. (The unique ID will be provided to the submitting laboratory by the Registry Project Officer). The Registry Project Officer will liaise between the submitting laboratory and the CDC Laboratory to coordinate the submission of specimens.

Recruitment/Reporting:

CDC DSTDP will inform its grantees (e.g., National Network of Prevention Training Centers-NNPTC, state and territorial health departments) academic, clinical, and laboratory partners about the *Mycoplasma genitalium* Treatment Failure Registry ("the Registry") through various communication channels (e.g., direct email). The NNPTC will send out a recruitment email to its network of providers nationwide. (Att 3) Cases may come to the attention of CDC through

contacts with academic research centers and clinical inquiry systems such as CDC-INFO or the STD Clinical Consultation Network (STDCCN). CDC will establish a designated Registry email address where providers can communicate directly with the Registry staff.

Reporting to the registry is voluntary and only warranted for cases of treatment failure. Clinicians staffing the CDC INFO for DSTDP and the STD Clinical Consultation Network for NNPTC will be instructed to direct clinicians reporting M. genitalium treatment failure to Registry staff, so that reporting of cases may be facilitated. Information letters will be provided for clinicians to assist them in understanding the purpose and value of the Registry.

Informed consent: Data will be reported directly from the healthcare provider, patients will not be asked to provide informed consent.

Data analysis plan: Quantitative data from the case report forms will be analyzed using the Statistical Packages for the Social Sciences (SPSS) software program to calculate descriptive statistics of patient-level sociodemographic variables. This includes frequencies and cross-tabulations, as well as univariate distributions and correlations. The frequency analysis will give various chi-squared tests for association for categorical ordinal or nominal data. The reporting provider's state will be analyzed to determine whether treatment failure cases appear to cluster regionally within the US.

Results will be presented in graphic, written and verbal forms with annual written reports distributed throughout DSTDP, manuscripts and presentations at scientific conferences. Results may be shared with health departments and other government agencies, and/or healthcare organizations.

Privacy/data confidentiality protections:

The Privacy Act is applicable. Records are covered under CDC Privacy Act System of Records Notice (SORN) No. 0920-0136 "Epidemiologic Studies and Surveillance of Disease Problems" and SORN No. 09-20-0113, "Epidemic Investigation Case Records Systems Notice."

The Health Insurance Portability and Accountability Act (HIPAA) permits covered entities such as clinicians to disclose patient's protected health information (PHI) to public health authorities for public health purposes without the patient's authorization. The Registry will consist of a limited data set of variables, there will be no other PHI other than full dates of treatment (month, day, year). The data will only be used for the purposes for which it is intended, i.e., surveillance of *M. genitalium* treatment failure to inform clinical recommendations and guidelines. In the Case Report Form, CDC is collecting full dates of treatment (month, day, year) as a public health authority, defined in the HIPAA and its implementing regulations. Standards for Privacy of Individually Identifiable Health Information (45 CFR § 164.501), ("Privacy Rule").

There are several safeguards in place to handle data submitted to the CDC. Data will be stored and managed based on current CDC/OCISO (Office of the Chief Information Security Officer) requirements and standards. This includes protecting stored data within the CDC Internet Firewall. The data are stored and managed based on current CDC/OCISO requirements and standards which also includes the process for handling security incidents and the event

monitoring and incident response. All administrative controls required by OCISO are validated through a "Certification and Authorization" (C&A) process as conducted by OCISO prior to moving any software application into "Production" on the CDC network.

Files are backed up daily and stored both onsite in accordance with CDC standards and OCISO guidelines. All users' access is "role based" and reflects a "need to know" policy established by CDC. Accountability is maintained with a user access log file which tracks users' access to the system. Records will be retained and destroyed in accordance with the applicable CDC Records Control Schedule as mandated by OCISO. (http://aops-mas-iis.od.cdc.gov/Policy/Doc/policy449.htm)

The CDC will not include any information in reports that may identify cases or patients, including specified dates of diagnosis and treatment. Only deidentified data will be presented in case reports or in aggregate. Aggregate data will not be stratified into subcategories that might allow for identification of individuals.

References

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Mycoplasma genitalium Treatment Failure Registry

CASE REPORT FORM

The purpose of this form is to collect clinical information on cases of *Mycoplasma genitalium* that fail antibiotic therapy

All reported information will be maintained in the strictest confidence. Questions? Contact xxx at XXX@cdc.gov

Confidentiality Note: The information in this form includes confidential information intended only for the use of the individual or entity named below. If the reader of this form is not the intended recipient, you are hereby notified that any dissemination, distribution or copy of this form is strictly prohibited and may result in civil and criminal penalties under federal law. If you have received this form in error, please immediately notify us immediately at the number above.

PLEASE COMPLETE BY__/__/____and fax to our confidential fax line (xxx)xxx-xxxx.

PROVIDER INFORMATION:

Provider Name	Provider Phone #	Provider Fax #	
Provider Email Address	Practice/Clinic Name		
Address	City	State	Zip

PATIENT UNIQUE IDENTIFIER* (First Initial, Last initial, 2-digit year of birth, last 4 digits of Medical Record Number) Example: John Smith, born 1973, MRN 1234567 = JS734567

PATIENT AGE:

PATIENT PREVIOUSLY REPORTED TO THE REGISTRY? ☐ Yes ☐ No

PATIENT DEMOGRAPHIC INFORMATION:

1. Race (check all that apply)
- ☐ Unknown
- ☐ White
- ☐ Asian
- ☐ Black or African American
- ☐ American Indian / Alaska Native
- ☐ Native Hawaiian / Other Pacific Islander
- ☐ Other _____

2. Ethnicity
☐ Unknown ☐ Hispanic / Latino ☐ Not Hispanic / Latino

3a. Sex assigned at birth
- ☐ Male
- ☐ Female

3b. Gender identity
- ☐ Male
- ☐ Female
- ☐ Transgender male to female
- ☐ Transgender female to male
- ☐ Gender non-binary
- ☐ Unknown

4. Gender of sex partners in past year (check all that apply)
- ☐ Male
- ☐ Female
- ☐ Transgender male to female
- ☐ Transgender female to male
- ☐ Gender non-binary
- ☐ Unknown

5. HIV Status
- ☐ HIV-positive
- ☐ HIV-negative
- ☐ Unknown/Never tested

DIAGNOSTICS/ TREATMENT

Indication for M. genitalium testing (check all that apply): 1) Symptoms: ☐Urogenital (e.g., discharge, dysuria) ☐Anorectal (tenesmus, discharge, pain) ☐Pelvic/abdominal (pain, dyspareunia) 2) Clinical Syndrome (w/ objective findings): ☐Urethritis (documented discharge or pyuria) ☐Cervicitis (discharge, friability, + swab test) ☐PID ☐Proctitis ☐Other _____

M. genitalium diagnosis confirmed with nucleic acid amplification test? ☐ Yes ☐ No ☐ Unknown	**Laboratory performing M. genitalium testing. (e.g., Quest, LabCorp, name of hospital, etc)** _____	**Testing for macrolide resistance performed?** ☐Yes ☐ No **If yes, mutation detected?** ☐Yes ☐ No

Testing for fluroquinolone resistance performed? ☐Yes ☐ No

If yes, mutations detected: ☐S83I ☐parC unspecified

Date of initial treatment initiation ____/____/_____ ☐ Unknown	**Date of 2nd course treatment initiation** ____/____/_____ ☐ Unknown	**Date of 3rd course treatment initiation** ____/____/_____ ☐ Unknown
Initial treatment prescribed (check all that apply), and dose/frequency/duration (e.g., doxycycline 100 mg po BID x 7 days)	**Second treatment prescribed (check all that apply), and dose/frequency/duration**	**Third treatment prescribed (check all that apply), and dose/frequency/duration**
☐ Azithromycin _____x days	☐ Azithromycin _____x days	☐ Azithromycin _____x days
☐ Doxycycline _____x days	☐ Doxycycline _____x days	☐ Doxycycline _____x days
☐ Moxifloxacin _____x days	☐ Moxifloxacin _____x days	☐ Moxifloxacin _____x days
☐ Minocycline _____x days	☐ Minocycline _____x days	☐ Minocycline _____x days
	☐ Other _____x days	

☐ Other _____x days		☐ Other _____x days
Response to initial therapy (check all that apply) ☐ Persistent symptoms (subjective only) ☐ Persistent symptoms (subjective) plus objective findings (e.g, discharge, +urine dip, elevated WBC) ☐ Positive NAAT post treatment	**Response to second therapy (check all that apply)** ☐ Resolution of symptoms ☐ Persistent symptoms (subjective only) ☐ Persistent symptoms (subjective & objective findings, e.g., discharge, +urine dip, elevated WBC) ☐ Positive NAAT post treatment	**Response to third therapy (check all that apply)** ☐ Resolution of symptoms ☐ Persistent symptoms (subjective only) ☐ Persistent symptoms (subjective and objective findings, e.g., discharge, +urine dip, elevated WBC) ☐ Positive NAAT post treatment
Date of 4th course treatment initiation ____/____/_____ ☐ Unknown	**Date of 5th course treatment initiation** ____/____/_____ ☐ Unknown	**Date of 6th course treatment initiation** ____/____/_____ ☐ Unknown
Fourth treatment prescribed (check all that apply), and dose/frequency/duration ☐ Azithromycin _____x days ☐ Doxycycline _____x days ☐ Moxifloxacin _____x days ☐ Minocycline _____x days ☐ Other _____x days	**Fifth treatment prescribed (check all that apply), and dose/frequency/duration** ☐ Azithromycin _____x days ☐ Doxycycline _____x days ☐ Moxifloxacin _____x days ☐ Minocycline _____x days ☐ Other _____x days	**Sixth treatment prescribed (check all that apply), and dose/frequency/duration** ☐ Azithromycin _____x days ☐ Doxycycline _____x days ☐ Moxifloxacin _____x days ☐ Minocycline _____x days ☐ Other _____x days
Response to fourth therapy (check all that apply) ☐ Resolution of symptoms ☐ Persistent symptoms (subjective only) ☐ Persistent symptoms (subjective and objective findings, e.g., discharge, +urine dip, elevated WBC) ☐ Positive NAAT post treatment	**Response to fifth therapy (check all that apply)** ☐ Resolution of symptoms ☐ Persistent symptoms (subjective only) ☐ Persistent symptoms (subjective and objective findings, e.g., discharge, +urine dip, elevated WBC) ☐ Positive NAAT post treatment	**Response to sixth therapy (check all that apply)** ☐ Resolution of symptoms ☐ Persistent symptoms (subjective only) ☐ Persistent symptoms (subjective and objective findings, e.g., discharge, +urine dip, elevated WBC) ☐ Positive NAAT post treatment

PARTNER TREATMENT

Does patient have a primary sexual partner? ☐☐Yes ☐ No ☐ Unknown

If yes, was the primary partner symptomatic? ☐☐Yes ☐ No ☐ Unknown

Was the primary partner treated? ☐☐Yes ☐ No ☐ Unknown

If yes, was the primary partner examined by you or another clinician prior to treatment? ☐☐Yes ☐ No ☐ Unknown

Partner treatment prescribed (check all that apply), and dose/frequency/duration ☐ Azithromycin _____x days ☐ Doxycycline _____x days ☐ Moxifloxacin _____x days ☐ Minocycline _____x days ☐ Other _____x days	**Partner response to therapy (Check all that apply)** ☐ Resolution of symptoms ☐ Persistent symptoms (subjective only) ☐ Persistent symptoms (subjective and objective findings, e.g., discharge, +urine dip, elevated WBC) ☐ Positive NAAT post treatment ☐ Unknown, partner not examined **If partner has persistent symptoms or NAAT following therapy, please complete a separate case report form for the partner.**

Notes: