

Sexually Transmitted Infections Caused by *Mycoplasma genitalium* and *Neisseria gonorrhoeae*: Diagnosis and Treatment

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ABSTRACT

Objective: To review the management of patients with *Mycoplasma genitalium* and *Neisseria gonorrhoeae* infections.

Methods: Review of the literature.

Results: *Mycoplasma genitalium* and *Neisseria gonorrhoeae* are organisms that cause urethritis, cervicitis, and pelvic inflammatory disease. There is increasing antibiotic resistance to both organisms, which poses significant challenges to clinicians. Additionally, diagnostic tests for *M. genitalium* are not widely available, and commonly used tests for both organisms do not provide antibiotic sensitivity information. The increasing resistance of both *M. genitalium* and *N. gonorrhoeae* to currently used antimicrobial agents is alarming and warrants cautious monitoring.

Conclusion: As the yield of new or effective antibiotic therapies has decreased over the past few years, increasing antibiotic resistance will lead to difficult treatment scenarios for sexually transmitted infections caused by these 2 organisms.

Keywords: *Mycoplasma genitalium*, *Neisseria gonorrhoeae*, antibiotic resistance, sexually transmitted infections, STIs.

The World Health Organization (WHO) estimates that more than 1 million cases of sexually transmitted Infections (STIs) are acquired every day worldwide,¹ and that the majority of STIs have few or no symptoms, making diagnosis difficult. Two organisms of interest are *Mycoplasma genitalium* and *Neisseria gonorrhoeae*. In contrast to *Chlamydia trachomatis*, which is rarely resistant to treatment regimens, *M. genitalium* and

N. gonorrhoeae are becoming increasingly resistant to antibiotic treatment and pose an impending threat. These bacteria can cause urethritis, cervicitis, and pelvic inflammatory disease (PID). Whereas antibiotic resistance to *M. genitalium* is emerging, resistance to *N. gonorrhoeae* has been a continual problem for decades. Drug resistance, especially for *N. gonorrhoeae*, is listed as a major threat to efforts to reduce the impact of STIs worldwide.² In 2013, the U.S. Centers for Disease Control and Prevention (CDC) classified *N. gonorrhoeae* drug resistance as an urgent threat.³ As the yield of new or effective antibiotic therapies has decreased over the past few years, increasing antibiotic resistance will lead to challenging treatment scenarios for STIs caused by these 2 organisms.

Epidemiology and Pathogenesis

M. genitalium

M. genitalium is an emerging pathogen that is an etiologic agent of upper and lower genital tract STIs, such as urethritis, cervicitis, and PID.⁴⁻¹³ In addition, it is thought to be involved in tubal infertility and acquisition of other sexually transmitted pathogens, including HIV.^{7,8,13} The prevalence of *M. genitalium* in the general U.S. population in 2016 was reported to be approximately 17.2% for males and 16.1% for females.¹⁴ Infections are more common in patients aged 30 years and younger than in older populations.¹⁵ Also, patients self-identifying as black were found to have a higher prevalence of *M. genitalium*.¹⁴ This organism was first reported as being isolated from the urethras of 2 men with non-gonococcal urethritis (NGU) in London in 1980.^{15,16} It is a significant cause of acute and chronic

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NGU in males, and is estimated to account for 6% to 50% of cases of NGU.^{17,18} *M. genitalium* in females has been associated with cervicitis^{4,9} and PID.^{8,10} A meta-analysis by Lis et al showed that *M. genitalium* infection was associated with an increased risk for preterm birth and spontaneous abortion.¹¹ In addition, *M. genitalium* infections occur frequently in HIV-positive patients.^{19,20} *M. genitalium* increases susceptibility for passage of HIV across the epithelium by reducing epithelial barrier integrity.¹⁹

Beta lactams are ineffective against *M. genitalium* because mycoplasmas lack a cell wall and thus cell wall penicillin-binding proteins.²¹ *M. genitalium*'s ability to invade host epithelial cells is another mechanism that can protect the bacteria from antibiotic exposure.²⁰ One of the first reports of antibiotic sensitivity testing for *M. genitalium*, published in 1997, noted that the organism was not susceptible to nalidixic acid, cephalosporins, penicillins, and rifampicin.²² In general, mycoplasmas are normally susceptible to antibiotics that inhibit protein synthesis,²³ and initial good sensitivity to doxycycline and erythromycin was noted but this has since decreased. New antibiotics are on the horizon, but they have not been extensively tested in vivo.²³

N. gonorrhoeae

Gonorrhea is the second most common STI of bacterial origin following *C. trachomatis*,²⁴⁻²⁶ which is rarely resistant to conventional regimens. In 2008, the World Health Organization (WHO) estimated that 106 million cases of *N. gonorrhoeae* infection were acquired annually and that 36.4 million adults were infected with *N. gonorrhoeae*.²⁷ In the United States, the CDC estimates that gonorrhea cases are under-reported. An estimated 800,000 or more new cases are reported per year.²⁸

The most common clinical presentations are urethritis in men and cervicitis in women.²⁹ While urethritis is most likely to be symptomatic, only 50% of women with acute gonorrhea are symptomatic.²⁹ In addition to lower urogenital tract infection, *N. gonorrhoeae* can also cause PID, ectopic pregnancy, infertility in women, and epididymitis in men.^{29,30} Rare complications can develop from the spread of *N. gonorrhoeae* to other parts of the body including the joints, eyes, cardiovascular system, and skin.²⁹

N. gonorrhoeae can attach to the columnar epithelium

and causes host innate immune-driven inflammation with neutrophil influx.²⁹ It can avoid the immune response by varying its outer membrane protein expression. The organism is also able to acquire DNA from other *Neisseria* species³⁰ and genera, which results in reduced susceptibility to therapies.

The Gonococcal Isolate Surveillance Project (GISP), established in 1986, is a collaborative project involving the CDC and STI clinics in 26 cities in the United States along with 5 regional laboratories.³¹ The GISP monitors susceptibilities in *N. gonorrhoeae* isolates obtained from roughly 6000 symptomatic men each year.³¹ Data collected from the GISP allows clinicians to treat infections with the correct antibiotic. Just as they observed patterns of fluoroquinolone-resistant *N. gonorrhoeae*, there has been a geographic progression of decreasing susceptibility to cephalosporins in recent years.³¹

The ease with which *N. gonorrhoeae* can develop resistance is particularly alarming. Sulfonamide use began in the 1930s, but resistance developed within approximately 10 years.^{30,32} *N. gonorrhoeae* has acquired resistance to each therapeutic agent used for treatment over the course of its lifetime. One hypothesis is that use of single-dose therapy to rapidly treat the infection has led to treatment failure and allows for selective pressure where organisms with decreased antibiotic susceptibility are more likely to survive.³⁰ However, there is limited evidence to support monotherapy versus combination therapy in treating *N. gonorrhoeae*.^{33,34} It is no exaggeration to say gonorrhea is now at risk of becoming an untreatable disease because of the rapid emergence of multidrug resistant *N. gonorrhoeae* strains worldwide.³⁵

Diagnosis

Whether the urethritis, cervicitis, or PID is caused by *N. gonorrhoeae*, *M. genitalium*, or other non-gonococcal microorganisms (eg, *C. trachomatis*), no symptoms are specific to any of the microorganisms. Therefore, clinicians rely on laboratory tests to diagnose STIs caused by *N. gonorrhoeae* or *M. genitalium*.

M. genitalium

Gram Stain. Because *M. genitalium* lacks a cell wall, it cannot be identified by routine Gram stain.

Culture. Culturing of this fastidious bacterium might offer the advantage of assessing antibiotic susceptibility;³⁶ however, the procedure is labor intensive and time consuming, and only a few labs in the world have the capability to perform this culture.¹² Thus, this testing method is primarily undertaken for research purposes.

Serological Testing. Because of serologic cross-reactions between *Mycoplasma pneumoniae* and *M. genitalium*, there are no standardized serological tests for *M. genitalium*.³⁷

Nucleic Acid Amplification Tests. *M. genitalium* diagnosis currently is made based exclusively on nucleic acid amplification testing (NAAT) methodology (polymerase chain reaction [PCR] or transcription-mediated amplification [TMA]), which is the only clinically useful method to detect *M. genitalium*. TMA for *M. genitalium* is commercially available in an analyte-specific reagent (ASR) format, but this has not been approved by the Food and Drug Administration (FDA).³⁸ A study analyzing urogenital specimens from female patients via this TMA product found a 98.7% true-positive result when confirmed with repeat testing or alternative-target TMA, and only a 0.5% false-negative rate.³⁸ There is evidence that this TMA product can be used to identify *M. genitalium* in urine, stool, and pharyngeal samples.³⁹ These assays are currently available in some reference labs and large medical centers but are not widely available. **Table 1** summarizes the diagnostic methods for *M. genitalium*.

N. gonorrhoeae

Gonococcal infection can involve the urogenital tract, but can also be extra-urogenital. The method of diagnoses of urogenital infections has expanded from Gram stain of urethral or cervical discharge and the use of selective media culture (usually Thayer-Martin media)⁴⁰ to molecular methods such as NAATs, which have a higher sensitivity than cultures.^{41,42}

Gram Stain. A Gram stain that shows polymorphonuclear leukocytes with intracellular gram-negative diplococci can be considered diagnostic for *N. gonorrhoeae* urethritis infection in symptomatic men when samples are obtained from the urethra.⁴³ A retrospective study of 1148 women with gonorrhea revealed that of 1049 cases of cervical gonorrhea, only 6.4% were positive by smear

alone; and of 841 cases of urethral gonorrhea, only 5.1% were positive by smear alone; therefore, other diagnostic methods are generally preferred in women.⁴⁴ Because Gram stain of vaginal specimens is positive in only 50% to 60% of females, its use in women and in suspected extragenital gonococcal infections is not recommended.⁴³⁻⁴⁵ When Gram stain was performed in asymptomatic men, the sensitivity was around 80%.³⁹ Thus, in asymptomatic men with a high pre-test probability of having the infection, the use of other additional testing would increase the rate of detection.⁴³

Culture. Urethral swab specimens from males with symptomatic urethritis and cervical swab samples from females with endocervical infection must be inoculated onto both a selective medium (eg, modified Thayer-Martin medium or Martin Lewis medium) and a nonselective medium (eg, chocolate agar). A selective medium is used because it can suppress the growth of contaminating organisms, and a nonselective medium is used because some strains of *N. gonorrhoeae* are inhibited by the vancomycin present in the selective medium.⁴⁰ Specimens collected from sterile sites, such as blood, synovial fluid, and cerebrospinal fluid, should be streaked on nonselective medium such as chocolate agar. The material used for collection is critical; the preferred swabs should have plastic or wire shafts and rayon, Dacron, or calcium alginate tips. Materials such as wooden shafts or cotton tips can be toxic to *N. gonorrhoeae*.⁴⁰ The specimen should be inoculated immediately onto the appropriate medium and transported rapidly to the laboratory, where it should be incubated at 35° to 37°C with 5% CO₂ and examined at 24 and 48 hours post collection.⁴⁰ If the specimens cannot be inoculated immediately onto the appropriate medium, the specimen swab should be delivered to the lab in a special transport system that can keep the *N. gonorrhoeae* viable for up to 48 hours at room temperature.⁴⁶

The following specimen collection techniques are recommended by the CDC:⁴⁰

- In males, the cotton swab should be inserted about 2 to 3 cm into the urethral meatus and rotated 360° degrees 2 or 3 times.
- In females, collection of cervical specimens requires inserting the tip of the swab 1 to 2 centimeters into the cervical os and rotating 360° 2 or 3 times.

Table 1. **Test Methods for Diagnosis of *Mycoplasma genitalium* Infection**

Method	Characteristics
Gram stain	Cannot be identified by routine Gram stain
Culture	Isolation possible but the procedure is slow and labor intensive
Serological testing	No serological tests available for <i>M. genitalium</i>
Nucleic acid amplification tests	Only useful method, but not widely available

- Samples obtained outside of the urogenital tract: rectal specimens may be obtained by inserting the swab 3 to 4 cm into the rectal vault. Pharyngeal specimens are to be obtained from the posterior pharynx with a swab.

Culture tests allow the clinician to assess antimicrobial susceptibility and are relatively low cost when compared with nucleic acid detection tests. The sensitivity of culture ranges from 72% to 95% for symptomatic patients, but drops to 65% to 85% for asymptomatic patients.⁴⁵⁻⁴⁷ This low sensitivity is a major disadvantage of culture tests when compared to NAATs. Other disadvantages are the need for the specimens to be transported under conditions adequate to maintain the viability of organisms and the fact that 24 to 72 hours is required to report presumptive culture results.⁴² Antimicrobial sensitivity testing generally is not recommended; however, it is advisable to perform antimicrobial sensitivity in cases of treatment failure or disseminated gonococcal infection.¹²

Nucleic Acid Amplification Tests. NAATs use techniques that allow the amplification and detection of *N. gonorrhoeae* DNA or RNA sequences through various methods, which include assays such as PCR (eg, Amplicor; Roche, Nutley, NJ), TMA (eg, APTIMA; Gen-Probe, San Diego, CA), and strand-displacement amplification (SDA; Probe-Tec; Becton Dickinson, Franklin Lake, NJ). While PCR and SDA methods amplify bacterial DNA, TMA amplifies bacterial rRNA.⁴¹

The FDA has cleared NAATs to test endocervical, vaginal, and urethral (men) swab specimens and urine for both men and women. There are several NAATs available to test rectal, oropharyngeal, and conjunctival specimens; however, none of them are FDA-cleared. Some local and commercial laboratories have validated the

reliability of these extra-urogenital NAATs.^{12,48} Compared to cultures, NAATs have the advantages of being more sensitive and requiring less strict collection and transport conditions. However, they are costlier than cultures, do not provide any antimicrobial susceptibility information, and have varying specificity.^{49,50}

Rapid Tests. NAAT results are usually available in approximately 1 to 2 days, so there has been significant interest in creating technologies that would allow for a more rapid turnaround time. The GeneXpert CT/NG is a newly developed real-time PCR-based assay that can simultaneously detect *C. trachomatis* and *N. gonorrhoeae*. The advantage of this technique is the 90-minute turnaround time and its ability to process more than 90 samples at a time. The specificity of this test for *N. gonorrhoeae* is similar to that of other NAATs (> 99.3%), suggesting that cross-reactivity is not a significant problem.⁵¹ **Table 2** summarizes the test methods used for diagnosing *N. gonorrhoeae*.

Treatment

M. genitalium

M. genitalium, *Mycoplasma hominis*, and the ureaplasmas (*U. urealyticum* and *U. parvum*) are generally transmitted sexually, and the natural habitat of this Mycoplasmataceae family of bacteria is the genitourinary tract. All the mycoplasmas can cause NGU, cervicitis, and PID. Presently, multiple-drug resistant *M. hominis* and ureaplasmas remain uncommon, but the prevalence of *M. genitalium* resistant to multiple antibiotics has increased significantly in recent years.^{23,52}

In the 1990s, *M. genitalium* was highly sensitive to the tetracyclines in vitro,⁵³ and doxycycline was the drug of choice for treating NGU. However, it later became ap-

Table 2. Test Methods for Diagnosis of *Neisseria gonorrhoeae* Infection

Method	Characteristics
Gram stain	Diagnostic tool for the evaluation of urethritis in symptomatic men; not recommended for use in women
Culture	Offers the advantage of assessing antibiotic susceptibilities High sensitivity and specificity Lower cost compared with DNA amplification techniques
Nucleic acid amplification tests (NAATs)	Supported by the Centers for Disease Control and Prevention Preferred diagnostic method Most sensitive and specific tests available to screen for gonorrhea
Rapid test	
GeneXpert CT/NG assay	Newly developed real-time PCR-based assay Results available in approximately 90 minutes Specificity similar to that of other NAATs in other published studies (> 99.3%) Can simultaneously detect <i>C. trachomatis</i> and <i>N. gonorrhoeae</i>

parent that doxycycline was largely ineffective in treating urethritis caused by *M. genitalium*.^{54,55}

Subsequently, azithromycin, a macrolide, became popular in treating urethritis in males and cervicitis in females because it was highly active against *C. trachomatis*⁵⁴ and *M. genitalium*⁵⁶ and it can be given orally as a single 1-g dose, thus increasing patients' compliance. However, azithromycin-resistant *M. genitalium* has rapidly emerged and rates of treatment failure with azithromycin as high as 40% have been reported in recent studies.^{57,58} The resistance was found to be mediated by mutations in the 23S rRNA gene upon exposure of *M. genitalium* to azithromycin.^{15,57-59} Multiple studies conducted in various countries (including the United States, Netherlands, England, and France) all found high rates of 23S rRNA gene mutations.^{15,57-59} *M. genitalium* samples were analyzed using reverse transcription-PCR and Sanger sequencing of the 23S rRNA to assess rates of macrolide resistance markers. The study found that 50.8% of female participants and 42% of male participants harbored mutations indicating macrolide resistance.¹⁵

An in vitro study conducted in France showed that the respiratory fluoroquinolone moxifloxacin was highly active against mycoplasmas, including *M. genitalium*.⁶⁰

This study and others led to the use of moxifloxacin in treating infections caused by azithromycin-resistant *M. genitalium*. Moxifloxacin initially was successful in treating previous treatment failure cases.⁶¹ Unfortunately, the success has been short-lived, as researchers from Japan and Australia have reported moxifloxacin treatment failures.⁶²⁻⁶⁴ These treatment failures were related to mutations in the *parC* and *gyrA* genes.⁶²

Because *M. genitalium* exhibits significantly increased resistance to the tetracyclines, macrolides, and fluoroquinolones, leading to treatment failures associated with the resistance, the recently published CDC sexually transmitted diseases guidelines (2015) do not specifically recommend or endorse one class of antibiotics over another to treat *M. genitalium* infections; this contrasts with their approach for other infections in which they make specific recommendations for treatment.¹² The lack of clear recommendations from the CDC makes standardized treatment for this pathogen difficult. The CDC guidelines do identify *M. genitalium* as an emerging issue, and mention that a single 1-g dose of azithromycin should likely be recommended over doxycycline due to the low cure rate of 31% seen with doxycycline. Moxifloxacin is mentioned as a possible alternative, but it is noted that

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the medication has not been evaluated in clinical trials and several studies have shown failures.¹²

Although the existing antibiotics to treat *M. genitalium* infections are far from desirable, treatment approaches have been recommended:⁶⁵

- Azithromycin or doxycycline should be considered for empiric treatment without documented *M. genitalium* infection.
- Azithromycin is suggested as the first choice in documented *M. genitalium* infections.
- In patients with urethritis, azithromycin is recommended over doxycycline based on multiple studies. A single 1-g dose of azithromycin is preferred to an extended regimen due to increased compliance despite the extended regimen being slightly superior in effectiveness. The single-dose regimen is associated with selection of macrolide-resistant strains.⁶⁵
- Women with cervicitis and PID with documented *M. genitalium* infection should receive an azithromycin-containing regimen.

Although the existing antibiotics on the market could not keep up with the rapid mutations of *M. genitalium*, a few recent studies have provided a glimmer of hope to tackle this wily microorganism. Two recent studies from Japan demonstrated that sitafloxacin, a novel fluoroquinolone, administered 100 mg twice a day to patients with *M. genitalium* was superior to other older fluoroquinolones.^{66,67} This fluoroquinolone could turn out to be a promising first-line antibiotic for treatment of STIs caused by *M. genitalium*. Bissessor and colleagues conducted a prospective cohort study of *M. genitalium*-infected male and female patients attending a STI clinic in Melbourne, Australia, and found that oral pristinamycin is highly effective in treating the *M. genitalium* strains that are resistant to azithromycin and moxifloxacin.⁶⁸ Jensen et al reported on the novel fluoroketolide solithromycin, which demonstrated superior in vitro activity against *M. genitalium* compared with doxycycline, fluoroquinolones, and other macrolides.⁶⁹ Solithromycin could potentially become a new antibiotic to treat infection caused by multi-drug resistant *M. genitalium*.

N. gonorrhoeae

Because of increasing resistance of *N. gonorrhoeae* to fluoroquinolones in the United States, the CDC recom-

mended against their routine use for all cases of gonorrhea in August 2007.⁷⁰ In some countries, penicillin-, tetracycline-, and ciprofloxacin-resistance rates could be as high as 100%, and these antibacterial agents are no longer treatment options for gonorrhea. The WHO released new *N. gonorrhoeae* treatment guidelines in 2016 due to high-level of resistance to previously recommended fluoroquinolones and decreased susceptibility to the third-generation cephalosporins, which were a first-line recommendation in the 2003 guidelines.⁴⁵ The CDC's currently recommended regimens for the treatment of uncomplicated and disseminated gonorrheal infections are summarized in **Table 3** and **Table 4**.¹² Recommendations from the WHO guidelines are very similar to the CDC recommendations.⁴⁵

In light of the increasing resistance of *N. gonorrhoeae* to cephalosporins, 1 g of oral azithromycin should be added to ceftriaxone 250 mg intramuscularly in treating all cases of gonorrhea. The rationale for adding azithromycin to ceftriaxone is that azithromycin is active against *N. gonorrhoeae* at a different molecular target at a high dose, and it can also cover other co-pathogens.⁷¹ Unfortunately, susceptibility to cephalosporins has been decreasing rapidly.⁷² The greatest concern is the potential worldwide spread of the strain isolated in Kyoto, Japan, in 2009 from a patient with pharyngeal gonorrhea that was highly resistant to ceftriaxone (minimum inhibitory concentration of 2.0 to 4.0 µg/mL).⁷³ At this time, *N. gonorrhoeae* isolates that are highly resistant to ceftriaxone are still rare globally.

Although cefixime is listed as an alternative treatment if ceftriaxone is not available, the 2015 CDC gonorrhea treatment guidelines note that *N. gonorrhoeae* is becoming more resistant to this oral third-generation cephalosporin; this increasing resistance is due in part to the genetic exchange between *N. gonorrhoeae* and other oral commensals actively taking place in the oral cavity, creating more resistant species. Another possible reason for cefixime resistance is that the concentration of cefixime used in treating gonococcal pharyngeal infection is subtherapeutic.⁷⁴ A recent randomized multicenter trial in the United States compared 2 non-cephalosporin regimens: a single 240-mg dose of intramuscular gentamicin plus a single 2-g dose of

Table 3. CDC Recommended Regimens for Treatment of Uncomplicated Gonococcal Infections

Condition	Recommended Regimen	Alternative Regimen
Cervix, urethra, and rectum infection	Ceftriaxone 250 mg IM in a single dose plus azithromycin 1 g orally in a single dose	Cefixime 400 mg orally in a single dose plus azithromycin 1 g orally in a single dose
Pharyngitis	Ceftriaxone 250 mg IM in a single dose plus azithromycin 1 g orally in a single dose	
Conjunctivitis	Ceftriaxone 1 g IM in a single dose plus azithromycin 1 g orally in a single dose	

IM, intramuscularly; IV, intravenously.

Table 4. CDC Recommended Regimens for Treatment of Disseminated Gonococcal Infections

Condition	Recommended Regimen	Alternative Regimen
Arthritis and arthritis-dermatitis syndrome ^a	Ceftriaxone 1 g IM or IV every 24 hours plus azithromycin 1 g orally in a single dose	Cefotaxime 1 g IV every 8 hours or ceftizoxime 1 g IV every 8 hours plus azithromycin 1 g orally in a single dose
Meningitis and endocarditis ^b	Ceftriaxone 1–2 g IV every 12–24 hours plus azithromycin 1 g orally in a single dose	

IM, intramuscularly; IV, intravenously.

^aWhen treating for the arthritis-dermatitis syndrome, the provider can switch to an oral agent guided by antimicrobial susceptibility testing 24 to 48 hours after substantial clinical improvement, for a total treatment course of at least 7 days.

^bTherapy for meningitis should be continued with recommended parenteral therapy for 10 to 14 days. Parenteral antimicrobial therapy for endocarditis should be administered for at least 4 weeks.

oral azithromycin, and a single 320-mg dose of oral gemifloxacin plus a single 2-g dose of oral azithromycin. These combinations achieved 100% and 99.5% microbiological cure rates, respectively, in 401 patients with urogenital gonorrhea.⁷⁵ Thus, these combination regimens can be considered as alternatives when the *N. gonorrhoeae* is resistant to cephalosporins or the patient is intolerant or allergic to cephalosporins.

Because *N. gonorrhoeae* has evolved into a “superbug,” becoming resistant to all currently available antimicrobial agents, it is important to focus on developing new agents with unique mechanisms of action to treat *N. gonorrhoeae*-related infections. Zoliflodacin (ETX0914), a novel topoisomerase II inhibitor, has the potential to become an effective agent to treat multi-drug resistant *N. gonorrhoeae*. A recent phase 2 trial demonstrated that a single oral 2000-mg dose of zoliflodacin microbiologically cleared 98% of gonorrhea

patients, and some of the trial participants were infected with ciprofloxacin- or azithromycin-resistant strains.⁷⁶ An additional phase 2 clinical trial compared oral zoliflodacin and intramuscular ceftriaxone. For uncomplicated urogenital infections, 96% of patients in the zoliflodacin group achieved microbiologic cure versus 100% in the ceftriaxone group; however, zoliflodacin was less efficacious for pharyngeal infections.⁷⁷ Gepotidacin (GSK2140944) is another new antimicrobial agent in the pipeline that looks promising. It is a novel first-in-class triazaacenaphthylene that inhibits bacterial DNA replication. A recent phase 2 clinical trial demonstrated that 1.5-g and 3-g single oral doses eradicated urogenital *N. gonorrhoeae* with microbiological success rates of 97% and 95%, respectively.⁷⁸

Test of Cure

Because of the decreasing susceptibility of *M. genitali-*

um and *N. gonorrhoeae* to recommended treatment regimens, the European Guidelines consider test of cure essential in STIs caused by these 2 organisms to ensure eradication of infection and identify emerging resistance.⁷⁹ However, test of cure is not routinely recommended by the CDC for these organisms in asymptomatic patients.¹²

Sexual Risk-Reduction Counseling

Besides aggressive treatment with appropriate antimicrobial agents, it is also essential that patients and their partners receive counseling to reduce the risk of STI. A recently published systematic review demonstrated that high-intensity counseling could decrease STI incidents in adolescents and adults.⁸⁰

Conclusion

It is clear that these 2 sexually transmitted "superbugs" are increasingly resistant to antibiotics and pose an increasing threat. Future epidemiological research and drug development studies need to be devoted to these 2 organisms, as well as to the potential development of a vaccine. This is especially important considering that antimicrobials may no longer be recommended when the prevalence of resistance to a particular antimicrobial reaches 5%, as is the case with WHO and other agencies that set the standard of $\geq 95\%$ effectiveness for an antimicrobial to be considered as a recommended treatment.³² With current resistance rates for penicillin, ciprofloxacin, and tetracycline at close to 100% for *N. gonorrhoeae* in some countries,^{30,79} it is important to remain cognizant about current and future treatment options.

Because screening methods for *M. genitalium* are not available in most countries and there is not an FDA-approved screening method in the United States, *M. genitalium* poses a significant challenge for clinicians treating urethritis, cervicitis, and PID. Thus, the development of an effective screening method and established screening guidelines for *M. genitalium* is urgently needed. Better surveillance, prudent use of available antibiotics, and development of novel compounds are necessary to eliminate the impending threat caused by *M. genitalium* and *N. gonorrhoeae*.

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