The Management of Gonorrhea in the Era of Emerging Antimicrobial Resistance

What Primary Care Clinicians Should Know

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KEYWORDS

- *Neisseria gonorrhoeae* • Gonorrhea • Sexually transmitted infections
- Antimicrobial resistance

KEY POINTS

- *Neisseria gonorrhoeae*'s ability to develop resistance to antimicrobials remains a challenge.
- Nucleic acid amplification tests are considered the preferred test for the detection of *N. gonorrhoeae*; however, culture is the only modality that allows for comprehensive antimicrobial susceptibility testing.
- The recommended treatment for uncomplicated gonorrhea in adults and adolescents at all anatomic sites is ceftriaxone 500 mg intramuscular once as it is the only remaining highly effective single-dose regimen; thus, a reported beta-lactam allergy should prompt a review to determine whether a true allergy is present.
- Test of cure is recommended for everyone diagnosed with pharyngeal gonorrhea.
- Clinicians should work with local and state partners to manage suspected gonorrhea treatment failure cases.

BACKGROUND

Gonorrhea is caused by *Neisseria gonorrhoeae*, a gram-negative diplococcus. The bacterium, a strictly human pathogen transmitted primarily by sexual contact, causes both symptomatic and asymptomatic infections. Asymptomatic infections can contribute to delays in medical care, onward transmission in a community, and

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complications such as pelvic inflammatory disease (PID). Gonorrhea is a public heath challenge, particularly due to the organism's ability to develop antimicrobial resistance. Current control methods rely on prevention, timely diagnosis, and appropriate treatment.

Epidemiology

Gonorrhea is the second most commonly reported bacterial infection in the United States (US) with 710,151 cases reported to the Centers for Disease Control and Prevention (CDC) in 2021.[1] After decades of declining gonorrhea rates, the early 2000s initiated a reverse in trends with continuously increasing rates. However, the true incidence of disease is uncertain due to underdiagnosis and under reporting. It is estimated that 1.6 million incident gonococcal infections occur in the US annually and 82.3 million occur globally.[2,3]

Gonorrhea epidemiology highlights major health disparities in the US, mostly attributed to environmental factors, limited resources, and unequal access to health care.[4] Differences appear by age, gender, geographic region, race, and sexual orientation. Overall, gonorrhea is more common in men than in women and is highest in both men and women aged 20 to 24 years.[1] The US South region and non-Hispanic Black or African American persons have the highest reported case rates. Additionally, test positivity for gonorrhea was highest among gay, bisexual, and other men who have sex with men (MSM) at 22.7%, followed by men who have sex with women only (MSW) at 12.2%, and women at 5.9%.[1]

Antimicrobial Resistance in Gonorrhea

Neisseria gonorrhoeae's ability to develop resistance to antimicrobials has been a persistent challenge since the early 20th century.[5] Sulfonamides were introduced in the late 1930s and by the 1940s resistance to high doses of sulfonamides was widespread. In the 1940s and 1950s, penicillins, aminoglycosides, and macrolides were introduced, with penicillins becoming the preferred treatment. Despite early resistance development, penicillin was able to be used for gonorrhea treatment for over 40 years due to its safety and tolerability allowing gradual increases of curative dosing until the 1980s. Tetracyclines, introduced in the 1960s, were used as an alternative to penicillin until resistance became widespread in the 1980s.

Newer antimicrobials like cephalosporins and fluoroquinolones were introduced in the 1980s. By the 1990s, resistance to fluoroquinolones began to appear and quickly spread across the US in the early 2000s. Third-generation cephalosporins were left as the drugs of choice for gonococcal treatment.[5] Because of signs of developing resistance to cefixime and reported treatment failures in 2010, cefixime was removed as a recommended regimen,[6] and rising rates of azithromycin with elevated minimum inhibitory concentrations (MICs) led to the drugs removal as an alternative treatment in 2015, and as a co-therapy in 2020.[7] Now, ceftriaxone, the injectable third-generation cephalosporin, is the last remaining highly effective single-dose drug available for empiric single-dose gonorrhea treatment. *Neisseria gonorrhoeae*'s constant adaptation to different antimicrobials has required regular updates to national gonorrhea treatment recommendations to maintain effective treatment options.

Clinical Manifestations and Transmission

Neisseria gonorrhoeae initially infects non-cornified epithelium, the mucous membranes, of the urogenital tract, the rectum, the oropharynx, and conjunctivae. In some cases, the organism can cross into the blood stream from these mucosal sites and cause a disseminated infection (**Table 1**).

Urogenital Infection

Gonorrhea is associated with urogenital clinical syndromes including urethritis, epididymitis, cervicitis, and PID. However, a high proportion of persons with urogenital gonorrhea may be asymptomatic; up to 70% of women with cervical infections may not present with symptoms.[8] The relative proportion of urethral infection that remains asymptomatic is somewhat unclear. Clinic-based studies suggest that urethral gonorrhea is primarily a symptomatic infection,[9,10] but some population-based studies estimate that up to 60% of men with urethral gonorrhea may be asymptomatic or present only with mild symptoms.[11,12] Epididymitis is the most common local complication of gonococcal urethritis, though the frequency of urethral infection progression to epididymitis in the modern era of antimicrobial therapy remains unknown.[13] PID has been estimated to occur in 10% to 20% of those with untreated cervical gonorrhea.[14,15]

Rectal Infection

Although rectal gonococcal infections have been associated with receptive anal intercourse, they can be detected in the absence of reported rectal sexual exposure. In a systemic review of extragenital gonorrhea, the prevalence of rectal infection among MSM was estimated to be 6% (median; range 0.2%–24%) compared with 3% (median; range 0%–5.7%) among MSW and 2% (median; range 0.6%–36%) among women.[16] In women, anorectal gonorrhea may be acquired through autoinoculation in the absence of receptive anal intercourse. Among men who report no receptive anal intercourse the route of transmission is unclear, but may be due to analingus.[17] Gonococcal infections at the rectum are typically asymptomatic, though proctitis may occur.[18]

Pharyngeal Infection

The pharynx is a common site of gonococcal infection and is typically asymptomatic. The prevalence of pharyngeal gonorrhea, among MSM, has been found to be greater than 10%, and among women and heterosexual men, 2% to 10%.[16,19] Additionally, among heterosexual contacts to gonorrhea, approximately 20% to 50% test positive at the throat.[20,21] Pharyngeal gonorrhea is thought to be acquired primarily via oral-genital contact, though some literature suggests kissing could be a primary transmission mode.[22]

Conjunctival Infection

Historically, gonococcal conjunctivitis was a disease of infants due to acquisition from untreated mothers during birth; however, it can also occur in adults and adolescents as a result of autoinoculation from an anogenital infection. Person-to-person nonsexual contact, fomites, and vectors have been reported in outbreaks of gonococcal conjunctivitis.[23,24] Gonococcal conjunctivitis in infants (ie, ophthalmia neonatorum) has been a rare event in the modern era due to routine prophylaxis with antibiotic eye ointment application to infants at birth.[25]

Disseminated Gonococcal Infection

Historically, disseminated gonococcal infection (DGI) has been rare, occurring in 0.5% to 3% of untreated gonococcal infections[26]; however, as rates of gonorrhea continue to increase, clinicians may see rare gonococcal clinical presentations more frequently. Clinical manifestations of DGI include skin lesions, tenosynovitis, asymmetric polyarthralgia, septic arthritis, and, on rare occasions, endocarditis, meningitis, or osteomyelitis. Since 2019, DGI clusters and increases in DGI cases have been reported in some US states, Manitoba, Canada, and England.[27–30] Among 274 DGI cases

Table 1
Clinical syndromes and infections caused by *Neisseria gonorrhoeae*

Anatomic Site of Infection	Associated Syndrome	Signs and Symptoms	Complications	Comments
Male urogenital infections				
Urethra	Urethritis	Copious urethral discharge, purulent or mucopurulent in color; dysuria	Periurethral abscesses, penile edema, penile lymphangitis, prostatitis	Discharge may not be distinguishable on examination from the discharge seen in nongonococcal urethritis
Epididymis	Epididymitis	Unilateral testicular pain, testicular swelling, dysuria	Abscess, testicular infarction, decreased fertility	N/A
Female urogenital infections				
Cervix	Cervicitis Or Asymptomatic	Mucopurulent discharge, vaginal pruritus, menorrhagia, bleeding in between menstrual cycles; friable cervical mucosa and frank discharge on physical examination	Pelvic inflammatory disease, chronic pelvic pain, ectopic pregnancy	A normal-appearing cervix does not rule out presence of gonococcal cervicitis
Upper reproductive tract (uterus, ovaries, fallopian tubes)	Pelvic inflammatory disease	Pelvic/abdominal pain, dyspareunia, and abnormal vaginal bleeding; physical examination findings may include abdominal tenderness, uterine tenderness, and adnexal or cervical motion tenderness	Infertility, chronic pelvic pain, ectopic pregnancy	Signs and symptoms are not specific to gonococcal-related PID

All genders				
Rectum	Proctitis Or Asymptomatic	Anorectal bleeding, anorectal pain, tenesmus, constipation, rectal fullness or incomplete defecation, and mucopurulent discharge	Stricture or stenosis, fistulas	N/A
Pharynx	Pharyngitis Or Asymptomatic	Pharyngeal erythema and pain; pharyngeal exudates, cervical lymphadenitis	N/A	N/A
Conjunctiva	Conjunctivitis	Range of severity from conjunctival injection to severe mucopurulent discharge, periorbital edema	Uveitis, severe keratitis; corneal ulceration, perforation, and blindness if left untreated	N/A
Other	Disseminated gonococcal infection	Fevers, chills, malaise, skin lesions (typically described as pustular or vesicopustular, though can be hemorrhagic macules, papules, bullae, and nodules), polyarthralgias, tenosynovitis, arthritis, synovial effusion	Septic arthritis, osteomyelitis; meningitis; endocarditis, can result in significant valvular dysfunction and heart failure	Persons with DGI are often asymptomatic at the mucosal site of infection (urogenital, pharyngeal, and/or rectal site) at the time of clinical presentation

voluntarily reported in the US to CDC between 2020 and 2022, 85.8% required hospitalization, 41.2% underwent related surgeries, and 2.2% died.[31] DGI cases are often asymptomatic at the mucosal site of infection (urogenital, pharyngeal, and/or rectal site) at the time of presentation[32]; thus, clinicians should maintain a high degree of suspicion for patients presenting with signs and symptoms of DGI.

PREVENTION AND CONTROL STRATEGIES

Since the 1970s, gonorrhea prevention and control has relied on screening asymptomatic persons and treating sex partners. Now, 2 novel biomedical prevention strategies are on the horizon—post-exposure prophylaxis (PEP) with doxycycline and a vaccine (See "Novel Approaches and Advances in STI Treatment and Prevention").

Gonorrhea Screening

Given the high proportion of asymptomatic gonorrhea, screening is an important tool for identifying individuals with gonorrhea and providing treatment and other management strategies to reduce the risk of complications and decrease transmission in the community. Recommendations and considerations for gonorrhea screening vary by population, age, and sexual behavior and are published by US Preventive Services Task Force, the CDC, and the HIV Medicine Association of the Infectious Diseases Society of America (See "A Practical Approach to STI Screening for the Primary Care Clinician").

Post-Exposure Prophylaxis with Doxycycline

Randomized controlled trials have evaluated the use of doxycycline taken within 72 hours after sexual activity for the prevention of bacterial sexually transmitted infections (STIs) (ie, chlamydia, gonorrhea, and syphilis), an intervention known as STI PEP.[33] There is concern, however, that early reductions in incident gonorrhea will be followed by major increases in antimicrobial resistance rendering the intervention ineffective for gonorrhea within 10 to 20 years.[34] Additionally, 2 groups have demonstrated that selection for tetracycline resistance also selects for resistance in other antimicrobials which may have more widespread effects on gonorrhea antimicrobial resistance.[35,36]

Vaccination

Gonococcal vaccine research efforts were renewed by the possible protective effects of group B outer membrane vesicle (OMV) meningococcal (MenB) vaccines. In 2017, New Zealand reported a decline in gonorrhea after the large-scale distribution of their meningococcal (MeNZB) vaccine, with an estimated vaccine efficacy of 31%.[37] Other studies using different MenB vaccines have also demonstrated reductions in gonorrhea.[38] Although the MenB vaccine used in New Zealand no longer exists, the 4CMenB, Bexsero (GlaxoSmithKline, UK), vaccine has the same OMV components as the MeNZB vaccine. The impact of meningococcal vaccines on gonococcal infections is promising, but results from additional studies are needed to determine vaccine efficacy and duration of protection.

CLINICAL MANAGEMENT

Gonorrhea Diagnosis

Persons at risk for or suspected of having gonorrhea based on symptoms should undergo evaluation and testing to confirm the microbiologic diagnosis, ensure

appropriate treatment, and further management.[39] Diagnostic tests to identify gonorrhea include microscopy, nucleic acid amplification tests (NAAT), and culture; each type has benefits and limitations under different scenarios due to differences in test performance, characteristics, and result turnaround time.

Microscopy

Although not routinely used in current practice, microscopy with Gram stain is a point-of-care (POC) test that can be used with male urethral swabs to differentiate gonococcal urethritis from urethritis due to other pathogens (ie, non-gonococcal urethritis). Gram stain of a male urethral specimen with polymorphonuclear leukocytes with intracellular gram-negative diplococci is highly specific (>95%) and can be considered diagnostic for gonorrhea.[40] Gram stain microscopy is not a reliable tool for diagnosis at any other anatomic sites because of low specificity due to possible presence of other nonpathogenic gram-negative diplococci.[41]

Nucleic Acid Amplification Tests

NAAT are the preferred test for the detection of gonorrhea in patients with or without symptoms given their high sensitivity and specificity and relatively fast turnaround time. NAAT manufacturer product inserts should be reviewed carefully since approved specimen types (eg, urine, urethral, vaginal, cervical) and collection methods, as well as performance, vary by test manufacturer.[39] Two NAAT have been cleared by US Food and Drug Administration (FDA) for detection of gonorrhea and chlamydia from rectal and oropharyngeal samples—Xpert CT/GC Assay (Cepheid, Sunnyvale, CA, USA) and Aptima Combo 2 Assay (Hologic, San Diego, CA, USA), though NAAT from other manufacturers can be used for extragenital specimen collection following laboratory validation. One of the benefits of NAAT is their shelf-stability and ease of use which allow patients to self-collect samples. Patient-collected specimens can be considered for testing outside of clinical spaces.[42]

Point-of-Care Nucleic Acid Amplification Tests

The FDA recently cleared a few near-patient and rapid POC NAAT for the detection of gonorrhea.[43] POC tests allow patients to receive test results and treatment during the same clinic visit. When implemented in places without microscopy or for persons with known sexual exposure to gonorrhea, POC NAAT has the potential to reduce the widespread use of empiric antimicrobials. At present, all gonorrhea POC NAAT are cleared only for urogenital specimens. The GeneXpert assay (Cepheid, Sunnyvale, CA, USA) demonstrated high sensitivity and specificity (95.6%–100% and 99.9%–100%, respectively) for the detection of *N. gonorrhoeae* and *Chlamydia trachomatis* and results in 90 minutes,[44] whereas the Binx io Platform (Binx Health, Limited, Trowbridge, UK and Boston, MA, USA) results in 30 minutes.[45] Both the Gene Xpert and the Binx io require an on-site Clinical Laboratory Improvement Ammendments (CLIA)-certified laboratory and investment in the processing instrument. However, the Visby Medical Sexual Health Test device (Visby Medical, San Jose, CA, USA) is a single-use rapid device approved for detection of *N. gonorrhoeae*, *C. trachomatis*, and *Trichomonas vaginalis* in self-collected vaginal swabs in under 30 minutes.[46] Other POC tests are in development.

Culture

Culture is critical in the management of suspected gonorrhea treatment failures as it is the only testing modality that performs comprehensive antimicrobial susceptibility testing. It is no longer the testing standard in routine clinical care due to lower

sensitivity (which varies by anatomic site of infection), long turnaround time, and both clinical and laboratory technical requirements.[47] Although not used routinely, clinics that diagnose gonorrhea should consider a plan for obtaining gonorrhea culture in cases of suspected treatment failure.[39]

Gonorrhea Treatment

Recommended treatment for uncomplicated gonococcal infections

The 2021 CDC STI Treatment Guidelines recommend a single 500 mg intramuscular (IM) dose (for persons weighing ≥ 150 kg, a single 1 g IM dose) of ceftriaxone for treatment of uncomplicated urogenital, anorectal, and pharyngeal gonorrhea (**Box 1**).[39] During 2015 to 2020, CDC recommended dual therapy with a single 250 mg IM dose of ceftriaxone and a single 1 g oral dose of azithromycin as first-line treatment of uncomplicated gonococcal infections. The recommendations were re-evaluated and updated in 2020 due to increasing concerns for antimicrobial stewardship and the potential impact of dual therapy on commensal organisms and concurrent STI pathogens, in addition to continued low incidence of ceftriaxone resistance and increased incidence of azithromycin resistance.[7] The rationale for increasing the dose of ceftriaxone to 500 mg was based on recent pharmacokinetics and pharmacodynamics studies of ceftriaxone for gonorrhea treatment.[7] If co-infection with chlamydia has not been excluded, doxycycline 100 mg orally twice daily for 7 days is recommended (or azithromycin 1 g if doxycycline is contraindicated or there are adherence concerns).[39] Persons treated for gonorrhea should abstain from sexual activity for 7 days after treatment and until all sex partners are treated (7 days after receiving treatment and resolution of symptoms if present) to minimize risk of re-infection.[39] All persons diagnosed with gonorrhea should be retested in 3 months due to high rates of reinfection.[39]

Alternative regimens for uncomplicated gonococcal infections

There are currently few reliable alternative antimicrobial treatment regimens for gonorrhea. In cases in which patients report a beta-lactam allergy, it is critical that clinicians first attempt to determine whether it is a true allergy by performing a

Box 1
Recommended and alternative treatment regimens for uncomplicated gonococcal infections

Recommended regimens for uncomplicated gonococcal infections (cervix, urethra, pharynx, or rectum)
Ceftriaxone 500 mg IM as a single dose (*persons weighing <150 kg*)
Ceftriaxone 1 g IM as a single dose (*persons weighing ≥150 kg*)
Test-of-cure is recommended for anyone diagnosed with pharyngeal gonorrhea after initial gonorrhea treatment by using either gonorrhea culture or NAAT

Alternative regimens for uncomplicated gonococcal infection (cervix, urethra, or rectum only)
Gentamicin 240 mg IM as a single dose *plus* azithromycin 2 g orally as a single dose
OR
Cefixime 800 mg orally as a single dose
No reliable alternative treatments are available for pharyngeal gonorrhea
For persons with an anaphylactic or other severe reaction (eg, Stevens-Johnson syndrome) to ceftriaxone, consult an infectious disease specialist

If chlamydial infection has not been excluded
Doxycycline 100 mg orally twice daily for 7 days
OR
Azithromycin 1 g as a single dose (if doxycycline is contraindicated)

thorough patient history (eg, type of reaction, timing of reaction, and previous prescription records) and allergy skin testing.[39] Though the prevalence of reported penicillin allergy has been estimated to be 10% among US population, less than 1% likely have a true penicillin allergy. Clinicians often avoid cephalosporin use (eg, ceftriaxone) in patients with reported penicillin allergies, though the cross-reactivity between penicillin and third-generation cephalosporins is rare.[48,49] Additionally, a majority (80%) of patients with a true IgE-mediated penicillin allergy will lose their hypersensitivity after 10 years[49]; thus, patients with remote allergic reactions may no longer have a hypersensitivity reaction. The use of third-generation cephalosporins (ceftriaxone, cefixime) for the treatment of gonorrhea is safe for patients without a history of any IgE-mediated symptoms (eg, anaphylaxis, urticaria) from penicillin during the preceding 10 years.[39]

For patients with a true beta-lactam allergy and anogenital gonorrhea, the recommended alternative treatment is dual therapy with a single IM gentamicin 240 mg dose and oral azithromycin 2 g once. Though not yet FDA-cleared, laboratory-developed NAAT with gyrase A (gyrA) testing have been shown to be highly sensitive and specific for predicting *N. gonorrhoeae* ciprofloxacin susceptibility.[50] If gyrA testing is available and indicates ciprofloxacin susceptibility, patients with a true beta-lactam allergy can be treated with ciprofloxacin 500 mg orally once.[39] If there are not concerns for a beta-lactam allergy, but ceftriaxone cannot be administered, an 800 mg oral dose of cefixime can be considered as an alternative cephalosporin regimen. Oral cefixime use for the treatment of gonorrhea should be limited as it does not provide the high, sustained bactericidal blood levels as a 500 mg IM dose of ceftriaxone.[39]

There is no recommended alternative regimen for the treatment of pharyngeal gonorrhea. Presently, ceftriaxone is the only available antimicrobial that reliably eradicates gonorrhea at the pharynx.

Future treatments

Historically, public health has relied on new antimicrobial development to overcome gonorrhea's expanding antimicrobial resistance. Zoliflodacin and gepotidacin (new type II topoisomerase inhibitors) have demonstrated *in vitro* activity against *N. gonorrhoeae* with known ciprofloxacin resistance.[51,52] Both drugs are in clinical trials and are expected to be oral therapeutic options for gonorrhea treatment in the relatively near future.

Repurposing currently available drugs is a faster method to new treatments. Ertapenem, a beta-lactam and carbapenem, with demonstrated *in vitro* activity against *N. gonorrhoeae,* was found to be non-inferior to ceftriaxone at anogenital sites in a large randomized controlled trial; however, efficacy against ceftriaxone-resistant strains is uncertain.[53]

Additional Patient Management

Pharyngeal gonorrhea test- of cure

Pharyngeal gonococcal infections consistently have lower cure rates than anogenital gonococcal infections, regardless of antibiotic class. Although this is likely due to variable drug concentrations at the pharynx, including for ceftriaxone, there are many unanswered questions about gonorrhea at this anatomic site. Clinically, most ceftriaxone treatment failures have occurred at the pharynx. Although treatment failure at the pharynx has occurred with susceptible organisms, there have also been treatment failures with strains demonstrating high ceftriaxone MICs (>0.25 μg/mL).[54,55] Due to concerns of potential persistent asymptomatic infection,

the unclear penetration of recommended drugs, and the risk of antimicrobial resistance development at the pharynx, the 2021 CDC STI Treatment Guidelines recommended test of cure (TOC) for anyone diagnosed with pharyngeal gonorrhea 7 to 14 days after initial gonorrhea treatment by using either gonorrhea culture or NAAT.[7,39] However, a subsequent study assessing time to clearance of *N. gonorrhoeae* at the pharynx found that positive pharyngeal gonorrhea TOC prior to 12 days after treatment are likely false-positive results, and in the absence of re-exposure, may warrant repeat testing.[56] Prior to retreatment, a confirmatory culture should be attempted for any positive TOC NAAT.[7] All positive TOC cultures should undergo antimicrobial susceptibility testing to assess for resistance.[39] If pharyngeal TOC is persistently NAAT positive and culture negative, clinicians may consider testing on a different NAAT platform since false positives can occur due to cross-reactivity with commensal *Neisseria* species.[47,57]

Management of Sex Partners

Partner notification

Clinicians serve an important role in reducing patients' risk for reinfection by ensuring patients' sex partners are notified of exposure and clinically evaluated.[58] All sex partners from the prior 60 days should be referred for clinical evaluation, testing, and empiric gonorrhea treatment.[39] If the patient's most recent sexual exposure was greater than 60 days before onset of symptoms or diagnosis, the most recent sex partner should be tested and treated for gonorrhea.[39] When feasible, providers should encourage patients to bring their primary sex partner to clinic when returning for treatment so both can be treated concurrently. Providing written information to patients to share with their sex partners can increase rates of partner treatment.[39,59]

Expedited partner therapy

Expedited partner therapy (EPT) is the clinical practice of treating sex partners of persons diagnosed with chlamydia or gonorrhea who are unable or unlikely to seek timely treatment by providing medications to the partner in the absence of a clinical evaluation. EPT is permissible or potentially allowable in all 50 states,[60] and should be offered if the sex partner's access to clinical evaluation and treatment is limited; clinicians should be aware of local EPT regulations.[39] The recommended regimen for gonorrhea EPT is cefixime 800 mg as a single oral dose which can be provided to the partner by the patient or a collaborating pharmacy as permitted by law.[39] The partner should also receive doxycycline 100 mg twice daily for 7 days (or azithromycin 1 g if doxycycline is contraindicated) if the patient has chlamydia or chlamydia has not been ruled out.[39] If the partner is of child-bearing potential and pregnancy status is unknown, azithromycin 1 g for chlamydia EPT can be provided.[61] EPT is supported by evidence from 3 US clinical trials that included heterosexual men and women with gonorrhea or chlamydia and found that more partners were treated when patients were offered EPT and gonorrhea reinfection rates declined.[62,63] There are limited data regarding use of EPT for gonorrhea among MSM. Providers and patients who are MSM should use shared clinical decision-making regarding EPT.[39]

Managing Persistent Gonococcal Infections and Suspected Treatment Failures

Ceftriaxone remains the sole recommended regimen for empiric single-dose gonorrhea treatment but increasing international reports of patients failing ceftriaxone-based therapies have highlighted the need to quickly identify and appropriately treat

all suspected treatment failures.[7] The first published report of a gonorrhea ceftriaxone treatment failure occurred in Sweden in 2010.[64] By 2018, the UK reported the first case of a gonococcal treatment failure in the setting of ceftriaxone resistance combined with high-level azithromycin resistance, followed by a similar case in Australia.[7] Although there have been no "resistance-related" ceftriaxone treatment failures identified in the US, gonococcal isolates with high ceftriaxone MIC levels have been reported and public health authorities are concerned about the inevitability of a treatment failure in the US.[65,66]

Suspected gonorrhea treatment failures present either with persistent clinical symptoms or a positive TOC after recommended treatment and in the absence of reinfection (**Table 2**). Alternatively, identification of a concerning laboratory result (ie, antimicrobial MIC value or molecular test result) can lead to suspicions of resistance. Symptomatic persistent infections may lack expected symptom resolution 3 to 5 days after treatment. Asymptomatic persistent infections can only be identified through repeat testing (ie, TOC). Concerning TOC results are either positive cultures greater than 72 hours or positive NAAT greater than 12 (pharyngeal)[56] or NAAT greater than 7 (anogenital) days after recommended treatment.[67]

In the US, reinfections are more likely to occur than true treatment failures. Providers should take a thorough sexual history including asking about timing of symptom resolution, new onset of symptoms, treatment completion and tolerance, abstinence after treatment, treatment of sex partners, and new sex partners since treatment.[68] Additionally, providers should ask regarding recent travel and sexual contacts outside of the US, as most of the internationally reported treatment failures have been associated with travel to Asia.[7,39,64,69] In addition to repeating a gonorrhea NAAT and attempting to perform culture, other sexually transmitted pathogens that produce similar symptoms should be ruled out.[39] Specifically, persistent urogenital symptoms may be due to concurrent infection with *Mycoplasma genitalium* or *T. vaginalis*. Management and treatment next steps should be tailored to the suspected diagnosis.

Once treatment failure is suspected, reinfection is ruled out, and testing has been completed (ie, repeat NAAT and culture specimens obtained), single doses of IM gentamicin 240 mg plus oral azithromycin 2 g can be administered if there is concern that the *N. gonorrhoeae* isolate has an elevated ceftriaxone MIC,[39] though gentamicin is unlikely to be curative for pharyngeal infections.[70] All providers managing a suspected cephalosporin treatment failure are strongly encouraged to consult an infectious disease specialist or an STI clinical expert (https://www.stdccn.org/render/Public) for assistance with clinical management.

Local and state health departments can often help providers with managing suspected gonorrhea treatment failures. Providers are encouraged to communicate with their health departments and public health laboratories. Although culture for *N. gonorrhoeae* should be collected for antimicrobial susceptibility testing,[39] not all laboratories have the capacity to culture *N. gonorrhoeae* or perform susceptibility testing. If local laboratories do not have the capacity to perform this testing, CDC can assist in connecting providers to a laboratory that does. All positive samples should be saved for shipment to CDC through local and state public health mechanisms.[39]

To ensure that potentially resistant strains of gonorrhea are contained, it is important to encourage sex partners to present for testing and treatment, and counsel patients to abstain from sexual activity until their infection has been confirmed to be eradicated. Health departments can help with partner notification and culture evaluation of patients and sex partners with suspected gonorrhea treatment failure.

Table 2
Important considerations when managing a suspected gonococcal treatment failure

Step 1: Evaluate for Persistent Infection

Symptomatic	*Asymptomatic*
Patient with persistent symptoms • Symptoms do not resolve (3–5 d) after treatment	Patient with positive test-of-cure (TOC) result(s) • Positive culture (>72 h) after treatment • Positive NAAT (pharyngeal: >12 d or anogenital: >7 d) after treatment

Step 2: Evaluate for Treatment Failure

1. Take a thorough sexual history
2. Evaluate for re-exposure to gonorrhea
3. Evaluate for appropriate gonococcal treatment
4. Evaluate for other diagnoses that can present similarly

Alternative Diagnosis	*Gonococcal Re-infection*	*Suspected Gonococcal Treatment Failure*
Patient with positive test result(s) for another diagnosis • Treat based on diagnosis identified	Patient with positive gonorrhea test result(s), including TOC, when *re-exposure is likely* • Re-treat with initial therapy • If a pharyngeal infection is identified, perform TOC	Patient with positive gonorrhea test result(s), including TOC, when *re-exposure is unlikely* • Prepare for antimicrobial resistance evaluation from all positive anatomic sites • Abnormal laboratory results (ie, antimicrobial MIC value or molecular test result) are managed as suspected treatment failures

Step 3: Evaluate for Antimicrobial Resistance

1. Contact local/state health department to notify of suspected treatment failure
2. Collect sample for culture and NAAT (simultaneously, unless culture sample(s) already collected as part of TOC)
3. Contact laboratory prior to submission of culture sample for instructions, recommendations, and additional support
   - If laboratory is unable to perform culture or susceptibility, contact local/state health department for alternative laboratory options
   - If alternative laboratory options are unknown, contact CDC (gcfailure@cdc.gov) for additional recommendations
4. Submit sample to a laboratory for possible culture growth and resistance testing
   - Request susceptibility testing be performed (at minimum request testing for ceftriaxone, cefixime, and ciprofloxacin)
5. Consult an infectious disease specialist or an STD clinical expert (https://www.stdccn.org/render/Public) for assistance with clinical management

Step 4: Management of Suspected Treatment Failure

Culture positive or NAAT positive result(s) identified

1. Contact local/state department to notify of culture and NAAT results
2. Health departments can assist with partner investigation, notification, testing, and treatment
3. Save all positive samples (cultures and NAAT), in case additional testing is needed
4. Notify CDC (gcfailure@cdc.gov) and submit case information using the Suspected Gonorrhea Treatment Failure Consultation Form to receive additional recommendations and guidance

SUMMARY

Gonorrhea rates continue to rise in the US and different populations disproportionally carry the burden of disease. Complicating the management is *N. gonorrhoeae's* propensity to develop resistance to all therapies that have been used for gonococcal treatment. As antimicrobial resistance increases in the US, there are few new antimicrobials being developed. Ceftriaxone is the last remaining highly effective single-dose recommended regimen for gonococcal treatment. The 2021 CDC STI Treatment Guidelines increased the dose of ceftriaxone to 500 mg (1 g if $\geq$ 150 kg) for uncomplicated infections. An increasing number of ceftriaxone-based treatment failures have been reported internationally, most commonly at the pharynx. Therefore, all pharyngeal gonococcal infections are recommended to undergo TOC 7 to 14 days after treatment. It is recommended that all providers, laboratorians, and public health staff become aware of antimicrobial resistant gonorrhea and be able to identify, appropriately manage, and report any suspected gonorrhea treatment failure case.

CLINICS CARE POINTS

- Gonorrhea cases and reported rates continue to increase. National surveillance efforts for gonorrhea and antimicrobial resistant gonorrhea continue to monitor trends across different populations.
- As rates of gonorrhea continue to increase, clinicians will likely see rare clinical presentations of gonorrhea more frequently. Clinicians should maintain a high degree of suspicion for gonorrhea—including rare gonococcal clinical syndromes such as DGI.
- NAAT are considered the preferred test for the detection of gonorrhea in patients with or without symptoms given their high sensitivity and specificity.
- The recommended treatment for uncomplicated gonorrhea in adults and adolescents at urogenital, rectal, and pharyngeal anatomic sites is ceftriaxone 500 mg IM once in a single dose.
- Test of cure is recommended for anyone diagnosed with pharyngeal gonorrhea.
- A reported beta-lactam allergy should prompt a review to determine whether a true allergy is present since there are limited reliable alternative gonorrhea treatment regimens; a very small proportion of the population likely have true penicillin allergies, and the cross-reactivity between penicillin and third-generation cephalosporins is rare.
- If a gonococcal treatment failure is suspected, all efforts should be made to (1) rule out reinfection; (2) obtain simultaneous culture and NAAT samples to evaluate for resistance; (3) provide appropriate treatment after all samples have been collected; and (4) notify state and local health departments. Clinicians should work with local partners to understand policies and procedures for managing suspected treatment failure cases.

DISCLAIMER

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC).

DISCLOSURE

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