Update on Treatment Options for Gonococcal Infections

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The incidence of *Neisseria gonorrhoeae* infections in the United States has grown over the past decade. The most recent data provided by the Centers for Disease Control and Prevention (CDC) indicate that reported cases have increased by almost 10% over the last 5 years. In conjunction with this rise, the presence of multidrug-resistant strains of *N. gonorrhoeae* has also emerged. The 2015 CDC guidelines recommend dual therapy with intramuscular ceftriaxone and oral azithromycin as first-line treatment, although components of this regimen are met with a high level of resistance. Although ceftriaxone resistance has not yet been reported in the United States, it is only a matter of time before such isolates are detected, thus ushering in a new era of difficult-to-manage uncomplicated gonococcal infection. The potential public health crisis and patient-associated sequelae (e.g., pelvic inflammatory disease, epididymitis, and human immunodeficiency virus infection) linked with untreatable gonorrhea are cause for great concern. To try to stem this tide, a number of new agents targeted against *N. gonorrhoeae* are being investigated in clinical trials. In this article, we review the various agents, both currently available and under clinical investigation, and provide recommendations for the management of gonococcal infections.

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Background and Epidemiology

In this era of ever-increasing multidrug-resistant pathogens, the emergence of older bacteria previously managed with narrow-spectrum therapies now requiring more broad-spectrum antimicrobials continues to be of great concern. One such organism is *Neisseria gonorrhoeae* (gonococcus). Gonorrhea is an ancient disease, documented in the Old Testament.[1] Before its formal identification in 1879 by German bacteriologist Albert Neisser, gonorrhea was referred to as "the clap" and is still referred to as such colloquially. The term likely derives from an old Parisian territory known as Les Clapiers, where prostitutes resided (in old French, *clapier* translates to brothel).[1] Prior to the advent of antibiotics, less effective treatment options included thermotherapy, plant-based extracts (cubebs, copaiba), and metals (mercury, arsenic). Not until the 1930s did the first reliable antibiotic (sulfonamides) prove effective against gonorrhea. However, gonococcal bacteria possess an extraordinary capacity for genetic mutation, and since that time, antimicrobial resistance has become an international problem.[1]

N. gonorrhoeae is the second most commonly reported bacterial sexually transmitted infection (STI) in the United States, after *Chlamydia trachomatis*.[2] Although this review focuses solely on gonococcal infection, comanagement of both chlamydial and gonococcal infections is considered standard of practice unless the absence of one organism is confirmed, as 10–30% of patients diagnosed with a gonococcal infection will have a concomitant chlamydial infection.[3]

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N. gonorrhoeae infecting the lower genital tract (urethra/cervix), rectum, and/or pharyngeal sites is classified as uncomplicated, whereas complicated infections encompass the upper genital tract and nongenital or extragenital tracts.[2] Gonococcal infections most commonly present as urethritis or cervicitis. Rectal and pharyngeal gonorrhea are frequent sites of coinfection in men who have sex with men (MSM) but, based on sexual practice, may also be identified in women.[2]

Although the Centers for Disease Control and Prevention (CDC) reported more than 333,000 cases of *N. gonorrhoeae* in the United States in 2013, the true number is estimated to be as high as 820,000 cases.[4] In 2013, 106.1 cases of *N. gonorrhoeae* per 100,000 persons were reported, representing an 8.2% increase in incidence from 2009.[4] The southern United States had the highest reported incidence of gonorrhea cases (128.6 cases per 100,000 individuals), followed by the Midwest (108.6 cases per 100,000), the Northeast (85.5 cases per 100,000), and the West (83.5 cases per 100,000).[4] From 2012–2013, the rate of infection decreased by 7.3% in the Northeast, 5.0% in the Midwest, and 1.5% in the South, and increased 15.0% in the West.[4] In 2013 rates of reported cases were highest among men and women aged 20–24 years.[4] Among the 47 jurisdictions submitting data regarding race and ethnicity, the highest rate of reported cases was found among those of black/African-American heritage (426.6 cases per 100,000).[4] This rate was 12.4 times the rate reported among whites (34.5 cases per 100,000).[4] The prevalence of this infection has strong economic implications, as in 2008, the total lifetime direct medical cost of *N. gonorrhoeae* infections in the United States was estimated to be $162.1 million.[5] This value, however, may also be an underestimate, given underreporting of the infection in low-risk urban and rural populations, as well as inadequate STI surveillance for incidence monitoring.

Due to the emergence of extended-spectrum cephalosporin (ESC)-resistant *N. gonorrhoeae* in Europe and Asia, the CDC developed a public health response plan in 2012 aimed at improving disease surveillance and mitigating the impact of *N. gonorrhoeae* resistance to ceftriaxone and cefixime.[6] Experts caution that if cephalosporin-resistant *N. gonorrhoeae* becomes more widely disseminated, the potential public health impact over the next 10 years could be staggering. It was estimated that an additional 75,000 cases of pelvic inflammatory disease (PID), 15,000 cases of epididymitis, and 222 cases of human immunodeficiency virus (HIV) infection would be seen, with the latter more easily transmitted in patients coinfected with gonorrhea.[5] Furthermore, the estimated direct medical costs would total $235 million.[5]

Antimicrobial Resistance in *Neisseria gonorrhoeae* in the United States

In 1986 the CDC established the Gonococcal Isolate Surveillance Project (GISP) to monitor antimicrobial susceptibility trends in the United States and to establish a basis for determining empiric treatment for gonococcal infection. The objectives of GISP are 3-fold: to monitor trends in antimicrobial susceptibility of *N. gonorrhoeae*, to characterize male patients with *N. gonorrhoeae* infection, and to phenotypically characterize antimicrobial-resistant isolates of *N. gonorrhoeae*.[7]

Clinical and demographic data, along with antimicrobial susceptibility data on urethral gonococcal isolates, are submitted monthly to regional laboratories from the first 25–30 male patients with gonococcal urethritis from the sentinel STI clinics in 26 cities. A graphic representation of these locations is shown in Figure 1.[7] Isolates are tested for β-lactamase production and antimicrobial susceptibility to penicillin, tetracycline, spectinomycin, ciprofloxacin, ceftriaxone, cefixime, and azithromycin. Minimum inhibitory concentrations (MICs) are determined by agar dilution and interpreted according to Clinical and Laboratory Standards Institute (CLSI) recommendations, when applicable.

Because increasing MICs can predict the emergence of resistance, lower cephalosporin MIC breakpoints than those defined by CLSI were established by GISP for surveillance purposes to provide greater sensitivity in detecting declining gonococcal susceptibility.[8] An MIC of 0.25 μg/ml or higher for cefixime and 0.125 μg/ml or higher for ceftriaxone were defined by GISP as elevated, and reduced susceptibility was defined as an MIC higher than 0.5 μg/ml for both cefixime and ceftriaxone.[8] The CLSI does not define azithromycin resistance criteria; however, the GISP defines decreased azithromycin susceptibility as an MIC of 2.0 μg/ml or higher.[8] Table 1 outlines the susceptibility criteria used by GISP as part of its 2013 update.

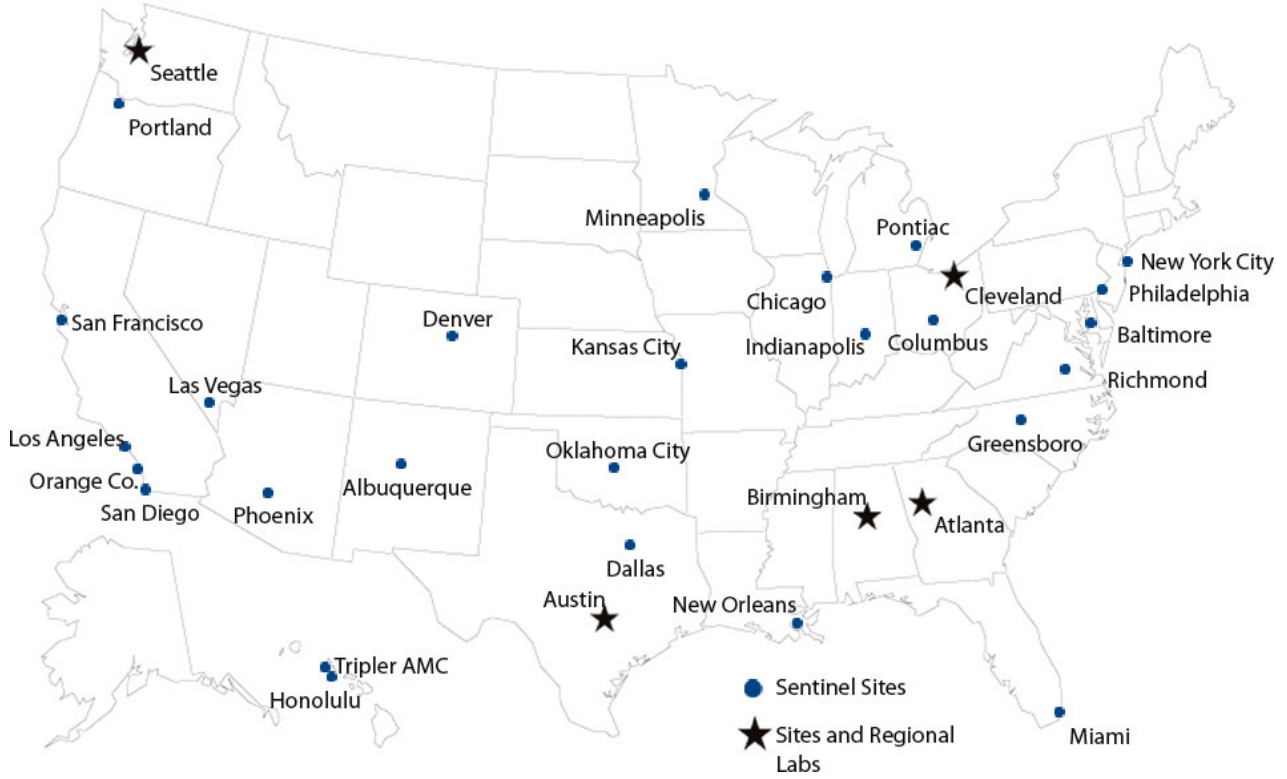

Figure 1. Locations of the Gonococcal Isolate Surveillance Project (GISP) sentinel sites of the sexually transmitted infection clinics submitting clinical and demographic data and antimicrobial susceptibility data from urethral gonococcal isolates on a monthly basis to the Centers for Disease Control and Prevention, as well as the GISP sites with regional laboratories that perform the susceptibility testing. AMC = Army Medical Center. (Reprinted with permission from reference 7.)

Table 1. Gonococcal Isolate Surveillance Project Antimicrobial Susceptibility Criteria: 2013 Update[8]

Pharmacologic agent	MIC breakpoint
Azithromycin	≥ 2.0 μg/ml (elevated MIC)
Cefixime	≥ 0.25 μg/ml (elevated MIC) ≥ 0.5 μg/ml (decreased susceptibility)
Ceftriaxone	≥ 0.125 μg/ml (elevated MIC) ≥ 0.5 μg/ml (decreased susceptibility)
Ciprofloxacin	0.125–0.5 μg/ml (intermediate resistance) ≥ 1.0 μg/ml (resistance)
Penicillin	≥ 2.0 μg/ml (resistance)
Spectinomycin	≥ 128 μg/ml (resistance)
Tetracycline	≥ 2.0 μg/ml (resistance)

MIC = minimum inhibitory concentration.

Penicillin

Penicillin has not been a first-line treatment option for gonorrhea for a number of decades, but it is still tested for surveillance purposes. In 2012, ~13.1% of *N. gonorrhoeae* from the GISP survey were resistant to penicillin.[9] Of the 4545 isolates with penicillin resistance, 3740 (82.3%) exhibited chromosomal penicillin resistance; 805 (17.7%) produced penicillinase.[9]

Ceftriaxone

Susceptibility testing for ceftriaxone began in 1987 and continues to date. The percentage of gonococcal isolates from the GISP survey that exhibited elevated ceftriaxone MICs increased from 0.1% in 2008 to 0.4% in 2011.[4] Five isolates with decreased ceftriaxone susceptibility (MIC 0.5 μg/ml) were previously identified in San Diego, California (1987), Cincinnati, Ohio (1992 and 1993), Philadelphia, Pennsylvania (1997), and Oklahoma City, Oklahoma (2012).[4]

The percentage of gonococcal isolates with elevated ceftriaxone MICs from MSM has been observed to be higher than isolates obtained from men who have sex exclusively with women (MSW).[9] Isolates with decreased susceptibility in MSM increased from 0% in 2006 to 0.9% in 2010, and remained stable through 2012.[9] During the same time period, susceptibility rates remained unchanged at 0.1% for MSW.[9]

Cefixime

Cefixime susceptibility testing began in 1992, was discontinued in 2007 due to lack of drug supply in the United States, and was restarted in 2009. The percentage of isolates with elevated cefixime MICs increased from 0.1% in 2006 to 1.4% in 2010 and 2011.[4] The proportion of isolates with elevated cefixime MICs declined to 1.0% in 2012 and further declined to 0.4% in 2013. In 2013, no isolates displayed cefixime MICs of 0.5 μg/ml or higher.[4]

Similar to ceftriaxone, from 2006–2012, the prevalence of elevated cefixime MICs was higher in isolates from MSM than from MSW. Specifically, isolates with decreased susceptibility from MSM increased from 0% in 2006 to 3.9% in 2010 and then decreased to 2.9% in 2012.[9] For the same time period, the proportion with elevated MICs from MSWs ranged from 0.1% in 2006 to 0.5% in 2011.[9]

Azithromycin

Azithromycin susceptibility testing began in 1992 and continues today. In 2012 ~0.3% of GISP gonococcal isolates had decreased susceptibility against azithromycin.[4, 8] From 2005–2013, most gonococcal isolates had azithromycin MICs of 0.125–0.25 μg/ml. Most of these isolates were collected from the West census region (66.7%) and from MSM (69.7%).[8] One isolate from a MSW (Hawaii) had an azithromycin MIC of256 μg/ml or higher, the highest reported to date in the United States.[8]

Ciprofloxacin

Susceptibility testing for ciprofloxacin began in 1990 and continues to be tested today, despite no longer being recommended as a treatment modality. The proportion of GISP isolates with ciprofloxacin resistance peaked in 2007 at 14.8%.[9] Following a decline in 2008 and 2009, the proportion increased again from 9.6% in 2009 to 14.7% in 2012.[9] In 2013, 16.1% of isolates were resistant to ciprofloxacin.[4, 9]

During the 2000s, gonococcal ciprofloxacin resistance increased in MSW and MSM; however, the increase was especially compelling in isolates from MSM.[7, 8] In 2006 resistance peaked in the MSM population at 38.9% and steadily declined in subsequent years to 20.1% in 2009.[7–9] However, since 2010, resistance has been increasing. Most recently for 2013, almost 28% of submitted *N. gonorrhoeae* isolates were resistant to ciprofloxacin.[8]

A similar ciprofloxacin resistance trend was seen in the MSW population, but the percentages were drastically lower, never reaching more than 9% during 2006–2011.[7] In 2012, 8.7% of isolates from MSW demonstrated ciprofloxacin resistance, whereas 9.8% did in 2013.[7, 8]

Spectinomycin

In 2013, all tested isolates were susceptible to spectinomycin.[7] The last known resistant strain was isolated in 1994.[4]

Multidrug Resistance

In 2012, 33.4% of GISP isolates were resistant to penicillin, tetracycline, ciprofloxacin, or some combination of those antimicrobials.[7] Despite the fact that these antimicrobials are no longer recommended for treatment by the CDC, the resistance phenotypes remain common. In 2013 the proportion of isolates demonstrating resistance to these three antimicrobials was largely unchanged at 33.9%.[4]

Mechanisms of Antimicrobial Resistance in *Neisseria gonorrhoeae*

N. gonorrhoeae is a bacterial species with an innate ability to rapidly develop antimicrobial resistance. It is capable of using a number of mechanisms to confer resistance and oftentimes harbors multiple mechanisms, including using enzymes to degrade antibiotics, modifying targets or decreasing binding affinity, and decreasing drug influx and increasing drug efflux.[1, 10] Furthermore, gonococcal pharyngeal infection is more difficult to eradicate than urogenital infection and often asymptomatic, thus providing an optimal nidus for selecting resistance mutations. It is hypothesized that many of the resistance mechanisms evolve from specific mutations from commensal *Neisseria* species that inhabit the oral cavity. Because *N. gonorrhoeae* is uniquely capable of assimilating external DNA during its life cycle, the transfer of chromosomally encoded resistance genes from commensal *Neisseria* species that have acquired resistance to various antimicrobials is rapid and extensive.[11, 12]

β-Lactams

Penicillin

Penicillins exert their antibacterial activity by inhibition of bacterial cell wall synthesis via a mechanism by which enzymes that catalyze the final step of cell wall assembly are inhibited.[9] *N. gonorrhoeae* becomes resistant to penicillin via several methods: alteration of the penicillin-binding proteins (PBPs), plasmid-mediated production of penicillinases, and alterations in influx and efflux pumps.[10, 12]

Alterations in the *penA* and *ponA* genes that encode for the PBP2 and PBP1, respectively, decrease the affinity of penicillin for PBPs. These chromosomally mediated mutations in *penA* represent the most common mechanism of resistance. There are five to nine mutations in the *penA* gene that result in up to an 8-fold decrease in penicillin susceptibility to gonococcal bacteria.[10, 13] Changes in the affinity of penicillin to the PBP1 via mutation in the *ponA* gene may also be observed in high-level resistance gonococcal isolates that harbor *penA* mutations. The *ponA* mutation is the result of a single amino acid substitution that has been associated with a 16-fold lower penicillin acylation rate compared with wild-type PBP1.[1, 10]

The $bla_{\text{TEM-1}}$ gene codes for a TEM-1-type β-lactamase that lyses the β-lactam ring and renders the penicillin inactive. These plasmid-mediated resistance mechanisms were initially described in the late 1970s and rapidly disseminated internationally.[9, 12] Mutations in the multitransferable resistance (*mtr*) gene, which encodes a transcriptional repressor or promoter, are well described as contributing to antimicrobial resistance in gonococci.[12] Specifically, overexpression of the MtrC-MtrD-MtrE (MtrCDE), part of a family of resistance modulation cell division pumps, contributes to bacterial resistance in antimicrobials including penicillins, cephalosporins, fluoroquinolones, tetracyclines, and macrolides.[1, 13]

Decreased antimicrobial uptake through the outer membrane channel porin PorB1b, due to mutations of *penB*, is a less common means of resistance exhibited by *N. gonorrhoeae*. An unknown factor, dubbed the factor X, can also increase penicillin MICs by 3- to 6-fold.[1, 13]

Cephalosporins (Ceftriaxone and Cefixime)

Similar to the penicillins, cephalosporins exert their antibacterial activity by inhibition of bacterial cell wall synthesis by binding to PBPs.[9] Resistance to the ESCs occurs as a result of mutations that modify the affinity to PBPs and via alterations in influx and efflux pumps.[12, 14]

More extensive amino acid mutations to the *penA* gene render the organism resistant to both penicillin and ESCs. In contrast to the 5–9 *penA* mutations for penicillin resistance, the ESC *penA* resistance contains 60–70 amino acid alterations.[10, 13, 15] In addition to the reduced susceptibility (e.g., MICs of 0.125 μg/ml or higher for ceftriaxone and 0.25 μg/ml or higher for cefixime), high-level resistance can also be seen against these antibiotics. Gonococcal isolates associated with treatment failures from Japan, France, and Spain have displayed high ceftriaxone and cefixime MICs (2–4 μg/ml and 8 μg/ml, respectively) and were linked to alterations in PBPs.[14–19] The amino acid alterations associated with high-level ESC resistance differs from those associated with reduced susceptibility by up to 12 or more amino acids including five substitutions that had not been previously described in *N. gonorrhoeae*.[13, 14]

Although *penA* mutations are the primary modes for ESC resistance in *N. gonorrhoeae*, increased efflux and decreased influx of antimicrobials also play a role.[12, 18] Gonococcal strains expressing high-level ESC resistance have been observed to have a single nucleotide "A" deletion in the *mtrR* promoter of the MtrCDE efflux pump.[17] Despite having other efflux pumps that export fluoroquinolones and macrolides (*macA, macB*, and *norM*), the MtrCDE is best characterized as a contributor to ESC antimicrobial resistance in gonococci.[18]

Macrolides

Macrolides inhibit protein synthesis by binding to the 50S ribosomal subunit, preventing translocation of the peptidyl–transfer ribonucleic acid (tRNA), and blocking the peptide exit channel in 50S subunits by interacting with 23S ribosomal RNA (rRNA).[9] Resistance to the macrolide class is primarily due to alterations in the 23S ribosomal subunit and, to a lesser degree, mutations of the MtrCDE efflux pump.[19] Erm genes encode for RNA methylase, which blocks macrolides from binding with the 23S subunit. On their own, erm genes only confer low-level resistance against azithromycin; however, if coupled with an efflux or influx pump alteration, they can result in high-level resistance.

N. gonorrhoeae has four 23s rRNA alleles, and resistance to azithromycin depends on the number of alleles with mutations.[19, 20] Common modification sites include A2059G and C599T.[20] Isolates with three mutations in the A2059G allele were observed to have azithromycin MICs up to 4096 μg/ml, whereas those with only one mutation had MICs not unlike wild-type isolates.[19]

Fluoroquinolones

Ciprofloxacin

Fluoroquinolones target topoisomerase II (DNA gyrase) and topoisomerase IV in *N. gonorrhoeae*, resulting in inhibition of DNA synethesis.[9] Gonococcal resistance to fluoroquinolones is mediated through single or multiple amino acid alterations in the quinolone-resistance determining region (QRDR) of *gyrA* and/or *parC*. Such mutations reduce binding affinity to DNA gyrase and topoisomerase IV, resulting in elevated MICs and the potential for clinical failure.[9, 21, 22] These mutations are plasmid mediated and have been identified in a high proportion of gonococcal isolates despite the fact that this class of antimicrobials has not been recommended since 2007. The global dissemination of ciprofloxacin resistance ranges from 35% to more than 95% in many countries.[21]

The most common *gyrA* mutations are point mutations of Ser-91 to Tyr/Phe, Ala-75 to Ser, and Asp-95 to Asn/Gly. Mutations in *parC* include Ser-88 to Pro, and Glu-91 to Gly. Isolates with a single *gyrA* mutation are often observed to have moderately elevated MICs compared with wild-type isolates, whereas isolates with multiple substitutions involving the QRDR exhibit high-level fluoroquinolone resistance and reduced clinical response.[22, 23]

Tetracyclines

Tetracyclines inhibit the binding of aminocycl-tRNA to the messenger RNA–ribosome complex, primarily by binding to the 30S ribosomal subunit and inhibiting protein synthesis.[9] The first mechanism of tetracycline resistance is via the *tetM* gene, which binds to bacterial ribosomes and subsequently causes release of the tetracycline molecule. In addition, alterations in target structures (via the tet-2 mutation), an increase in efflux pumps, and a decrease in influx pumps can contribute to the tetracycline resistance seen in gonorrhea.[9]

Laboratory Testing for *Neisseria gonorrhoeae*

Multiple methods are available to aid clinicians in the detection of *N. gonorrhoeae* from genital and nongenital sites. These tests include methods for direct detection of *N. gonorrhoeae* by Gram's staining, culture, and nonculture sampling. Whereas Gram's staining and culture have high rates of sensitivity and specificity, each reported to exceed 95%, there are significant limitations to these practices including prolonged turnaround times and difficulty maintaining viable samples while in transport to a laboratory. Thus direct culturing of *N. gonorrhoeae* from urogenital and nonurogenital sites is primarily used to determine antimicrobial susceptibility and for reporting of surveillance and outbreak data.

The nonculture testing methods available for *N. gonorrhoeae* include enzyme immunoassays (EIAs) and nucleic acid hybridization tests detecting DNA and/or RNA sequences. Neither of these testing methods requires viable organisms for detection, and they can detect an active infection from a sample with only one copy of DNA/RNA. At this time, the CDC recommends the use of nucleic acid amplification testing (NAAT) to aid in the identification and detection of *N. gonorrhoeae* in asymptomatic or symptomatic women and men, such as pharyngeal or rectal infection.[9, 24] The rationale behind this is that NAAT testing methodologies have up to 35% greater sensitivity compared with EIA testing.[24] In addition, NAATs do not require invasive bodily fluids for sampling, can provide results without a long turnaround time, and can simultaneously detect multiple pathogens. Additional uses for nonculture methods include a test of cure for patients experiencing treatment failure or for those receiving second-line therapies. Table 2 outlines the current testing recommendations for *N. gonorrhoeae*.

Symptoms and Complications of *Neisseria gonorrhoeae* Infections

Women infected with *N. gonorrhoeae* may be asymptomatic, but up to 50% exhibit nonspecific symptoms including odorless mucopurulent vaginal discharge; vaginal bleeding, especially after intercourse; and dyspareunia.[25] In contrast, 90% of men with an *N. gonorrhoeae* urethral

Table 2. U.S. Preventive Services Task Force Laboratory Testing Recommendations for *Neisseria gonorrhoeae*[2]

Gender	Recommendation
Female	NAAT recommended in asymptomatic or symptomatic patients
	Routine annual genitourinary screening is only indicated in certain high-risk patients (e.g., age ≤ 25 yrs, previous sexually transmitted infection)
	Endocervical swab sampling is necessary to evaluate antibiotic susceptibility in certain patients
Male	NAAT recommended in asymptomatic or symptomatic patients
	Routine genitourinary screening in heterosexual men is not indicated
	Routine annual extragenital screening in men having sex with men is recommended
	Urethral swab sampling is necessary to evaluate antibiotic susceptibility in certain patients

NAAT = nucleic acid amplification test.

infection have symptomatic mucopurulent penile discharge and dysuria. In men, these symptoms commonly occur 2–6 days after exposure. Dysuria and urinary frequency can be misdiagnosed as a urinary tract infection, especially in females, if proper patient history is not conducted. Undetected or improperly treated urogenital infection may lead to bacteria ascending the upper genital tract and causing reproductive complications. Up to 20% of women with *N. gonorrhoeae* develop PID, which can lead to infertility in up to 15%. Thus proper identification and management of *N. gonorrhoeae* is especially important to reduce the risk of reproductive complications. Men with inadequate or delayed treatment can develop epididymitis. Lastly, as previously mentioned, infection with *N. gonorrhoeae* can also facilitate transmission of HIV.[26]

Treatment Guidelines

The World Health Organization and CDC have recommended that the treatment options for *N. gonorrhoeae* should be easily accessible and cost effective, and have more than a 95% cure rate as a single dose.[27, 28] The CDC updated the treatment guideline for the management of gonococcal infections in 2015 (Table 3).[2] For all uncomplicated gonococcal infections of the cervix, urethra, and rectum, the recommended therapy is a combination of one dose of intramuscular ceftriaxone 250 mg plus one dose of oral azithromycin 1000 mg. Due to the prevalence of tetracycline resistance, doxycycline

Table 3. Current CDC Treatment Recommendations for Cervical, Urethral, Rectal, and/or Pharyngeal Gonococcal Infection[2]

Type of gonococcal infection	Regimen
Uncomplicated	
Recommended regimen	Ceftriaxone 250 mg i.m. × 1 + azithromycin 1000 mg p.o. × 1
Alternative regimen for cervical, urethral, or rectal infection only	Cefixime 400 mg p.o. × 1 + azithromycin 1000 mg p.o. × 1 (test of cure should be performed 1 wk later)
Alternative regimens for severe β-lactam/ cephalosporin allergy for cervical, urethral, or rectal infection only	Gemifloxacin 320 mg p.o. × 1 + azithromycin 2000 mg p.o. × 1 (test of cure should be performed 1 wk later)
	Gentamicin 240 mg i.m. × 1 + azithromycin 2000 mg p.o. × 1 (test of cure should be performed 1 wk later)
Complicated	Refer to the 2015 CDC sexually transmitted diseases treatment guidelines[2]

CDC = Centers for Disease Control and Prevention.

100 mg twice/day for 7 days is now only recommended in cases of azithromycin allergy. The combination of ceftriaxone plus azithromycin or doxycycline also provides adequate coverage against potential chlamydial infections.[2] If ceftriaxone is not available, clinicians may substitute oral cefixime 400 mg for one dose in combination with azithromycin. The 400-mg oral dose of cefixime does not provide as high, or as sustained, bactericidal levels as intramuscular ceftriaxone; therefore, patients should return for a test of cure 1 week later with culture and susceptibility testing.[27] Currently, a phase I open-label dose-escalating study is being conducted that will investigate the safety and tolerability of higher doses of cefixime (up to 800 mg every 8 hrs for three doses) to see if this regimen may overcome the reduced susceptibility seen in *N. gonorrhoeae* and provide outcomes more comparable with intramuscular ceftriaxone.[29]

For patients with severe β-lactam/cephalosporin allergies, azithromycin plus either gemifloxacin or gentamicin are potential treatment options. Likewise, a test-of-cure visit is recommended 1 week after receipt of treatment.[2] Patients treated with alternative regimens who fail their test of cure should be immediately treated with one dose each of intramuscular ceftriaxone

250 mg and oral azithromycin 2000 mg. An infectious diseases consultation and report to the CDC should also be performed.[2]

The only recommended treatment regimen for patients presenting with uncomplicated pharyngeal infection is one dose each of intramuscular ceftriaxone 250 mg and oral azithromycin 1000 mg.[2] An infectious diseases consultation is recommended for patients who are unable to receive this regimen.

Treatment with one dose each of oral cefixime 400 mg and azithromycin 1000 mg should be offered to any sexual partners of the index patient in the preceding 60 days. The partner prescription can be facilitated in a number of ways including through expedited partner therapy programs. If expedited partner therapy is an allowable practice in the state, the index patient's provider may supply a prescription or medication for the partner without physically seeing the partner themselves.[2]

Combination Therapy

The CDC recommends combination therapy with ceftriaxone plus azithromycin as a first-line regimen due to the increased rate of *N. gonorrhoeae* resistance to multiple antimicrobial agents.[2] Several recent in vitro studies have assessed the susceptibility of antimicrobial combinations against clinical isolates of *N. gonorrhoeae*.[29–31]

One study[32] tested ceftriaxone and cefixime in combination with azithromycin, doxycycline, and gentamicin against 32 *N. gonorrhoeae* isolates collected between 2007 and 2012 at a Seattle STI clinic. The isolate with the highest azithromycin MIC (16 μg/ml) had a 2-fold reduction in the MIC to azithromycin (3 μg/ml) in the presence of either cephalosporin. Indifference was also observed for the combinations of cefixime or ceftriaxone plus gentamicin. Although the combination regimen is theoretically attractive as a means to reduce antimicrobial resistance development, this benefit has not been rigorously investigated in a clinical study in patients.

Another study[33] investigated the efficacy and safety of two novel combinations, single doses of azithromycin 2000 mg plus either oral gemifloxacin 320 mg or intramuscular gentamicin 240 mg, in a multicenter randomized open-label study in patients aged 15–60 years with microbiologically confirmed uncomplicated urogenital gonorrhea. The primary outcome measure was microbiologic eradication of *N. gonorrhoeae*, defined as a negative urogenital culture 10–17 days after receipt of the study medication. Microbiologic eradication of rectal and pharyngeal infections was a secondary end point. Microbiological eradication was observed in 100% of the gentamicin/azithromycin group (202/202) and in 99.5% of gemifloxacin/azithromycin group (198/199). No serious adverse events were reported; however, gastrointestinal events were common in both groups (nausea 27.5% vs 37.7%, diarrhea 18.8% vs 23.1%, and vomiting 7.4% vs 5% in the gentamicin/azithromycin vs gemifloxacin/azithromycin groups). Antimicrobial susceptibility was determined for 421 isolates from 396 patients. Azithromycin MICs of 2 μg/ml or higher were reported in only 0.5% of isolates, and elevated gemifloxacin MICs (1 μg/ml or higher) were reported in 17.1%. No isolates were resistant to gentamicin. Both combination treatments demonstrated excellent microbiological efficacy for patients with urogenital gonococcal infection. These regimens are now listed as potential alternative therapies for patients with severe β-lactam/cephalosporin allergy in the updated 2015 guidelines.[2]

A group of authors[34] conducted a retrospective study of patients with pharyngeal gonorrhea treated at a single site from 1993–2011. The objective of the study was to determine the proportion of repeat positive tests performed 7–180 days after treatment with an agent active against *N. gonorrhoeae*. Positive tests of the pharynx, including either culture or NAAT, were performed during the time period. Throughout the entire study period, intramuscular ceftriaxone 250 mg was recommended for pharyngeal gonorrhea. Treatment of chlamydial infection with azithromycin or doxycycline was administered to all patients treated for gonorrhea until 2011, unless the patient had a negative test at the time of treatment.

Of 1440 cases, 360 (25%) had repeat pharyngeal tests performed during the study period. The proportion of patients with repeat positive tests was lowest in those receiving a combination of an oral cephalosporin and azithromycin (7%) or intramuscular ceftriaxone alone (9.1%), and it was highest in those receiving an oral cephalosporin alone (29.8%) or oral cephalosporin/doxycycline combination (33.3%). The results of this study suggest that combination treatment with an oral cephalosporin plus azithromycin provides similar efficacy compared with intramuscular ceftriaxone alone for pharyn-

geal gonorrhea, and both regimens appear to be superior to treatment with an oral cephalosporin alone or in combination with doxycycline.

New Agents

Table 4 summarizes the agents currently in phase 2 and 3 studies for the treatment of gonorrhea.

Solithromycin

Drug Class and Mechanism of Action

Solithromycin (CEM-101) is a fluoroketolide, structurally similar to telithromycin but with increased stability and antimicrobial activity.[35, 36] Solithromycin, similar to macrolide/ketolide antibiotics, binds to the 50S ribosomal subunit, inhibiting protein synthesis.[35]

Pharmacokinetics

The pharmacokinetic (PK) properties of solithromycin were evaluated in single and multiple oral dosing strategies in healthy adults.[37] In the single-dose arm, the time to peak concentration (T_{max}) ranged from 1.5–6 hours, with the plasma half-life ranging from 3.16–7.42 hours.[37] In the multidose arm, the time-to-peak concentration at steady state ranged from 3.5–4 hours, whereas the plasma half-life at steady state ranged from 5.84–8.72 hours. This study also found that high-fat food content did not alter the oral bioavailability of solithromycin. A phase 1 study of 14 male and 14 female adult subjects evaluating the PK properties of a single 1000-mg oral dose within plasma, vaginal, cervical, seminal, rectal, and pharyngeal samples is under way.[38]

In Vitro Activity

The in vitro activity of solithromycin was evaluated in over 200 isolates of *N. gonorrhoeae*.[39] Reported MICs required to inhibit the growth of 50% (MIC_{50}) and 90% (MIC_{90}) of tested isolates was an MIC_{50} of 0.125 μg/ml and MIC_{90} of 0.25 μg/ml, respectively, with the overall MIC range 0.001–32 μg/ml. Furthermore, no isolates displayed resistance to solithromycin. By comparison, the reported MIC_{50} and MIC_{90} data from other tested antibiotics were as follows: 1 and 16 μg/ml for ampicillin, 0.5 and 8 μg/ml for azithromycin, 0.032 and 0.25 μg/ml for cefixime, and 0.016 and 0.125 μg/ml for ceftriaxone. It was noted that solithromycin retained activity against resistant gonococcal strains, particularly those resistant to ESCs.

Clinical Trials

To date, only one phase II trial has been published evaluating the efficacy of solithromycin in the management of gonococcal infections.[40] In that study, the authors recruited otherwise healthy patients, aged 19 years or older, who had evidence of an uncomplicated urogenital gonococcal infection and assigned them to receive either a single dose of solithromycin 1000 or 1200 mg in an open-label fashion. Subjects received urethral, cervical, rectal, and/or pharyngeal culture swabbing at enrollment and 7 days later. The primary outcome was bacterial eradication rates as determined by conversion from a positive to a negative *N. gonorrhoeae* culture. Secondary outcomes included eradication or persistence of *N. gonorrhoeae*, safety and tolerability of solithromycin, and the in vitro MICs of isolated gonococcal strains. Forty-one subjects received solithromycin (13 in the 1000-mg

Table 4. Agents in Phase 2 and 3 Trials for the Treatment of *Neisseria gonorrhoeae* Infections[35–46]

Drug name	Class	Mechanism of action	Dose	Phase of study	Adverse reactions
AZD0914	Spiropyrimidinetrione	Inhibits DNA biosynthesis and accumulation of double-strand cleavages	2000 mg or 3000 mg p.o. × 1	Phase II	Transient dysgeusia, mild headache
GSK2140944	Topoisomerase II inhibitor	Inhibits DNA replication through interactions with the *gyrA* subunit of DNA gyrase and the *parC* subunit of bacterial topoisomerase IV	1500 mg or 3000 mg p.o. × 1	Phase II	Not reported
Solithromycin	Fluoroketolide	Binds to the 50S ribosomal subunit, inhibiting protein synthesis	1000 mg p.o. × 1	Phase III	Diarrhea

group and 28 in the 1200-mg group), with 31 subjects being evaluable and 100% experiencing gonococcal eradication.

An ongoing phase III study is seeking to evaluate the efficacy and safety of a single dose of solithromycin 1000 mg versus a single dose of intramuscular ceftriaxone 500 mg plus oral azithromycin 1000 mg in patients aged 15 years or older with laboratory-confirmed *N. gonorrhoeae* infections.[41] This study is currently recruiting patients in the United States and Australia, with a target enrollment of 300 subjects and an estimated completion date of August 2015.

Dosing

Based on the previously described trial data, solithromycin is expected to be dosed as a single oral dose of 1000 mg.

Adverse Drug Events

From the available literature, solithromycin appears to be safe and well tolerated; however, these data are drawn from a small sample size and should be cautiously applied. In the one published study of solithromycin use in gonococcal infections, the most common adverse effect, experienced by ~40% of all study subjects, was mild diarrhea.[37] This effect was seen in a large proportion of patients (61% [17/28]) who received the 1200-mg oral dose. By comparison, only 15% of subjects ([2/13]) who received the 1000-mg oral dose experienced diarrhea.

GSK2140944

Drug Class and Mechanism of Action

GSK2140944 is a novel bacterial topoisomerase inhibitor. It selectively inhibits bacterial topoisomerase II through a binding mode different from that of the fluoroquinolones.[42] It selectively inhibits bacterial DNA replication through interactions with the *gyrA* subunit of DNA gyrase and the *parC* subunit of bacterial topoisomerase IV.[42]

Pharmacokinetics

A group of authors published, in abstract form, their PK findings from a study of 24 healthy subjects evaluating single oral doses of GSK2140944 800, 1500, 2300, and 3000 mg.[43] The available PK data are limited to a reported clearance of 83.8 L/hour, a range of 9.4–51% in the reported variability in clearance, zero-order absorption, and an absorption lag time.

In Vitro Activity

Published in vitro data for GSK2140944 is not currently available.

Clinical Trials

GSK2140944 is currently undergoing a phase II randomized open-label study designed to determine the optimal oral dose and evaluating efficacy, safety, and tolerability in patients with uncomplicated urogenital gonorrhea.[44] Approximately 100 subjects will be enrolled who must be 18 years of age or older, male or female, and have clinical suspicion of a urogenital gonococcal infection due to prior culture, NAAT, Gram's stain, or sexual contact with a partner diagnosed with gonorrhea within the past 14 days. Subjects will undergo safety and microbiologic assessments on day 1 and be randomly assigned to receive either a single 1500-mg or 3000-mg oral dose of GSK2140944. The primary outcome measure is culture-confirmed eradication of urogenital gonococcal bacteria at the test-of-cure visit (days 4–8). Secondary outcome measures include the number of subjects with adverse events at any point during the study, as well as vital sign assessments, clinical laboratory assessments, electrocardiogram assessments, and physical examinations.

AZD0914

Drug Class and Mechanism of Action

AZD0914 is the first member of a novel class, spiropyrimidinetriones, with a mechanism of action different from other available antimicrobials. AZD0914 inhibits DNA biosynthesis and accumulation of double-strand cleavages.[23, 45]

Pharmacokinetics

AZD0914 was investigated in a phase I study to assess the safety, tolerability, and PK following a single oral dose in healthy volunteers aged 18–55 years.[45] Doses ranging from 200–4000 mg demonstrated that AZD0914, generally, displayed dose-proportional increases in plasma concentration up to 800 mg. Doses above

800 mg consistently led to slightly less than dose-proportional increases up to 4000 mg. The median T_{max} ranged from 1.50–2.26 hours, and the mean terminal elimination half-life was relatively consistent, ranging from 5.29–6.31 hours.

In terms of food effects, an increase in geometric mean area under the curve was observed for both the 1500 mg and 3000 mg dose groups in the fed state compared with fasting; however, these increases were deemed to be clinically insignificant. The elimination half-life was 5–7 hours during both the fasting or fed periods. For both doses, median T_{max} was 2.50 hours for fasted subjects and 4.00 hours for fed subjects. In future trials, AZD0914 will be administered without regard to meals.

Dosing

Single doses of 2000 or 3000 mg were selected for the phase II study in patients with uncomplicated gonorrhea.[42, 46]

In Vitro Activity

The in vitro antibacterial activity of AZD0914 was determined against 250 *N. gonorrhoeae* isolates including 100 consecutive clinical isolates, 121 selected strains, and 29 international reference strains.[45] The AZD0914 MIC_{90}s against these groups were 0.125, 0.25, and 0.125 μg/ml, respectively. One group investigated the ability of AZD0914 to suppress the emergence of resistance in vitro to *N. gonorrhoeae* and also examined the propensity of resistance development in fluoroquinolone- and ESC-resistant isolates. AZD0914 had a low rate of resistance development that was not impacted by the resistance phenotype of the gonococcal isolate. In addition, the increased MICs for AZD0914 in *N. gonorrhoeae* were mapped to *gyrB,* as opposed to *gyrA,* which is seen most commonly with ciprofloxacin, further supporting its unique mechanism of action relative to the fluoroquinolone class of antibiotics.[23]

Clinical Trials

A randomized open-label phase II study evaluating the efficacy and safety of a single oral dose of AZD0914 2000 or 3000 mg suspension compared with intramuscular ceftriaxone 500 mg in the treatment of uncomplicated gonorrhea is currently ongoing.[46] The study will be conducted at five sites in the United States, enrolling 180 healthy adult male and female subjects between the ages of 18 and 55 years. The primary study end point is the proportion of subjects with microbiological cure at urethral or cervical sites in each study. Secondary end points include microbiological cure rates of rectal and pharyngeal sites; rates of undetectable NAATs in urethral, cervical, rectal, and pharyngeal specimens; clinical cure rates in each study arm; and AZD0914 and ceftriaxone MIC values. With the exception of MIC values, which will be evaluated at baseline, all end points will be evaluated 6 days after drug administration.

Adverse Drug Events

In the completed phase I study, there were no deaths, serious adverse events, or drug discontinuations due to adverse events.[45] Transient dysgeusia (60%) was the most commonly reported adverse event in subjects receiving AZD0914 and was attributed to the suspension formulation. Mild transient headache (38%) was also observed.

No clinically significant changes in QTc or QRS intervals were observed in trials. No clinically relevant changes or trends in laboratory values, including hematology, clinical chemistry, and urinalysis variables, were observed during the study.

Delafloxacin

Delafloxacin (originally known as RX-3341), a fluoroquinolone antibiotic that is equally potent against both DNA gyrase and topoisomerase IV, is no longer under investigation as monotherapy for the treatment of gonorrhea. This is a result of an interim review concluding that a single dose of delafloxacin may not be sufficient to adequately treat patients with a gonococcal infection.[47] It continues to be investigated for skin and soft tissue infections.

Additional Agents Not Yet Evaluated in Human Subjects

Several compounds are being evaluated for potential use against *N. gonorrhoeae,* but data are largely limited to in vitro studies. These compounds include EDP-420 and EDP-322 (bicyclic macrolides); avarofloxacin, sitafloxacin, and WQ-3810 (fluoroquinolones); eravacycline (fluorocycline); and SM-295291 and SM-369926 (2-acyl carbapenems); as well as potential

expansion of dalbavancin (lipoglycopeptide), ertapenem (carbapenem), and tigecycline (glycylcycline) use.[1] Due to a lack of in vivo data, these agents will not be reviewed at this time.

Conclusion

Neisseria gonorrhoeae infection remains an important public health issue that continues to affect many individuals. The optimal treatment regimen is still left wanting. Globally, antimicrobial resistance of *N. gonorrhoeae* is increasing, including high-level resistance to both components of the first-line treatment regimen: ceftriaxone and azithromycin. Although ceftriaxone resistance has not yet been reported in the United States, it is only a matter of time before such isolates are detected, thus ushering in a new era of difficult-to-manage, uncomplicated, gonococcal infection. The potential public health crisis and patient-associated sequelae linked with untreatable gonorrhea are cause for great concern. The theoretical benefit of combination treatment with ceftriaxone and azithromycin, even with higher doses, will only provide temporary efficacy.

Future resources should be dedicated to enhanced surveillance and susceptibility testing. An increase in both the number of laboratories performing susceptibility testing and the quality of susceptibility tests is needed. The development of a commercially available rapid diagnostic test to detect the presence of gonococcal (urogenital and extragenital) infection and antimicrobial resistance, even to a single antimicrobial class, would be an invaluable tool. The use of such a testing method would allow for upfront, judicious use of last-line treatment agents in appropriate clinical scenarios. This practice of antimicrobial stewardship for gonococcal disease is currently not available.

The identification of gonococcal resistance to ceftriaxone has resulted in efforts to develop new and novel antimicrobial agents, discover and test new antimicrobial combinations, and repurpose older agents for the treatment of uncomplicated gonorrhea. Solithromycin, GSK2140944, and AZD0914 are promising novel agents in various stages of clinical trial evaluation for the treatment of *N. gonorrhoeae*. In addition, several compounds are not yet evaluated in human subjects that have potential for treatment options for gonorrheal infection. Until all of these agents are fully studied in human trials, and their full safety and efficacy profiles are known, conscientious approaches to the antibiotic management of *N. gonorrhoeae* infections using combination therapy with a β-lactam, preferably intramuscular ceftriaxone, and azithromycin is necessary.

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