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Preparing for an Era of Untreatable Gonorrhea

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Abstract

Purpose of Review—The proportion of *Neisseria gonorrhoeae* isolates with reduced susceptibility to extended-spectrum cephalosporins (ESC) has increased rapidly since 2006. Clinicians, researchers and public health officials need to be prepared for the possibility of an era of untreatable gonorrhea. This review focuses on the evidence for current gonorrhea treatment recommendations, potential future treatment options, and other methods to control gonorrhea.

Recent Findings—In addition to an increased in isolates with decreased susceptibility to ESCs, there have been reported treatment failure to both cefixime and ceftriaxone. In response, some countries have increased the recommended cephalosporin dose, and most now recommend dual-therapy with an ESC and azithromycin. The pharynx has been implicated as a site for acquiring resistance through transformation with commensal *Neisseria* species or induced resistance through subtherapeutic antimicrobial levels. Thus, appropriate screening of the pharynx and treatment with a regimen which eradicates gonorrhea from the pharynx is necessary. At present, several studies are evaluating various novel treatment regimens in preparation for an era of untreatable gonorrhea.

Summary—Screening for asymptomatic infections, maintaining culture capacity to monitor antimicrobial resistance, treating with ceftriaxone plus azithromycin, and ensuring that all sexual partners are treated, are among the best strategies to control gonorrhea in the current climate.

Keywords

Neisseria gonorrhoeae; antimicrobial resistance; novel treatments; extended spectrum cephalosporins

INTRODUCTION

With the growing number of reports on increasing resistance to extended-spectrum cephalosporins (ESC), [1–4] the threat of antimicrobial resistant (AMR) gonorrhea has become a major public health concern. [5] *Neisseria gonorrhoeae*, the gram-negative bacteria which causes the sexually transmitted disease (STD) gonorrhea, has adeptly developed resistance to all first-line antimicrobials since the arrival of the first

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antimicrobials in the 1930s, the sulfonamides, and subsequently developed resistance to penicillins, tetracyclines and fluoroquinolones.[6] Now, the last class of first-line therapy, the extended-spectrum cephalosporins, is being threatened. Between 2006 and 2011, there was a rapid rise in the proportion of isolates in the United States (US) with an elevated minimal inhibitory concentration (MIC)(the amount of an antimicrobial required to inhibit growth of a bacteria *in vitro*) to cefixime the oral ESC.[2] Although overall less than 2% of U.S. isolates demonstrate an elevated MIC to cefixime (see Figure 1), the rapidity of rise in a just five years coupled with reports of treatment failures to both cefixime[7–9] and ceftriaxone,[10, 11] the injectable ESC in Japan and Europe, prompted the head of the Centers for Disease Control and Prevention STD Division to “sound the alarm.”[12]

Although resistance and treatment failures are not widespread at present, the fear of an era of untreatable gonorrhea calls for urgent development of new treatments and other public health control methods to prevent the spread of AMR gonorrhea.

THE ROLE OF THE PHARYNX

Among men who have sex with men (MSM), and certain populations of women, gonococcal infections at the pharynx are common,[13–18] and among MSM extra-genital infections (pharyngeal and rectal) comprise the majority of all gonococcal infections (57% – 83%).[19, 20] Moreover, since these infections are typically asymptomatic,[17] they are often not screened for and go un-diagnosed. The CDC has recommended routine screening of MSM for pharyngeal gonorrhea since 2002 using culture, and in 2010 revised the testing method to promote nucleic acid amplification testing (NAAT) which is more sensitive than culture.[21] However, few MSM undergo pharyngeal screening, and currently there are no recommendations to screen women. In 2008, only 64% of MSM STD clinic patients were screened for pharyngeal gonorrhea.[22] Screening outside of STD specialty clinics is likely much lower. These common, asymptomatic, yet underscreened infections may drive the epidemic among MSM and other populations by acting as undetected reservoirs of *N. gonorrhoeae*.

In addition to serving as a reservoir of gonorrhea in a community, the pharynx may promote the emergence of antimicrobial resistance.[6, 23, 24] The gonococcus is adept at acquiring DNA from other *Neisseria* species. And, since several commensal *Neisseria* inhabit the oropharynx, it is thought that at least some of *N. gonorrhoeae*'s antimicrobial resistance has arisen due to acquisition of resistance genes from commensal *Neisseria* in the oropharynx. [6, 25, 26]

Lastly, pharyngeal gonorrhea is also important in the treatment of *N. gonorrhoeae* because it has been consistently shown that eradication of gonorrhea from the oropharynx is more difficult than eradication from urogenital sites. [23, 27, 28] The exact reason for this treatment differential remains unknown, but several theories exist ranging from differential host mucosal immunity at the pharynx as compared to the anogenital tracts, to selectively fit organisms with a predilection for the oropharynx, and from the idea that human sexual behavior may influence which gonococcal strains are preferentially transmitted among those who practice oral sex, to the most commonly held belief that antimicrobials do not achieve

high enough concentrations for a long enough period of time in the oropharynx as compared to the anogenital tract.[28] Moreover, current pharmacokinetic/pharmacodynamic (PK/PD) studies generally rely on antibiotic levels in the serum, but a different compartment, such as tonsillar tissue or saliva, may be a more appropriate measure of antimicrobial activity at the pharynx for *N. gonorrhoeae*.

EVIDENCE FOR CURRENT RECOMMENDED TREATMENT REGIMENS

Recommended therapy for uncomplicated gonococcal infections in the US, the United Kingdom (UK), and Europe currently include ceftriaxone plus azithromycin, with the recommended ceftriaxone doses (Table 1) ranging from 250mg in the US[29] to 500mg intramuscularly in the UK and Europe.[30, 31] The Japanese recommend 1g of ceftriaxone alone.[6] This broad range of doses reflects the lack of data to support one dose over another. One randomized, dose-ranging study of ceftriaxone for uncomplicated gonococcal exists, though it was published in 1981.[33] All subjects were cured (including 4 cases of pharyngeal gonorrhea) at doses of 125 mg, 250mg and 500mg. Notably, the ceftriaxone MIC₉₀ in that study was 0.016 µg/mL, similar to contemporary US isolates (MIC₉₀ 0.015 – 0.03 µg/mL).[34] Although the majority of the circulating gonococcal isolates in the US have a ceftriaxone MIC <0.03 µg/mL, there are no randomized controlled trials (RCT) comparing the efficacy of varying doses of ceftriaxone in contemporary times. A recent meta-analysis reviewed RCTs which compare ceftriaxone to other antimicrobials,[35] concluded that 250mg of intramuscular ceftriaxone is superior to 400mg oral cefixime, 2g intramuscular spectinomycin and 500mg of cefotaxime.

Although no empiric pharmacokinetic/pharmacodynamic (PK/PD) data exist to guide cephalosporin dosing, extrapolating from Jaffe's work with penicillin, the generally accepted PK criterion to treat uncomplicated anogenital gonorrhea recommends that the total serum antimicrobial level should exceed four times the MIC for 7 – 10 hours.[36] In a meta-analysis, Moran and Levine extrapolated from that criterion to estimate that pharyngeal gonorrhea requires total serum antimicrobial levels to exceed more than 20 hours over four times the MIC to be effective.[27] An alternative school of thought believes that because of the high degree of protein binding, the free serum cephalosporin level should be used. Under this theory, free serum cephalosporin levels only need to exceed the MIC for a comparable period of time.[37] Using pharmacokinetic factors for free serum levels, data suggest that for the vast majority of isolates seen in the US between 2007 and 2011 (MIC 0.03 µg/mL), 125 mg of ceftriaxone should be effective, as serum levels remains elevated more than four times the MIC for 32.9 hours.[37] However, as the MIC increases, a higher dose is necessary. For example, at an MIC of 0.125 µg/mL, 125 mg of ceftriaxone reaches target serum levels for only 15.6 hours, 250mg for 24.3 hours, 500mg for 32.8 hours, and 1 g for 41.3 hours. Similarly, a 400mg oral dose of cefixime should be effective for pharyngeal gonorrhea if the MIC is 0.06 µg/mL, or anogenital gonorrhea at an MIC of 0.125 µg/mL.[37] However, a recent case series has called into question these PK/PD parameters. Allen et al reported on 9 cefixime treatment failures, 7 anogenital cases and 2 pharyngeal cases, of which all of the isolates had an MIC of 0.12 µg/mL.[9] Additionally, six of the cases were treated with two drugs, either cefixime plus doxycycline (5/6) or cefixime (800mg) with azithromycin 1g (pharyngeal case). It has yet to be determined what dose is necessary to prevent the

development of resistance, but some attribute the decline in the proportion of isolates with decreased susceptibility to cefixime in 2012 as ecological evidence that the changed treatment recommendation to an increased dose of ceftriaxone in combination with a second drug stems the spread of resistance.[1, 38]

Although two-drug therapy for gonorrhea was originally implemented for the co-treatment of *Chlamydia trachomatis*, the rationale to specifically recommend the use of two-drug therapy for gonorrhea was largely borne out of clinical experience with other bacteria that acquire resistance quickly. Several retrospective studies now support the efficacy of combination therapy for pharyngeal gonorrhea,[39–41] though whether or not dual therapy stems the development of resistance has yet to be proven. In addition to endorsing the role of combination therapy in gonococcal therapy, these studies provide evidence for the superiority of the combination of a cephalosporin plus azithromycin over a cephalosporin plus doxycycline, and the CDC now emphasizes the preferential use of azithromycin.[29] The UK and Europe only recommend azithromycin as the second agent.[42]

POTENTIAL NOVEL TREATMENT REGIMENS

Because it is more difficult to treat pharyngeal gonorrhea, and because infections at the pharynx may go undiagnosed, most experts agree that all recommended treatment regimens be able to eradicate gonorrhea at the pharynx. Thus, in developing a new treatment for gonorrhea in anticipation of cephalosporin-resistance, it is important to examine the drug's impact on pharyngeal gonorrhea. Moreover, the World Health Organization (WHO) asserts that recommended gonococcal treatment regimens should be 95% efficacious and that regimens be discontinued when there is more than 5% resistance in the population.[42] In anticipation of an era of widespread cephalosporin-resistant *N. gonorrhoeae*, several options for novel treatments have been proposed including increasing the dose and duration of either cefixime or ceftriaxone, new combinations of older antimicrobials, recycling formerly used antimicrobials, and truly novel antimicrobials.

By abandoning the historical guide that STD treatment should be single dose therapy, it may be possible to increase either the dose or duration or both of the cephalosporins. This strategy has already been implemented without a clinical trial in some settings. The UK and Europe use 500mg and Japan uses 1g of ceftriaxone,[42] and Canada currently recommends 800mg of cefixime for uncomplicated GC in non-MSM and non-pharyngeal cases.[32] There is currently a Phase I clinical trial underway ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01949363) NCT01949363) testing the safety and tolerability 800mg of cefixime given every twelve or every eight hours in a 24 hour period. In pharmacokinetic models, these doses are expected to exceed serum cefixime levels of 4× the MIC of gonococci with MIC's 0.5 µg/mL for over 20 hours, and allow for a fully oral treatment regimen.

Of the older antimicrobials that could be brought back into use, spectinomycin, an aminoglycoside, is not reliable in the treatment of pharyngeal gonorrhea, induces the development of resistance quickly and is not available in all countries.[6] Gentamicin, also an aminoglycoside, has been used successfully as single dose therapy for urogenital gonorrhea in Malawi for years,[6, 43] but in a recent meta-analysis, single dose gentamicin

failed to meet the WHO's criteria of being 95% effective.[44] However, in combination with azithromycin 2g orally, gentamicin was extremely effective in a recent clinical trial.[45] This same CDC-funded study also found that the combination of gemifloxacin plus azithromycin was highly efficacious.

Many researchers have tested older antimicrobials against *N. gonorrhoeae* in the laboratory. Unemo and colleagues tested ertapenem *in vitro* and showed that it has preserved activity against ceftriaxone-resistant isolates.[46] But, as ertapenem is only available parenterally, it is a choice of last resort. Several *in vitro* synergy studies have tested combination therapies of existing antimicrobials in novel combinations.[47–49] Few have found synergistic combinations, but the lack of antagonism makes them promising still. In particular, the combinations of ceftriaxone plus fosfomycin and cefixime plus rifampin[49] are enticing possibilities as the second agents have not been used for gonococcal therapy previously. Additionally, ceftriaxone plus fosfomycin revealed partial synergy, and the cefixime plus rifampin combination provides a fully oral regimens. As exciting as these prospects are, these opportunities are far from ready for primetime. Prior to undertaking human studies with these combinations, much investigation into the pharmacokinetics and proper dosing will be necessary.

Two novel antibiotics are in or nearing Phase 3 clinical trial stage. Solithromycin is a fluoroketolide (a type of macrolide) which has had good activity against *N. gonorrhoeae*, *C. trachomatis*, and *Mycoplasma genitalium in vitro*, even among isolates with low-level azithromycin resistance.[50] And, solithromycin has a higher barrier to resistance than the macrolides as it binds to three sites on the ribosome as opposed to 2. Another Phase 3 trial will compare delafloxacin, a fluoroquinolone, to ceftriaxone and is poised to begin enrolling shortly ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02015637) NCT02015637). AZD0914 is another type of fluoroquinolone which will be tested in a Phase I PK study ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01929629) NCT01929629) in the near future. Laboratory studies suggest that it has preserved *in vitro* activity against ciprofloxacin-resistant gonorrhea.[51]

OTHER PUBLIC HEALTH CONTROL METHODS

Gonorrhea rates in the US decline nearly 80% between the 1970s and late 1990s, in large part due to the National Gonorrhea Control Program which encouraged routine screening of asymptomatic women and ensuring the treatment of sexual partners.[52] In the same way, if the pharynx and the rectum serve as reservoirs of gonorrhea among MSM, we might be able to decrease the burden of disease among MSM by increasing screening of asymptomatic extra-genital infections. The advent of NAAT-based testing has improved detection[19] significantly over culture-based testing which should assist with case-finding and treatment. NAAT-based testing also allows for patients to self-collect specimens[53] which permits for testing outside of traditional clinic settings, such as in the community or at home. With these enhanced opportunities to expand screening efforts, we may be able to help decrease the community prevalence of gonorrhea among MSM. Unfortunately, many MSM currently go unscreened; operational research to explore best ways to expand screening services is needed.

At the same time that NAAT may increase screening efforts, NAAT-based testing limits our capacity for antimicrobial resistance surveillance as it requires culturing the gonococcus. AMR surveillance is a key foundation to public health's efforts to monitor resistance patterns in circulating strains. How to best maintain culture capability while reaping the benefits of NAAT remains an open question. Some public health programs and STD clinics have chosen to culture all symptomatic urethritis as well as screen-positive sites in yet untreated persons. Additionally, many research groups are working on molecular methods to identify resistant gonococcal strains directly from the NAAT-based sample;[54] however, none are commercially available yet.

The second pillar of the National Gonococcal Control Program from the 1970s was ensuring partner treatment. Currently many states allow for Expedited Partner Therapy (EPT) which is the presumptive treatment of a patient's sex partners. EPT has been tremendously successful decreasing gonorrhea re-infection rates.[55] However, with the CDC's demotion of cefixime from first-line therapy to an alternative therapy, some have interpreted that to mean that EPT is no longer available, despite the CDC continuing to recommend cefixime and azithromycin for EPT for heterosexuals (EPT should not be used for MSM as decreased susceptibility GC disproportionately affects that population, and there is an increased likelihood of pharyngeal GC among MSM which may not be effectively treated with a fully oral regimen).[29] Some are concerned that abandoning EPT will have a negative impact on the overall community prevalence.[56]

CONCLUSION

Neisseria gonorrhoeae with decreased susceptibility to the ESC is on the rise around the globe, but our current strategy of using ceftriaxone plus azithromycin appears to be working for now. Research priorities to prepare for an era of untreatable gonorrhea include determining more accurate PK/PD parameters to help guide the development of new treatment regimens, operational research to help expand extra-genital NAAT-based screening in the highest risk community, and developing molecular methods as an adjuvant to NAAT-based testing for continued AMR surveillance. Additionally, while there are several novel treatment options in the pipeline, screening of at-risk populations and ensuring sex partner therapy may be our most effective weapon against the gonococcus at this time.

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KEY POINTS

- Gonococcal isolates with decreased susceptibility to cefixime increased rapidly between 2006 and 2011; however, in 2012 there was a slight decline in the proportion of isolates with elevated MICs to cefixime.
- Currently recommended therapy for gonorrhea in the U.S. includes ceftriaxone 250mg intramuscularly plus azithromycin 1g orally.
- Several studies are underway to develop novel treatments for the potential of cephalosporin-resistant *N. gonorrhoeae*.
- Screening asymptomatic infections, appropriate antimicrobial therapy, treatment of sexual partners and antimicrobial resistance surveillance are some of our best defense mechanisms at this time.

Figure 1.

Proportion of Gonococcal Isolates tested by Gonococcal Isolate Surveillance Program (GISP) with CDC 'alert value' MIC§ to Cefixime*, Ceftriaxone, Azithromycin; 2007 – 2012

§CDC defines alert value MIC to cefixime as 0.25 µg/mL, ceftriaxone 0.125 µg/mL, and Azithromycin 2.0 µg/mL. *Cefixime MIC were not tested in 2007 and 2008. Data compiled from CDC STD Surveillance Reports 2007 – 2012.

Table 1

Various Dosing Regimens of Ceftriaxone for *N. gonorrhoeae* throughout the world.

Country	Ceftriaxone Dose	Combination therapy recommended?	Recommended Second Agent	Reference
United States	250mg IM	Yes	Azithromycin (preferred) or, Doxycycline	[29]
United Kingdom	500mg IM	Yes	Azithromycin	[30]
Europe	500mg IM	Yes	Azithromycin	[31]
Japan	1g IV	No		[6]
Canada	250mg IM or 800mg Cefixime PO [^]	Yes	Azithromycin	[32]

[^] Cefixime is listed as an alternative treatment for MSM, but first-line therapy for heterosexuals.