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The use of cephalosporins for gonorrhea: an update on the rising problem of resistance

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Abstract

Introduction—Over the last several years, *Neisseria gonorrhoeae* has developed decreased susceptibility to extended-spectrum cephalosporins worldwide.

Areas covered—Gonococcal antimicrobial surveillance programs in multiple regions have documented the rise in *N. gonorrhoeae* isolates' minimum inhibitory concentrations to cephalosporins, and the first cases of ceftriaxone treatment failures have been reported. These developments have prompted the use of the term “superbug,” and concerns about the emergence of untreatable gonococcal infections. In response to this threat, a variety of treatment strategies have been proposed, including increasing the dose or providing multiple doses of cephalosporins, multidrug therapy, rotating therapeutic regimens, and individualized treatment based on susceptibility testing.

Expert opinion—A robust public health response is needed, and includes better diagnosis and treatment of pharyngeal gonorrhea, improved surveillance of antimicrobial resistance, informed treatment approaches, and reduction of the global burden of gonococcal infections.

1. Introduction

Since the publication of the last detailed review of the use of cephalosporins for gonorrhea in this journal,¹ several new developments have occurred; of primary importance is the global demonstration of decreasing susceptibility to extended-spectrum cephalosporins (ESCs). Indeed, some have applied the term “superbug” to multidrug resistant *Neisseria gonorrhoeae* isolates discovered in France and Japan, and have raised the specter of untreatable gonococcal infections.^{2–7} Increasing resistance is a large public health concern because the global burden of sexually transmitted *N. gonorrhoeae* infections is substantial; there were an estimated 88 million new cases of gonorrhea worldwide in 2005.⁸ If not effectively treated, gonococcal infections can result in pelvic inflammatory disease, infertility, chronic pain, and increased spread of HIV infection.^{6, 9–11}

Since the advent of antibiotic therapy, *N. gonorrhoeae* has repeatedly developed resistance to the drugs used to treat it, including sulfonamides, penicillin, tetracyclines, and fluoroquinolones.¹ This ability of *N. gonorrhoeae* to acquire resistance quickly is in large part a result of the ease with which it can integrate *Neisseria* DNA from the environment into its own genome. Several genetic alterations conferring resistance to ESCs have been described. The primary group consists of a single alteration (A501V) or multiple “mosaic”

alterations in the *penA* gene that codes for penicillin binding protein 2 (PBP2), the target site of ESCs and other beta-lactam antibiotics. These mosaic alterations have been classified by Roman numeral, with mosaic pattern X the initially identified mosaic associated with decreased susceptibility to oral cephalosporins in Japan.¹² Although specific amino acid alterations have been identified as important in conferring decreased susceptibility to ESCs, these alterations likely also depend on other mutations in the mosaic pattern resulting in substantial ESC minimum inhibitory concentration (MIC) changes.¹³ Other genetic alterations play a role as well, including alterations in the *mtrR* efflux pump system that increases efflux of antimicrobials from the cell,^{14, 15} the *penB* mutations affecting an outer membrane porin protein,^{16, 17} and at least one as yet undetermined factor.^{3, 18, 19} Although most of these alterations seem to affect both oral and injectable ESCs, there is significant variability so that organisms resistant to cefixime have remained generally susceptible to ceftriaxone. However, this might be changing, as evidenced by case reports of ceftriaxone treatment failures.

There is no comprehensive surveillance program for gonococcal antimicrobial resistance, however multiple country-wide and regional programs have documented the decrease in cephalosporin susceptibility globally. Antimicrobial surveillance is complicated by both inter-laboratory discrepancies and difficulty defining cephalosporin resistance, a result of relatively few cephalosporin treatment failures to inform the relationship between MIC of oral or injectable ESCs and clinical treatment failure.¹ Thus 'decreased susceptibility' to ceftriaxone itself is variably characterized, with some considering MICs 0.064 mg/L not susceptible,^{20, 21} while others use 0.125 mg/L,²² >0.125 mg/L,²³ or >0.25 mg/L as criteria to indicate decreased susceptibility.²⁴ Despite the observed decreasing susceptibility, given the lack of a proven suitable alternative treatment ESCs remain the mainstay of therapy in much of the world; both oral and injectable ESCs are used, but the injectable, ceftriaxone, has more advantageous pharmacokinetics and potent antigonococcal activity than the oral ESCs such as cefixime and others. In response to the threat of untreatable gonococcal infections, several agencies have made changes to treatment recommendations, and more attention is focused on expanding the systems in place to monitor antimicrobial resistance.

2. Cephalosporin treatment failures and the emergence of ceftriaxone resistance

The steady march upward in *N. gonorrhoeae* isolates' MICs to cephalosporins in the last few years has been accompanied by increasing reports of treatment failures. The first failures in treatment with oral ESCs were reported several years ago in Japan,^{25, 26} however more recently there have been oral ESC failures described in Hong Kong,²⁷ England,^{28, 29} Austria,³⁰ Norway,³¹ and France.² Much of the spread of cefixime-resistant gonorrhea appears to be a result of the dissemination of resistant clones, of which *N. gonorrhoeae* multiantigen sequence typing ST1407 is particularly common.^{2, 32} Accompanying the reports of oral ESC treatment failure and of even greater concern, new reports of treatment failure with injectable ceftriaxone and the isolation of organisms with high-level ceftriaxone resistance have emerged, leading to fear of untreatable gonococcal infections.

2.1 First reports of ceftriaxone treatment failure in treatment of pharyngeal gonorrhea

Reports of ceftriaxone treatment failure first emerged in the treatment of pharyngeal gonorrhea. Two cases were described in Australia in 2009; in both cases the infected individuals' coincident urogenital infections resolved after treatment with ceftriaxone 250mg IM, while the pharyngeal test-of-cure cultures remained positive for gonorrhea. The ceftriaxone MICs were 0.03 and 0.016 mg/L. The patients both required higher doses of ceftriaxone for cure (one received azithromycin 1gm orally followed a week later by ceftriaxone 500mg IM, and the other patient received ceftriaxone 1gm IM).³³ In Sweden in 2010, a patient developed pharyngeal gonorrhea with a ceftriaxone MIC of 0.125–0.25 mg/L; the infection failed to resolve after treatment with ceftriaxone 250mg IM on Day 26 or ceftriaxone 500mg IM on Day 43. The patient was cured after eventual treatment with ceftriaxone 1g administered intravenously on Day 71.³⁴ Pharyngeal gonococcal infections are more difficult to cure than anogenital infections,^{35, 36} and both the Australian and the Swedish treatment courses likely failed at least in part as a result of inherent differences by site of infection in response to treatment. The Swedish gonococcal isolate also exhibited decreased susceptibility to ceftriaxone which likely contributed to the clinical failure.³⁴

2.2 Identification of strains with high-level ceftriaxone resistance

In January 2011, Japan reported the first *N. gonorrhoeae* strain that was resistant to ceftriaxone (MIC of 2–4 mg/L) and most other antibiotics.^{3, 37} Molecular sequencing of this strain (H041), cultured from the pharynx of a commercial sex worker, revealed the presence of a new *penA* mosaic allele which appeared to have conferred ceftriaxone resistance. This new mosaic allele differed from the mosaic pattern X by 12 amino acids, four of which had not been identified before in *N. gonorrhoeae*.³ In December 2011 in France, the second *N. gonorrhoeae* strain (F89) was reported with resistance to ceftriaxone (MIC 1–2 mg/L);² the *penA* mosaic allele was identical to a mosaic allele previously described in San Francisco (pattern XXXIV),³⁸ Taiwan,³⁹ and Canada,⁴⁰ except for the addition of a single amino acid change previously associated with oral ESC resistance when present alone (A501V).⁴¹ The new mosaic allele was the likely determinant of ceftriaxone resistance.² These two resistant isolates, H041 and F89, are related to two different multilocus sequence typing (MLST) clones, both of which have been successful at spreading internationally, signifying a concerning development in the growing risk of globally-spread ceftriaxone-resistant gonorrhea.²

3. Surveillance programs

Over the past several years, gonococcal isolates with increasing resistance to multiple drugs have been identified, with reports of rising cephalosporin MICs in more regions of the world. There are established gonococcal antimicrobial surveillance programs in several locations, including the Western Pacific and South East Asian Regions, Australia, Russia, Western Europe, the United Kingdom, and the United States of America; Table 1 summarizes recent trends in *N. gonorrhoeae* isolates' decreasing susceptibility to cephalosporins reported by these surveillance programs. Susceptibility testing for ceftriaxone is standard; monitoring of resistance patterns of oral ESCs is becoming more common. Although significant progress has been made, large territories worldwide remain

with limited or absent surveillance programs, culture capacity, or ability to conduct antimicrobial resistance testing, including in regions such as Eastern Europe and Central Asia (formerly of the Soviet Union) which exhibit a significant burden of gonococcal infections.⁴²

4. Treatment recommendations

In the past, the World Health Organization (WHO) made global antimicrobial recommendations for gonorrhea,^{43, 44} however WHO now recommends that countries create their own treatment guidelines that are based on country-specific resistance information.⁴⁵ In response to the decreasing susceptibility of *N. gonorrhoeae* to ESCs, multiple countries have updated treatment recommendations.

In 2008, 15 countries in the WHO Western Pacific Region Gonococcal Antimicrobial Surveillance Program provided the type and dose of ESCs suggested for treatment; in nine countries ceftriaxone was the first-line treatment with most countries recommending doses of 250mg or higher.⁴⁶ Japan no longer recommends oral cephalosporins, and the recommended dose of ceftriaxone is 1gm IV.^{25, 46} In the urban regions in Australia, the current treatment for gonorrhea in public clinics is ceftriaxone 500mg IM.²¹ In 11 Eastern European, Caucasian, and Central Asian countries of the former Soviet Union surveyed, ceftriaxone 250mg to 1gm IM is the standard therapy.⁴⁷ In 2009, European guidelines recommended ceftriaxone 250mg IM, or cefixime 400mg orally, or spectinomycin 2gm IM for anogenital gonorrhea, and ceftriaxone 250mg IM for pharyngeal gonorrhea.⁴⁸

At least in part as an effort to combat emerging resistance, both the UK and the US have recently recommended two-drug regimens for gonorrhea. In the United Kingdom, guidelines issued in 2011 recommend ceftriaxone 500mg IM plus azithromycin, in addition to a test of cure in all cases.⁴⁹ The United States Centers for Disease Control and Prevention (CDC) issued updated treatment guidelines for gonorrhea in 2010. The recommendation is for dual therapy for gonococcal infections with ceftriaxone 250mg IM plus either azithromycin 1gm orally in a single dose or doxycycline 100mg BID for 7 days. If ceftriaxone is not an option, then cefixime 400mg orally may be administered with either azithromycin or doxycycline. Cefixime is not recommended for pharyngeal gonorrhea.⁵⁰ The 2010 CDC treatment guidelines did not recommend routine tests-of-cure, except in the presence of persistent symptoms following treatment.⁵⁰ However the following year, CDC released a report documenting changes in gonococcal susceptibility to cephalosporins in the U.S., and this report states that healthcare providers “might consider” obtaining tests-of-cure in patients with gonorrhea, and specifically highlights men who have sex with men in the western United States for consideration.⁵¹

5. Conclusions

N. gonorrhoeae is exhibiting decreasing susceptibility to ESCs worldwide, and this *in vitro* trend has been followed by ongoing reports of treatment failures to oral ESCs and new reports of failures to injectable ceftriaxone. There is rising concern that cephalosporin-

resistant gonorrhea will continue to spread throughout the world, as foreshadowed by the patterns seen with the response of *N. gonorrhoeae* to previous antimicrobials.

6. Expert Opinion

There is a pressing need for public health interventions to identify and stem the dissemination of resistant clones and reduce the global burden of disease. Several aspects regarding the development of gonorrhea resistance merit special attention.

6.1 Pharyngeal infections

Pharyngeal gonorrhea might be an overlooked ‘important reservoir of infection’³⁵ with the pharynx functioning as a site where *N. gonorrhoeae* can acquire DNA from other commensal *Neisseria* species resulting in further antibiotic resistance. Pharyngeal gonorrhea has not been a public health or clinical priority because it is nearly universally asymptomatic,⁵² was thought to be rare among patients without anogenital infection, and does not *directly* result in complications such as pelvic inflammatory disease and infertility. Nevertheless, pharyngeal gonorrhea is common with a prevalence of 5–9% among MSM and female sex workers,^{52–54} it can be transmitted to cause urethral infections,⁵⁵ it poses more of a therapeutic challenge than anogenital gonorrhea,^{35, 36} and oral ESCs do not consistently cure gonorrhea of the pharynx.^{36, 50} Ameyama and others have reported evidence that mosaic *penA* alterations have resulted from transformation with DNA from commensal *Neisseria* species^{7, 56} which colonize the pharynges of nearly all adults.⁵⁷ If clones with decreased susceptibility are being generated at an anatomic site that is not being actively screened nor effectively treated, ongoing transmission of gonorrhea and continued emergence of resistance would be expected. Improved diagnosis and treatment of pharyngeal gonorrhea might help reduce the spread of gonorrhea and slow the emergence of antibiotic resistance, while increased doses of ceftriaxone and recommendations for two-drug regimens for gonorrhea might help address the lower cure rate of pharyngeal infections. However, as reviewed above, ceftriaxone failures have now been documented in the treatment of pharyngeal infections with this recommended dose (250mg IM). Pharyngeal gonorrhea merits both further research to determine adequate treatment regimens and heightened public health attention to the importance of screening, treating, and, possibly, obtaining tests of cure.^{7, 34, 58}

6.2 Need for comprehensive surveillance

Worldwide surveillance of gonococcal antimicrobial resistance has improved substantially, however in some regions surveillance remains patchy and lacks uniformity. The lack of surveillance in resource-poor regions has led to concerns that “a silent epidemic of antimicrobial resistance may be occurring.”⁶ It is critical that antimicrobial resistance surveillance be initiated and improved in these areas.

The increase in the use of nucleic acid amplification tests for the detection of gonorrhea has improved sensitivity,⁵⁹ however this does not allow culture and susceptibility testing to be performed at a time when ongoing active surveillance of antimicrobial resistance patterns is essential. Culture remains critical to antimicrobial resistance surveillance; live isolates are

required to allow identification of uncharacterized molecular determinants of decreased susceptibility that would be missed by nucleic acid-based tests that can only be designed to detect known determinants. The recently described PCR assay to detect the resistant *N. gonorrhoeae* H041 strain is an example of such a molecular assay,⁶⁰ and shows particular promise in supplementing traditional methods of antimicrobial resistance surveillance, especially if these assays can be performed on routine specimens collected for diagnosis of gonorrhea. Molecular epidemiological analysis continues to provide valuable information about the modification and spread of cephalosporin-resistant gonococci, and a recent review recommended the use of DNA sequence-based typing methods as the primary means of typing *N. gonorrhoeae* isolates.⁶¹

6.3 Treatment options and alternatives

A number of authors have delineated various therapeutic strategies to try to address the problem of decreasing susceptibility to antibiotics.^{4, 7, 62–65} These strategies are limited by some inherent obstacles: the vast majority of infections are treated at the time of clinical presentation, most infections occur in resource-limited settings, and there are few new candidate antimicrobials in the development pipeline. Nevertheless, the most straightforward strategies - increased dose and multidrug regimens - have already been implemented in some places.

One approach to overcome increasing MIC is by increasing the dose of ceftriaxone. As described above, this has been recommended in many countries with Japan recommending the highest dose, ceftriaxone 1gm IV. This regimen, ceftriaxone 1gm IV, was 100% effective in a 2008 study of treatment for gonorrhea (urogenital [n=48] and/or pharyngeal [n=25]; ceftriaxone MIC range 0.004–0.25 mg/L).⁶⁶ It has been suggested that perhaps the rest of the world should follow suit and treat with comparable doses.⁶⁷

However, a pharmacodynamic analysis by Chisholm et al has cast doubt that even this dose would reliably cure all patients with ceftriaxone MICs ≤ 0.125 mg/L.⁶² The analysis reviewed and updated the pharmacokinetic criteria that should be used to select appropriate drugs and administration regimens. Previous data derived from treatment studies with penicillin found that total drug levels above 3–4 times the MIC for 7–10 hours were needed for reliable cure,⁶⁸ and these parameters were used without significant modification to select other drugs for treating gonorrhea, including ESCs.⁶⁹ However, as Chisholm points out, for highly protein-bound drugs such as ceftriaxone, free serum levels above MIC should be used.⁶² Chisholm uses other experimental data to question whether 7–10 hours above the MIC is sufficiently long²⁶ and proposes that 20–24 hours above the MIC is needed for cephalosporins.⁶² This led to the proposition of another treatment alternative to maximize the time above the MIC: give ceftriaxone IM followed by oral cefixime for a few days.⁶² Both increased dose and multiple doses would certainly increase time above the MIC; however, if penicillin is a model, simply increasing the dose in response to rising MICs ultimately will be a failed strategy, even if it did prolong penicillin's usefulness for more than 30 years.

While the end of the ability to safely use single-dose therapy for gonorrhea may be approaching, multidrug therapy for gonorrhea is another possible tactic.^{4, 7, 62} This is not a

new approach, however in the past two drugs frequently were prescribed when a patient presented with gonorrhea in order to treat coexisting chlamydial infection.⁶² Both the US and UK updated guidelines recommend two-drug therapy for treatment of gonorrhea in all cases,^{49, 50} which may help stem the development of resistance.^{7, 70} Yet the lack of available easy-to-administer antibiotics to include in multidrug regimens remains a concern. Doxycycline resistance is widespread.⁷⁰ There have been reports of emerging high-level resistance to azithromycin, most recently in Hawaii,⁷¹ with accompanying concerns that additional use of this drug may enable the spread of azithromycin resistance.⁶² At least one clinical trial is ongoing to assess the efficacy of two other multidrug regimens which include azithromycin (gentamicin + azithromycin and gemifloxacin + azithromycin).⁷² Additional studies are needed which evaluate higher doses of ceftriaxone in combination with a second (or even a third) antibiotic. Drugs such as ertapenem,⁷³ spectinomycin, and gentamicin^{62, 63, 74} are possible alternate drugs to be used alone or as part of a multidrug regimen, but many difficulties exist in choosing supplemental antibiotics including the lack of existing evidence, ongoing decreasing antibiotic susceptibility, lack of global availability of drugs, and varying efficacy at different anatomic sites of infection (*e.g.* spectinomycin is not adequate for treatment of pharyngeal gonorrhea⁷⁵). Yet, it seems clear that this approach of using multidrug regimens should be further explored. Innovation in the development of new drugs is warranted; solithromycin, the new fluoroketolide, showed promising *in vitro* activity against *N. gonorrhoeae* (including resistant isolates), but further evaluation and clinical studies are needed before this drug could be added to the treatment arsenal.⁷⁶ In the meantime the difficulty remains that there are few new drug prospects on the horizon, with none that are likely to arrive before ceftriaxone treatment failures become more common.

Syndromic treatment of patients at the time of presentation with or without collection of specimens for definitive diagnosis necessarily means that a treatment regimen must be selected based on national or regional recommendations and not on information about the specific organism infecting the individual patient. Because a regimen that is effective in less than 95% of infections cannot reliably be recommended,⁴³ whole classes of antibiotics must be discarded from use when resistance rises to greater than 5%. This has meant that the regimen recommended as first-line treatment is used for nearly all patients and provides nearly all the antibiotic pressure in a community, another possible factor in the serial evolution of resistance. One proposed solution to this problem is rotating recommended therapeutic regimens, however this is not likely to be a practical option given the limited number of reliable antibiotics for treatment⁶² and the difficulty in administering such an approach.⁶³ Ideally, treatment of gonorrhea would be individualized and guided by the results of susceptibility testing. Molecular susceptibility assays might eventually make that a more viable option, however that is likely many years away and is necessarily reliant on accurate correlation of molecular variations with clinical results. Even if available, if the assay is not a rapid point-of-care test, the impact would be limited to patients with asymptomatic infections treated on the basis of screening test results.

6.4 Public health interventions

Gonorrhea remains a common disease, and reducing the global burden of this infection should continue as a cornerstone of the public health approach to managing resistance.^{3, 7}

Preventing gonorrhea is critical to this effort because if a substantial number of the tens of millions of cases of gonorrhea that occur annually could be prevented, there will be less resistance and our remaining treatment options will last longer. Improper antibiotic use must be curtailed.⁷ Surveillance measures must be enhanced, with further investigation into affordable easy-to-use testing methods that can be utilized in resource-poor settings (such as the recently described cefpodoxime disc test which screens for mosaic PBP2-containing *N. gonorrhoeae* and decreased susceptibility to ESCs).⁷⁷ A recent study noted the rapid decrease in the prescribing of fluoroquinolones for treatment of gonorrhea after the CDC issued updated treatment guidelines, suggesting the importance of maintaining up-to-date national and international guidelines.⁷⁸ Preventing the emergence and spread of ever-more resistant gonococcal infections must remain at the forefront of international public health efforts.

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Table 1

Selected gonococcal antimicrobial surveillance programs and trends in *Neisseria gonorrhoeae* isolates' susceptibility to cephalosporins

Location	Program	Year(s) of surveillance reported	Trends in cephalosporin susceptibility	Highest MICs reported	Comment
Western Pacific Region (WPR) and South East Asian Region (SEAR) ⁷⁹	WHO WPR and SEAR Gonococcal Antimicrobial Surveillance Programmes	2009	CRO: wide variation in region, with significant percentages of gonococcal isolates in Brunei, China, Korea, and Mongolia reported as having 'decreased susceptibility' or resistance to ceftriaxone	MICs not available in report	
Australia ²¹	Australian Gonococcal Surveillance Programme	2010	CRO: 4.8% isolates had ceftriaxone MICs 0.06 mg/L (increase from 0.6% of isolates in 2006)	CRO: No isolates had a ceftriaxone MIC >0.125 mg/L	Oral ESCs are not available in Australia
Russia ⁸⁰	Russian Gonococcal Antimicrobial Susceptibility Programme	2005–2008	CRO: overall increase in ceftriaxone MICs during this period; in 2007 there were 14 isolates with MIC = 0.25 mg/L	CRO: No isolates had an MIC to ceftriaxone >0.25 mg/L	
Europe ⁸¹	European Gonococcal Antimicrobial Surveillance Programme	2009	CRO: Most commonly occurring MIC to ceftriaxone increased from 0.002 mg/L in 2004 to 0.008 mg/L in 2009 CFM: 5.1% isolates had cefixime MICs >0.125 mg/L (range 0–21.2% of isolates among participating countries)	CRO: No isolates had MIC >0.125 mg/L	First year that testing of cefixime MICs was included, therefore comparison cannot be made to prior years
England and Wales ²²	Gonococcal Resistance to Antimicrobials Surveillance Programme	2010	CRO: upward drift in MIC to ceftriaxone seen among isolates CFM: percentage of isolates (obtained from genitourinary medicine clinics) with MICs to cefixime 0.25 mg/L increased from 1.2% in 2009 to 6.3% in 2010	CRO: No isolates had ceftriaxone MIC 0.125 mg/L in 2010 (however there were 4 isolates with MIC 0.125 mg/L in 2009)	Percentage of isolates with elevated cefixime MICs was higher among MSM compared to heterosexual population
United States of America ⁵¹	Gonococcal Isolate Surveillance Project	2000–2010	CRO: percentage of isolates with MICs to ceftriaxone 0.125 mg/L increased from 0.1% to 0.3% CFM: percentage of isolates with MICs to cefixime 0.25 mg/L increased from 0.2% to 1.4%	CRO: No isolates had MIC to ceftriaxone 0.5 mg/L	Western states had the largest increases in cefixime MICs

CRO = ceftriaxone
CFM = cefixime