Challenges of Sexually Transmitted Disease Prevention and Control: No Magic Bullet, but Some Bullets Would Still Be Appreciated

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In his social history of venereal disease in the United States, *No Magic Bullet* [1], Brandt makes the case that, despite the germ theory, an understanding of disease control, and even effective antimicrobials, sexually transmitted diseases (STDs) have not been in control. He asserts that societal tension between morality and rationalism, as well as the difficulty in dealing simultaneously with both privacy and social responsibility in the context of sexual behavior, have been barriers to control. With regard to antibiotics, he makes the following point: “Unfortunately, however, the promise of the magic bullet has never been fulfilled….even those infections that respond to antibiotics are still prevalent….the magic bullet cannot combat the social and cultural determinants of these infections” [1, p. 161]. Although there is no “magic bullet,” those of us who treat patients with STDs and those of us who are charged with controlling the spread of these infections in the community certainly appreciate any ammunition we can get.

Effective antimicrobial therapy for bacterial STDs cures infection and prevents short- and long-term complications. Although public health STD-control programs encourage and support the use of effective treatment as secondary prevention (for preventing disease and complications) and tertiary prevention (for preventing disability and long-term complications), a major objective is to prevent transmission by curing infection. Antibiotics provide cure and recovery to the patient, as well as a reduced incidence and prevalence of infection for the community. Antibiotics may not be the answer to STDs, especially as the more prevalent viral STDs are unaffected by antibiotic therapy, but they remain the mainstay for treatment of gonorrhea, chlamydial infection, and syphilis. The progressive acquisition of antibiotic resistance in *Neisseria gonorrhoeae* over the past 30–35 years, and difficulties acquiring and administering remaining antibiotics have brought us to a point of increasingly limited options. Bullets, of any sort, are getting scarcer.

The article by California state and county public health sexually transmitted disease control officials and persons at the Centers for Disease Control and Prevention (CDC) in this issue of *Clinical Infectious Diseases* [2] documents the emergence of endemic quinolone-resistant *N. gonorrhoeae* (QRNG) in California during the period of 2000–2002 and describes the characteristics of its spread. The authors construct a picture of the introduction and spread of QRNG, starting with a first indication of an increase over a stable, low prevalence of QRNG among isolates from male STD clinical patients collected as part of the national Gonococcal Isolate Surveillance Project (GISP) to a level of 20%, with a preceding shift from intermediate susceptibility to resistance. They were able to determine that an early cluster of 6 patients in Orange County in 2000 were all born outside of the United States; 5 of these patients were heterosexual, and 3 had exposure to commercial sex; none reported antibiotic use, and there were no common exposures.

Expanded surveillance revealed an association between QRNG infection and travel, an increasing association with antibiotic use, and a high rate of multiple partners. In a case series, 40% of the patients with QRNG reported travel outside the continental United States within the previous 6 months. A cross-sectional study of 952 STD clinic patients with gonorrhea from 4 counties, 70 (7.4%) of whom had QRNG isolated, suggested variation in patterns of spread of QRNG in terms of...
race/ethnicity, sexual behavior, and sexual networks. From this cross-sectional study, one sees the introduction of QRNG first in southern California and then in San Francisco, with likely ongoing introductions related to travel. Transmission among men who have sex with men (MSM) seemed to predominate in San Diego and Long Beach County, whereas, during the time period under study, men who have sex with women (MSW) in San Francisco were more likely to have QRNG, with Orange County having equal rates for both MSM and MSW. The predominance of isolates recovered from men resulted from the overrepresentation of male subjects (and MSM) at the STD clinics. San Francisco had the lowest proportion of QRNG isolates and a larger proportion of isolates with intermediate susceptibility to fluoroquinolones, also suggesting later introduction on microbiologic grounds. Overall, temporal analysis suggested early introduction into a MSM social network in southern California and MSW in San Francisco, with about a 1-year lag for spread among MSW in southern California and MSM in San Francisco. In fact, findings of strain typing and molecular analysis were consistent, with an “outbreak strain” accounting for more than one-half the isolates.

This emergence and spread of QRNG is reminiscent of the emergence and spread of plasmid-mediated, penicillinase-producing \textit{N. gonorrhoeae} (PPNG) in the 1970s [3] and QRNG in Hawaii in the 1990s [4]. It began with travel to parts of the world where there was an increased prevalence of resistance, an implicated “founder effect” when the strain is introduced into a particular social/sexual network, followed by spread to other groups, and then endemic establishment. A similar experience is in evidence in the United Kingdom [5, 6]. In contradistinction, the apparent clonal emergence and spread of \textit{N. gonorrhoeae} with intermediate quinolone susceptibility in Cleveland (and surrounding areas in Ohio and Pennsylvania) seems to have been limited to one particular social network, without bridging to other groups or emergence of endemic resistance [7, 8]. In fact, quinolone susceptibility has returned to pre-emergence levels [9].

The emergence and spread of antibiotic-resistant gonococci is consistent with our understanding of emerging infections in general. STDs, however, have the added dimension of sexual behavior. The emerging problem of quinolone-resistant gonorrhea has recapitulated the emergence of PPNG [3, 10] and plasmid-mediated, high-level tetracycline resistance in \textit{N. gonorrhoeae} (TRNG) [11] and has similarities to the emergence of HIV infection. A better understanding of social networks and their characteristics will be necessary to enhance interventions to decrease the transmission of gonococcal infection. This is made more essential because of the emergence of resistance to one drug after another. Fortunately, this attention to networks and network theory, especially that of scale-free networks, is being more widely applied [12, 13].

The era of sulfonamide treatment of gonorrhea just barely lasted into World War II because of the rapid emergence of resistance. In 1943, a total dose of 160,000 U of penicillin was shown to be effective for the treatment of gonococcal urethritis [14]. Penicillin became the drug of choice for the next 40 years, but an inexorable decrease in penicillin susceptibility, mediated by chromosomal genetic mutations, required larger and larger doses of penicillin to achieve the same effectiveness. Recommended doses went to 600,000 U and to 2.4 million U over the next 20–30 years, until 1974, when the CDC was recommending 4.8 million U of intramuscular procaine penicillin, combined with 1 g of probenecid to inhibit renal excretion of the penicillin [15].

Then the emergence of PPNG led to abandonment of penicillin. The emergence of TRNG and the disadvantage of multiple dosing took tetracycline out of the running. Spectinomycin, a second-line parenteral drug for many years, had virtually no other indications and was, practically speaking, an orphan drug, and reports of treatment failure associated with high-level resistance made it less favorable as a first-line agent [16]. In 1985, ceftriaxone (250 mg in a single im injection) was recommended by the CDC as the treatment of choice for uncomplicated gonorrhea [17] (the discussion of therapy throughout is limited to uncomplicated gonococcal infection).

By 1993, a level of comfort with ceftriaxone at a dose of 125 mg was achieved, and this became the recommendation, with other recommended agents being oral cefixime, ciprofloxacin, and ofloxacin (alternatives included several other cephalosporins with less of a track record and spectinomycin) [18]. These recommendations were essentially carried forward in 1998 and 2002 guidelines [19, 20]. Success with intramuscular ceftriaxone has been substantial, and there has not been a problem with significant resistance—yet. Ceftriaxone has the added advantage of demonstrated efficacy for pharyngeal and anorectal infection [21]. However, in many practice settings, it is difficult to stock ceftriaxone and to administer it intramuscularly, so oral antibiotics (such as cefixime and especially fluoroquinolones) have been favored. As far as single-dose, oral medications go, quinolones are relatively inexpensive and easy to acquire.

The GISP tracks drugs that are used to treat patients as well as susceptibility. Ceftriaxone use reached a peak in the early 1990s, with a subsequent decrease in use to <40% of treatment courses. Parenteral treatment is more frequently provided in categorical STD clinics and other facility-based clinics. Quinolones accounted for another 40% of treatment courses in 2003, with cefixime being used in ∼15% of courses [9]. The CDC also recommends concurrent therapy with either a single dose of azithromycin or doxycycline for 7 days for treatment of 	extit{Chlamydia trachomatis} coinfection, unless such coinfection can be ruled out. This concurrent therapy may enhance efficacy of the primary treat-
ment regimen and suppress the emergence of resistance.

As documented by Bauer et al. [2] and by surveillance programs in other places, the prevalence of QRNG is increasing, especially among MSM [22]. This has led to a revised recommendation against the use of fluoroquinolones for gonorrhea in MSM or in individuals with travel exposures to areas with an increased prevalence of QRNG. However, experience tells us that it is only a matter of time that fluoroquinolones will not be recommended for any cases of gonorrhea. The problem of quinolone resistance in gonococci is compounded by a narrowing choice of alternative antibiotics that are effective, the difficulty of administering some alternatives, the limitations of the alternatives in terms of adequacy of therapy for various sites of infection, the cost of alternative agents, shortages of alternative drugs, and the decrease in research and development of antimicrobial agents.

Cefixime is the only recommended oral cephalosporin with accepted efficacy for single-dose treatment of uncomplicated gonorrhea. In November 2002, the US patent on cefixime (Suprax) expired, and Wyeth-Ayerst announced that it would discontinue production. Lupin received approval to market cefixime in the United States in February 2004, but supplies of tablets remain limited, although an oral suspension is generally available. In April 2001, Pharmacia announced that it would suspend production of spectinomycin (Trobicin), but it subsequently reversed that decision. Spectinomycin is available for the treatment of gonorrhea in patients with β-lactam allergies, but it is not readily available, because it is not stocked for any other purpose and requires intramuscular injection. Thus, among the 5 CDC-recommended treatment regimens for gonorrhea, the 3 fluoroquinolones are on the way out, and cefixime is in short supply. Alternative oral cephalosporins are being substituted when ceftriaxone is not available, but these agents, although they are expected to be effective, have not been fully evaluated. Likewise, azithromycin (in a 2-g oral dose) may be effective against uncomplicated gonorrhea, but this has not been established clinically, and many patients cannot tolerate that dose.

The use of second-line drugs also raises a question about the need for test-of-cure cultures and for more susceptibility testing. However, during the past 10 years, the means of diagnosis of gonococcal infection have moved overwhelmingly to nonculture methods, which may give positive signals for dead organism nucleic acid and do not provide an isolate for susceptibility testing.

Cost of drugs is another issue. Cefixime’s average wholesale price for a single 400-mg dose of suspension is $18.40 (in US dollars). Cefpodoxime proxetil costs $20.00 for 400 mg. Ceftriaxone costs $9.00 for a 125-mg dose, assuming that 2 doses are achieved from every 250-mg vial, and not including administration costs. Azithromycin (2 g) costs $40. Generic ciprofloxacin costs $3.00 per 500-mg tablet. Ofloxacin (Floxin [Ortho-McNeil Pharmaceutical]; 400 mg) costs $6.67, and levofloxacin (Levaquin [Ortho-McNeil Pharmaceutical]; 250 mg) costs $9.22. Thus, the loss of fluoroquinolones from the gonorrhea armamentarium has significant drug purchase cost implications for the health care delivery system.

As one antimicrobial agent after another was lost to emerging resistance, the pharmaceutical industry came up with new antibiotics, classes, or agents, with differing spectra of activity and pharmacokinetics. Those days are gone. Research and development in the area of antimicrobials has slowed markedly, and there are few existing business incentives for research or new drug development [23]. From all indications, all the bullets we will have are already in our ammunition belt.

There is no magic bullet for gonorrhea or other STDs, but with the inevitable loss of the quinolones, the lack of ready access to some older agents, and the lack of new agents on the horizon, we face an increasingly difficult challenge. There is no question that part of this challenge is going to be increasing cost, especially for the public health sector. But the real challenge is prevention—prevention of infection in the first place, as well as prompt intervention to prevent transmission. It will take focus on behavioral change, limitation of partners, consistent and correct use of condoms, and other proven methods of reducing risk. It will require enhanced understanding of sexual networks, how they operate, and how this knowledge can be used to one’s advantage in limiting the spread of infection. There is still a need for new antimicrobial agents, but there is also a need for an effective vaccine against gonorrhea. The more your ammunition is limited, the smarter you have to be when you use it.

Acknowledgments

Potential conflicts of interest. A.D.: no conflicts.

References

8. Klimarx PH, Knapp JS, Xia M, et al. Intercity spread of gonococci with decreased susceptibility to fluoroquinolones: a unique focus in