Clinical Infectious Diseases

REVIEW ARTICLE

A Brief History of Evolving Diagnostics and Therapy for Gonorrhea: Lessons Learned

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Progressively decreasing susceptibility of *Neisseria gonorrhoeae* to the antibiotics recommended for treatment has raised concerns about the public health threat of antibiotic resistant gonorrhea. This is not a new process, and the organism has reliably developed resistance to all modern antibiotics used for treatment since the dawn of the antibiotic era. The history of changing recommendations for gonorrhea therapy is complex, however, and has been influenced by diagnostic test methods and surveillance. Understanding the impact of these influences may provide insights into current approaches to address this reemerging public health challenge. We reviewed available methods for gonorrhea diagnosis, and public health recommendations for gonorrhea treatment. The literature review was supplemented by qualitative interviews with senior investigators whose research helped shape gonorrhea management strategies over the past 50 years. The process of development of antimicrobial resistance to the antibiotics widely used for treatment seems to be inexorable. Many currently voiced concerns are similar to those raised in the past. The public health threat of increasing antimicrobial resistance by *N. gonorrhoeae* has been amplified as a result of a smaller pipeline introducing new drugs for gonorrhea treatment. Improved methods for gonorrhea diagnosis have also repeatedly influenced appreciation of the burden of disease caused by *N. gonorrhoeae.* US Public Health Service leadership has also shaped and improved the management of this important public health problem.

Keywords. gonorrhea; gonococcal antimicrobial resistance; gonorrhea diagnosis; gonorrhea diagnostic tests; gonorrhea treatment.

Gonorrhea has been recognized as a sexually transmitted infection (STI) for centuries and, since the advent of modern antibiotics, has repeatedly demonstrated a capacity to develop resistance to antimicrobials used for treatment. More recently, continued increases in gonococcal antimicrobial resistance (AMR) and a reduced "pipeline" for new antimicrobial development have repeatedly combined to limit availability of readily available therapy for this continuing global public health threat. Increasing resistance was serially countered by increases in the penicillin dose used for treatment or recommendations for alternate antibiotics [1–3]. Although the publications on sexually transmitted disease surveillance and treatment guidelines from the Centers for Disease Control and Prevention (CDC) provide data on reported gonorrhea-associated morbidity since the 1940s, recent changes in recommended treatment and, over the past 30 years, trends in gonococcal susceptibility [1–4], there are few summaries of the sequence of earlier changes to treatment practice and guidance.

To address this lack, we reviewed available literature and conducted interviews with biomedical scientists who contributed to evolving gonococcal management strategies before the 1980s to summarize this history along the contours of 3 intersecting themes: continuing development of resistance by *Neisseria gonorrhoeae*, heightened appreciation of gonorrhea prevalence facilitated by improving diagnostic tests, and federally supported surveillance and treatment recommendations. This history provides a perspective for addressing current challenges to gonorrhea control in the face of the escalating threat of resistance to currently recommended antibiotics for gonorrhea therapy.

GONOCOCCAL AMR: A CONTINUOUS PROCESS

In the 1930s, introduction and availability of sulfa drugs permitted the first reliable medicinal gonorrhea therapy. However, by 1944 resistance had emerged, and treatment failure rates exceeded 30% in gonorrhea patients treated with maximal sulfonamide doses [5, 6]. Fortunately, in the 1940s gonorrhea was of sufficient import to have been one of the first infections treated with penicillin as investigators explored the potential uses of the "wonder drug" [5, 7]. Since then, gonorrhea therapy recommendations have evolved continuously, both through dose modification of existing drugs and introduction of new drugs.

Soon after its introduction, penicillin became preferred treatment for gonorrhea, in part because of its activity against *Treponema pallidum*, the causative agent of syphilis and a somewhat greater public health priority at the time [8]. Initially,

Received 11 December 2017; editorial decision 23 March 2018; accepted 3 April 2018; published online April 5, 2018.

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Clinical Infectious Diseases® 2018;67(8):1294–9

DOI: 10.1093/cid/ciy271

therapy for gonorrhea required multiple doses of parenterally administered penicillin [7]; however, these regimens were supplanted as longer-acting penicillin formulations became available. By the late 1950s and early 1960s, much gonorrhea therapy used penicillin aluminum monostearate, benzathine penicillin, or procaine penicillin [9] which—possibly reflecting the lack of an authoritative recommendation—were used in varying doses. Soon after penicillin became widely used for gonorrhea, numerous investigators [10, 11] also documented progressive increases in the penicillin minimal inhibitory concentrations (MICs) required to reliably inhibit growth of *N. gonorrhoeae* on artificial media. Increased penicillin MICs predicted the likelihood of treatment failure in patients [10].

Subsequently, despite continuing increases in penicillin MICs, periodic escalation of recommended penicillin doses took advantage of the drug's low toxic/therapeutic ratio and allowed penicillin to remain a preferred drug for gonorrhea for >40 years. During that period, the amount of drug recommended for gonorrhea treatment increased >100-fold, to an ultimate recommendation for 4.8 million units of aqueous procaine penicillin G [1]. In the early 1970s, penicillin efficacy was further enhanced after it was demonstrated that coadministration of probenecid increased penicillin serum levels and delayed excretion of the drug [12–14], increasing gonorrhea cure rates to close to 100%. In the mid-1970s, however, the era of penicillins as preferred gonorrhea therapy ended. Higher doses of procaine penicillin were problematic owing to increased procaine reaction rates and injection discomfort associated with medication volume. In addition, emergence of gonococci that not only carried multiple chromosomal AMR mutations but also carried β-lactamase plasmids (penicillinase-producing *N. gonorrhoeae* [PPNG]), allowing penicillin inactivation in a single step, created a pressing need for alternative, nonpenicillin gonorrhea therapy [11, 15–18].

Numerous scientific studies demonstrate that the progressive *N. gonorrhoeae* AMR reflects the cumulative effect of mutations for different mechanisms for decreased susceptibility [19, 20]. Some mechanisms are single-step events, such as the acquisition of plasmids for β-lactamase production or for high-level tetracycline resistance. Mutation of a single genetic locus such as *gyrA* or *parC* can also confer high-level resistance to fluoroquinolone antimicrobials. In addition, the organism has also demonstrated the ability to accumulate chromosomal mutations which act in cumulative fashion to decrease antimicrobial susceptibility. More than 50 chromosomal mutations that affect gonococcal antimicrobial susceptibility have now been described. Some mutations confer diminished susceptibility to multiple classes of antimicrobial agents (eg, the *mtr* mutation), and others affect a more limited spectrum of antibiotics.

Although penicillins remained widely used for gonorrhea treatment until the 1980s, alternative drugs were needed for persons reporting penicillin allergy. Oral regimens were desirable for convenience, avoiding therapeutic injections and the need to store parentally administered drugs. Therapy came to include oral penicillinlike drugs (ampicillin and amoxicillin), which were widely preferred over injectable procaine penicillin/probenecid despite documentation of slightly lower treatment efficacy [1, 21]. A 4-day course of tetracycline had also been demonstrated to be 96.2% effective for uncomplicated gonorrhea in the National Gonorrhea Therapy Monitoring Study, but this regimen had the disadvantages of requiring patient adherence to complete the course of therapy and being contraindicated in pregnancy [21].

In 1972, spectinomycin was also studied [22–24] and became used almost exclusively for gonorrhea therapy (its only major indication). Spectinomycin required reconstitution immediately before injection and had limited efficacy for pharyngeal infections [25] but nevertheless was relatively widely used in sexually transmitted disease clinics when penicillin and related drugs could not be used. This drug continued to be widely used for gonorrhea treatment for >30 years until limited availability curtailed its use in the 1990s [26]. Over the period of its use, unlike for other more widely used antibiotics, resistance to this drug was sporadic and relatively uncommon, occurring primarily in areas where it was heavily used [27].

In 1976, reports of *N. gonorrhoeae* with plasmid-mediated β-lactamase production (PPNG) signaled the end of the penicillin era and accelerated investigation of single-dose nonpenicillin antibiotic options [17, 18]. Reports describing the utility of norfloxacin [28, 29] and other newer fluoroquinolone antibiotics demonstrated high efficacy and good tolerability after single-dose oral administration [30–32]. Like spectinomycin, some fluoroquinolones were less efficacious for pharyngeal gonorrhea than for anogenital infection [32]. The fluoroquinolones were soon widely used for gonorrhea therapy, being recommended by the CDC until 2007, when demonstration of increasing in vitro resistance in the CDC's Gonococcal Isolate Surveillance Project (GISP) led to discontinuation of the recommendation for fluoroquinolones as preferred therapy [33].

At about the same time, a variety of second- and third- generation cephalosporins, including cefoxitin and cefotaxime, were also found to be effective for gonorrhea therapy [34, 35]. Among cephalosporins, ceftriaxone was particularly active in a variety of doses and studied for several other STIs including syphilis therapy. Ceftriaxone was recommended as preferred therapy for gonorrhea treatment in the mid-1980s [36, 37]. As with penicillin, the recommended dose has increased over time in the United States, the United Kingdom, and other nations [2, 38]. The oral cephalosporin cefixime was also recommended as first-line gonorrhea therapy until 2012 when, owing to increasing cefixime MICs and documented North American treatment failures, this drug was no longer recommended [39, 40]. In the second decade of the 21st century, after a substantial hiatus and spurred by reports of declining efficacy of cephalosporin

antibiotics, several new drugs entered the developmental pipeline of drugs being studied for gonorrhea treatment [20].

Lessons Learned

Development of AMR to drugs for gonorrhea treatment seems to be an inexorable process, which had been countered by either antimicrobial dose escalation or use of newer antimicrobials, to which the organism ultimately developed resistance. Spectinomycin may have been an exception to this generalization; it is unclear whether sustained spectinomycin efficacy reflected the fact that gonorrhea was the drug's only major indication. Current concerns regarding limited choices for gonorrhea therapy reflect the convergence of a long-standing tendency of *N. gonorrhoeae* to develop resistance to drugs used for treatment and a reduced development pipeline for new antimicrobials.

GONORRHEA DIAGNOSIS

Although clinically recognized for centuries, *N. gonorrhoeae* culture, particularly from microbiologically complex sites, such as the female genital tract, the rectum, and the pharynx, was challenging owing to frequent bacterial overgrowth. In about 1967, development and introduction of selective gonorrhea culture media permitted improved diagnosis, particularly for women, in whom culture yield was increased by >50% [41, 42]. These media provided an important tool to better define the high prevalence of gonorrhea and laid the groundwork for increased US Public Health Service (USPHS) emphasis on gonorrhea control. Using recently developed Thayer-Martin medium, the National Gonorrhea Therapy Monitoring Study (initiated in 1972 by the USPHS's CDC) systematically evaluated 4 regimens for gonorrhea therapy, confirming the efficacy of aqueous procaine penicillin G plus probenecid (96.8%), ampicillin plus probenecid (92.8%), tetracycline (96.2%), and spectinomycin (94.8%) [21]. These studies provided validation for the first formal CDC recommendations for gonorrhea therapy, released in 1972 [1].

Selective media remained the mainstay for gonorrhea diagnosis until the 1990s, when the availability of nucleic acid amplification tests (NAATs) for gonorrhea (and chlamydia) again provided more sensitive and easier-to-collect methods for gonorrhea diagnosis [43]. NAATs have since made STI screening easier for clinicians, allow detection of a larger proportion of infections, and have largely supplanted culture for gonorrhea diagnosis in developed nations. However, as a culture-independent method, this shift has made assessment of *N. gonorrhoeae* antimicrobial susceptibility more challenging for clinicians. NAATs are now appreciated to be far more sensitive than culture for detection of extragenital gonorrhea [43–45], demonstrating higher prevalences of extragenital infection than previously appreciated and raising concerns about both the contribution of extragenital gonorrhea to the evolution of gonococcal AMR and to national gonococcal morbidity.

Lesson Learned

Improved detection methods have enhanced estimation of gonorrhea rates at microbially complex sites. Current methods provide increased accuracy of detection but do not provide viable specimens to allow testing for AMR.

ROLE OF THE USPHS AND CDC

Even before availability of modern antimicrobials, the USPHS had been charged with control of syphilis and gonorrhea, as well as other public health threats. In 1918, the United States Congress approved the Chamberlain-Kahn Act, providing for federally funded venereal disease (VD) control and research programs, authorizing federal grants to states for VD control, and giving the government power to quarantine citizens suspected to have STIs [8]. This act created the Division of Venereal Disease in the USPHS, which ultimately evolved to become the Division of STD Prevention within CDC. Our interviews indicated that federal STI control and research during this time focused predominantly on syphilis, while gonorrhea, though far more common than syphilis, was less highly prioritized, possibly owing to both the lack of proven therapies and the fact that it was apparently considered less of a long-term threat to health [8].

In the 1940s, the curative effect of penicillin led to national syphilis control programs that were effective in reducing syphilis, changes that may also have contributed to declines in federal VD appropriations throughout the 1950s [46]. During the 1950s and 1960s *The VD Fact Sheet* from the CDC was regularly published by the USPHS and often commented on gonorrhea, describing a broad array of treatment regimens. The most widely used therapies for gonorrhea at the time used single doses of penicillin aluminum monostearate, a mixture of penicillin G and aluminum monostearate that provided far longer serum levels than penicillin G alone (73 vs ≤2–3 hours) in doses of 600 000 to 3.6 million units [47, 48]. Reflecting the focus on syphilis, penicillin aluminum monostearate treatments were often combined with benzathine penicillin to allow simultaneous treatment of syphilis and gonorrhea.

In the 1960s, the Venereal Disease Research Laboratory of the USPHS expanded its focus to consider gonorrhea more fully as a public health threat. These changes were facilitated by appreciation of rapidly increasing infection rates [4] resulting in part from increasing use of recently developed selective culture media [41, 42] In 1964, CDC authors reported that failure rates in women treated for uncomplicated gonorrhea ranged from 20% to 40% for 10 regimens, which included 1.2 million units of procaine or benzathine penicillin G, 3.0 g of tetracycline, single doses of streptomycin (1.0 g) or chloramphenicol (1.0 g), or 6 (500-mg) doses of tetracycline [9].

In 1970, the CDC also published results of a 14-year study of gonococcal susceptibility to penicillin, confirming that increasing penicillin MICs were associated with increased likelihood of treatment failure [11]. This study and documentation of

increasing gonorrhea rates seem to have helped catalyze the convening of an ad hoc committee to provide advice on gonorrhea therapy which led to publication of what seem to be the CDC's first formal national recommendations for gonorrhea treatment in the *Morbidity and Mortality Weekly Reports* (*MMWR*) of 11 March 1972 [1]. Soon thereafter, formal creation of a CDC-administered national Gonorrhea Control Program permitted increased screening for gonorrhea nationwide and expanded efforts for partner notification and anticipatory treatment for sexual partners of infected persons [49].

With an increased focus on *N. gonorrhoeae*, the CDC assumed a more central role for reporting gonococcal morbidity in the *MMWR* and for formally recommending preferred gonorrhea therapy. The CDC also increased monitoring of gonococcal antimicrobial susceptibility. These efforts were complemented by numerous public health and university-based investigators interested in STIs and their control. After 1972, the CDC worked to validate their recommendations through the National Gonorrhea Therapy Monitoring Study, demonstrating the efficacy of recommended treatment and correlating treatment outcomes with antimicrobial susceptibility [21]. Treatment recommendations were then periodically revised and disseminated in the *MMWR*.

In 1982, faced with sustained high levels of gonococcal and syphilis morbidity, coupled with appreciation of an increasing number of STIs and STI syndromes, the CDC convened an expert advisory committee whose deliberations led to an entire *MMWR* supplement, entitled *Sexually Transmitted Diseases Treatment Guidelines 1982* [36]. This advisory process has since also evolved to its most recent form, with recommendations now based on systematic reviews of the scientific literature and assessment of the strength of the evidence supporting those recommendations combined with expert input. The most recent (2015) guidelines [3] describe 27 distinct STIs and STI syndromes in a 137-page document containing nearly 900 references and serve as a global reference for optimal management of persons with and at risk for STIs.

In 1986, reacting to increasing PPNG rates and the challenge of progressive gonococcal AMR, and to guide treatment guideline updates, the CDC also inaugurated the GISP as a sentinel surveillance system [50]. Reasoning that infections in men would reflect trends for both heterosexual men and women, as well as men with male sex partners, this program monitors antimicrobial susceptibility trends among men with gonococcal urethritis. The GISP goals included monitoring US gonococcal antimicrobial susceptibility to antibiotics using standardized methods, to evaluate characteristics of persons with gonorrhea and to permit anticipatory adjustment to treatment recommendations in advance of major increases in treatment failures [50]. Though designed for sentinel surveillance, the GISP also provided data on trends in gonorrhea epidemiology, such as increasing gonorrhea among MSM [4]. Since implementation of the GISP, its data have provided insights into gonococcal antimicrobial susceptibility trends and contributed to multiple modifications of national recommendations for gonorrhea treatment.

Lessons Learned

Over the past century, the USPHS, and specifically the CDC, has played an increasingly central role in harmonizing management of gonorrhea in the United States, a process facilitated by data provided for >30 years by GISP surveillance.

DISCUSSION

Presently, continued declines in gonococcal antimicrobial susceptibility and a reduced pipeline for new antibiotics have raised the specter of untreatable gonorrhea, reaching beyond the scientific community [51]. This threat reflects not a new process but rather a convergence of ongoing contributors that include improved gonorrhea detection methods, better surveillance, continued development of AMR by *N. gonorrhoeae*, and fewer medications for gonorrhea treatment. We believe that our summary serves to validate the concept of gonococcal AMR development as an inexorable process with potentially profound public health impact.

The GISP [4, 50] seems to have served admirably in monitoring changes in gonococcal antimicrobial susceptibility and has provided data that help guide changes in national treatment recommendations before widespread treatment failures occurred. Recently, in addition to continued monitoring of phenotypic AMR as reflected by MIC determinations, there have been suggestions to supplement or even replace this with surveillance and analysis of the molecular markers for resistance. A possible strength of this approach might be freedom from the increasingly challenging task of obtaining specimens for in vitro susceptibility testing. However, molecular approaches rely on detection of recognized resistance mutations; such approaches are currently unproven and are not expected to provide data on resistance to new antimicrobial classes or newly developed mutations to existing drugs. Although we look forward to the study of molecular surveillance and evaluation of its ability to complement existing, phenotypic, culture-based surveillance, continued phenotypic AMR surveillance, which has worked well over the past 30 years, is needed.

Just as the availability of selective media helped demonstrate the high and increasing gonorrhea prevalence in the 1960s and 1970s, particularly among persons in whom earlier culture methods were insensitive, increased use of NAATs have now demonstrated pharyngeal and rectal infection prevalences higher than previously appreciated. At these same sites of infection, treatment failures have also been most often diagnosed [20, 40]. These data and the potential for other organisms often found in the pharynx to transfer resistance to *N. gonorrhoeae* warrant further consideration of several important research questions. For instance, it is not clear

whether rates of pharyngeal infection have truly increased in recent years or whether improved detection using NAATs has simply contributed to better appreciation of pharyngeal gonorrhea prevalence. In turn, questions as to the relative importance of pharyngeal infections as a public health threat (through transmission or as a cause of complications) and in the evolution of gonococcal AMR are also separate topics, each warranting careful study.

Limited data inform questions about the individual morbidity associated with pharyngeal gonorrhea. Although most infections are asymptomatic and may resolve spontaneously, they can also be transmitted to others and have been suggested to be associated with disseminated infection. In terms of the potential for pharyngeal gonorrhea to serve as a site where AMR is most likely to evolve, such infections occur at a microbiologically complex site where there is substantial potential for genetic exchange of resistance mutations; however, the frequency and impact of such exchange is unknown. Finally, treatment failures seem to occur more frequently with pharyngeal than with anogenital infections [36, 40]; however, it is unclear how much pharyngeal infections contribute to gonococcal morbidity or the emergence of AMR. Investigation of these knowledge gaps would inform pharyngeal screening recommendations and perhaps clarify whether clearance of pharyngeal infections should be considered a desired (as opposed to essential) characteristic of therapeutic approaches to gonorrhea. There is a need for a comprehensive research agenda to address the import of pharyngeal gonorrhea.

This article also does not address the confounding effect of coinfections in recommendations for 21st century STI control. Substantial data indicate that coinfections with *Chlamydia trachomatis*, *Mycoplasma genitalium*, and *Trichomonas vaginalis*, as well as other sexually transmissible pathogens, commonly coexist in infected persons. Many of these pathogens have their own challenges in terms of antimicrobial susceptibility and management, and though it would be desirable to have a "silver bullet" that would be efficacious for all potential coexisting pathogens, accomplishing this is more and more challenging.

This narrative has focused on the evolution of gonorrhea control efforts in the United States, with an emphasis on events before the 1970s, and does not provide a detailed description of the large amounts of high-quality research and recommendations for control conducted in parallel in other parts of the globe over the past 50 years, often led by the World Health Organization. Nor does it provide details on the numerous important contributions of the National Institutes of Health to basic gonococcal research or other STI public health threats. Despite these limitations, we believe that history should inform the present, and it is our hope that this document will provide a historical perspective to guide development of future interventions and make efforts to control gonorrhea more effective.

Notes

Acknowledgments. Thanks to Pamela Martin, Leslie C. Norins, MD, PhD, P. Fredrick Sparling, MD, King K. Holmes, MD, PhD, Harold Jaffe, MD, Jonathan Zenilman, MD, William C. McCormack MD, and Michael Rein, MD for their informative discussions and background information on the evolution of strategies for gonorrhea management.

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

Potential conflicts of interest. E. W. H. has received research support from Hologic, Roche Molecular Systems, Becton Dickinson, and Cempra Pharmaceutical. All other authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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