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EDITORIAL COMMENTARY

The Staying Power of Pharyngeal Gonorrhea: Implications for Public Health and Antimicrobial Resistance

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(See the Major Article by Barbee et al on pages 575–82.)

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Neisseria gonorrhoeae is one of the most common bacterial sexually transmitted infections (STIs), causing approximately 87 million new infections worldwide [1]. Cases of gonorrhea are increasing in many countries; in 2018, there were over 580 000 cases reported to the US Centers for Disease Control and Prevention (CDC), representing an increase of over 60% since 2014 [2]. Men who have sex with men (MSM) have been disproportionately affected by gonorrhea. In the United States, MSM at CDC surveillance sites were estimated to have experienced a 375% increase in gonorrhea incidence from 2010–2018 [2].

Antimicrobial resistance (AMR) in *N. gonorrhoeae* is an urgent global health threat. The pathogen is listed among the top 5 AMR threats by the CDC. *N. gonorrhoeae* is considered a high-priority pathogen by the World Health Organization [3, 4]. The CDC estimates there are 550 000 drug-resistant *N. gonorrhoeae* infections in the United States each year, approximately half of all new infections [3]. The bacterium has developed resistance to every class of antibiotics used for treatment. In December 2020, the CDC removed azithromycin from the treatment recommendation due to increasing incidence of azithromycin resistance and increased the recommended ceftriaxone dose from 250 mg to 500 mg intramuscular injection [5]. Other countries have also moved toward higher doses of ceftriaxone as monotherapy for gonorrhea [6–8]. Resistance to ceftriaxone is increasing worldwide, and treatment failures have been documented [9–11]. Those treatment failures serve as dire warnings that the era of untreatable gonorrhea is near.

Although oropharyngeal *N. gonorrhoeae* infections rarely cause symptoms or lead to significant morbidity, the oropharynx is an important site of infection. The oropharynx is considered to play a major role in the development of AMR in *N. gonorrhoeae*. The oropharynx is home to other commensal *Neisseria* species, which can harbor genetic antibiotic resistance elements developed through prior exposures to antibiotics [12–14]. The mixing of related bacterial species in the oropharynx creates an ideal environment for the transfer of antibiotic resistance through horizontal gene transfer and is postulated to be the primary mechanism for resistance to the extended spectrum cephalosporins [15–17]. In that way, the commensal *Neisseria* species can serve as a reservoir of resistance for *N. gonorrhoeae*. In addition, antibiotic concentrations in the oropharynx are suboptimal, which makes pharyngeal infections more difficult to eradicate and can lead to selection pressure for clones with increased minimum inhibitory concentrations to antibiotics [17]. Verified gonorrhea treatment failures to ceftriaxone have all involved pharyngeal infections [9, 10, 18]. The selection pressure exerted can be for both *N. gonorrhoeae*, as well as other commensal bacteria in the oropharynx, whereby overuse and misuse of antibiotics increases the resistome [12, 15, 19].

Although oropharyngeal infections are known to contribute to gonorrhea transmission [20], there is ongoing debate whether control of oropharyngeal infections can reduce community transmission. Key to that discussion is the duration of pharyngeal gonococcal infection and time to spontaneous clearance.

Until now, few studies investigating the natural history and duration of gonococcal infection have been performed. One study from 1979 included 17 patients with pharyngeal gonorrhea that were followed every other week with pharyngeal cultures for a total of 12 weeks; 41% were positive at 6 weeks, and all cultures were negative at 12 weeks [21]. Subsequently, a retrospective study of 60 patients with untreated pharyngeal gonorrhea who

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were cultured at 2–7 days following identification of infection found that 44% of patients were culture-positive 7 days later [22]. More recently, a systematic review used an epidemiologic approach to estimate the duration of infection as a quotient of prevalence by incidence. Based upon 2 studies of pharyngeal gonorrhea in MSM in Australia [23] and the United States [24], the estimated median duration of infection was 16.2–19.7 weeks [25].

In this issue of *Clinical Infectious Diseases*, Barbee and colleagues set out to determine the duration of pharyngeal gonococcal infection based upon the detection of gonococcal nucleic acid [26]. In a well-designed, prospective cohort study, the authors enrolled MSM to participate in a 48-week study, which included weekly, self-collected pharyngeal specimens for *N. gonorrhoeae* testing. The study included in-person enrollment and exit visits, while pharyngeal specimens were self-collected at home. Participants received weekly reminders to perform the specimen collection and to complete online surveys to assess sexual behavior. Self-collected specimens were mailed to the laboratory, where they were immediately frozen at −80°C. Testing was performed after study completion using the Aptima Combo 2 assay (Hologic Inc, San Diego, California, USA). Infections were defined as incident if there were ≥2 consecutive weekly tests positive for *N. gonorrhoeae* nucleic acid; clearance was defined as ≥2 consecutive negative weekly tests. Infections were censored if they were present in the final week of the study, if the subject was lost to follow-up, or if a positive test followed anti-gonococcal treatment.

The authors enrolled 140 men, of whom 28 (20%) were excluded due to not performing any at-home procedures. The remaining 112 men were followed up for a median of 39 weeks and contributed a total of 70.5 person-years of follow-up. In that period, there were 21 incident pharyngeal infections among 19 men. The estimated incidence was 31.7 per 100 person-years (95% confidence interval [CI]: 20.7–48.6). The estimated median duration of untreated pharyngeal gonococcal infection was 16.3 weeks (95% CI: 5.1–19.7 weeks). The authors found 25 single-positive specimens among 22 men during the study period. If those "blips" were included as infections, the duration of infection would have decreased to 10 weeks.

The estimated duration of infection reported by Barbee et al was twice as long as prior reports based on culture but similar to estimates based on epidemiologic analysis (16.2–19.7 weeks) [21, 22, 25]. The duration of infection lends support to the argument that the oropharynx might serve as an important reservoir of infection and can contribute to ongoing transmission. However, the benefit of screening for oropharyngeal gonococcal infections, both on community prevalence and transmission, remain unknown. Establishing a benefit for a screening program is important, as no program is without cost and potential harms. Increasing screening and treatment could increase antimicrobial consumption and further the development of AMR [27–29]. Clinical trials are needed to address this important public health question. Community randomized trials could be one approach, where different screening intervals are evaluated for their impact on community prevalence of *N. gonorrhoeae* and the development of AMR. Additionally, given the overlap of STIs and human immunodeficiency virus (HIV) infection, different screening approaches could be incorporated into new HIV prevention trials (eg, HIV Prevention Trials Network), whereby existing research infrastructure could be leveraged to investigate STI screening in the relevant population.

Although the Barbee et al study was rigorously conducted and represents the largest data set to date on the natural history of pharyngeal gonorrhea, there were limitations. The sensitivity of nucleic-acid amplification tests (NAATs) are far superior than culture and improve the detection of pharyngeal infection [30]. Still, they are not without drawbacks, which are related to the increased sensitivity and the inability to differentiate between positive test results detecting viable bacteria and those detecting remnant nucleic acids from nonviable bacteria. Several factors can contribute to the difficulty in interpreting a positive NAAT for *N. gonorrhoeae*, including recent gonorrhea treatment or recent sexual exposures, which can result in detectable nucleic acid from nonviable bacteria, or a contaminated clinic or laboratory environment. As the authors note, the potential for detection of RNA from nonviable bacteria might have led to an overestimation of infection duration. The effect was likely small, and the estimated duration of infection is consistent with the prior epidemiologic estimates [25].

Clinicians might wonder, how can we determine which positive results represent a true infection, and thus require antibiotic treatment, and which positive results represent remnant nucleic acids from nonviable organisms and should not be treated? That is an important question, especially considering the expansion of screening for pharyngeal infections. In 2020, the updated CDC gonorrhea treatment guidelines recommend performing a test of cure 7–14 days following treatment for pharyngeal gonorrhea [5]. Data suggest that 5–10% of treated pharyngeal infections will still have detectable gonococcal nucleic acid at that time, but whether that positive result represents persistent infection is unclear [31–34]. The new test-of-cure recommendation occurs in the context of increasing antibiotic resistance with the goal of identifying pharyngeal gonorrhea treatment failures. Viability assays have been developed for other bacteria, including *Chlamydia trachomatis* [35]. Newer diagnostic approaches (eg, various DNA dyes) and different molecular targets (eg, messenger RNA [mRNA] or ribosomal RNA [rRNA]) have been employed to determine bacterial viability [36]. Future research is needed to develop

a *N. gonorrhoeae* viability assay, which would aid efforts aimed at antibiotic stewardship, the interpretation of clinical test results, and the detection of true clinical treatment failure.

Notes

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