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Pharyngeal Gonococcal Infections: A Cross-Sectional Study in a Network of Sexually Transmitted Disease Clinics; Sexually Transmitted Disease Surveillance Network—January 2016 to June 2018

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Abstract

We conducted a cross-sectional analysis using sexually transmitted disease clinic data to determine test of cure rates among persons diagnosed with pharyngeal gonococcal infections who were treated with a nonceftriaxone, nonazithromycin therapy. Less than 10% returned for a test of cure, highlighting the need to understand factors that can lead to improved compliance.

In 2018, a gonorrhea treatment failure was reported in the United Kingdom.[1] The patient, a heterosexual man empirically treated with 1 g ceftriaxone at his initial visit, was found to have a persistent pharyngeal infection upon follow-up testing. The pharyngeal isolate, which demonstrated resistance (based on EU-CAST criteria[2]) to ceftriaxone (minimum inhibitory

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concentration = 0.5 mg/L) and high-level resistance to azithromycin (minimum inhibitory concentration >256 mg/L), was the first documented report of an isolate with this resistance pattern. The identification of this pattern, subsequently found in two nonepidemiologically linked patients in Australia,[3] underscored *Neisseria gonorrhoeae's* ability to develop resistance to recommended treatment, heightening concerns for the future management of gonorrhea, particularly pharyngeal infections, which are mostly asymptomatic.

In the United States, treatment recommendations for gonorrhea vary by anatomic site of infection. Since June 2015, the Centers for Disease Control and Prevention (CDC) guidelines have recommended an injectable cephalosporin (ceftriaxone 250 mg) plus 1-g azithromycin as first-line therapy for uncomplicated urogenital and rectal gonococcal infections.[4] Other regimens are suggested when ceftriaxone is not available, such as cefixime (an oral cephalosporin) plus azithromycin. Given evidence of poor antibiotic penetration into the pharyngeal tissues,[5–7] any person diagnosed with pharyngeal gonorrhea treated with other regimens should return 14 days after treatment for a test of cure (TOC).[4]

Conducting a TOC may allow clinicians to identify persons with persistent infections while simultaneously facilitating active public health surveillance for resistant gonococcal infections. However, little is known about compliance to CDC recommendations for TOC for pharyngeal infections treated with other regimens. This study aimed to describe the proportion of sexually transmitted disease (STD) clinic patients diagnosed with pharyngeal gonococcal infections, gonorrhea treatment practices and assess the proportion of patients who returned for a TOC.

We reviewed electronic medical records from STD clinics participating in the STD Surveillance Network (SSuN), a CDC-supported, sentinel surveillance project comprised of 10 state and city health departments that conduct facility-based surveillance in selected STD clinics within their jurisdictions (https://www.cdc.gov/std/ssun/default.htm). Jurisdictions (n = 8) that reported more than 50 positive pharyngeal testing visits from January 1, 2016, through June 30, 2018, were included in this analysis: Baltimore (2 clinics), Boston (1 clinic), Minneapolis/St. Paul (1 clinic), Multnomah County, OR (1 clinic), New York City (8 clinics), Philadelphia (2 clinics), San Francisco (1 clinic), and Seattle (1 clinic). We reviewed demographic, clinical and treatment data for all clinical encounters in participating STD clinics. Men who have sex with men (MSM) were defined as males who identified as gay or bisexual and/or who reported ever having sex with 1 or more male partner(s). Men who have sex with women (MSW) were defined as males not categorized as MSM who identified as heterosexual and/or reported only female sexual partners. Human immunodeficiency virus (HIV) infection status was based on patient self-report of HIV infection or a positive laboratory HIV test result documented in the clinic's medical record. Patients known to be living with HIV prior to the clinic visit where pharyngeal testing occurred were recorded. The SSuN activities are determined not to be research, and institutional review board approval was not required for this analysis.

We reviewed clinic visits from January 2016 to June 2018 in which a patient was tested for pharyngeal gonorrhea and identified visits at which there was a laboratory result positive for *N. gonorrhoeae* in the pharynx. As multiple positive test results in a short period may

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represent the same infection, a positive test was considered indicative of a new infection if more than 30 days had lapsed from a prior positive test. For each positive test, antibiotic regimens prescribed on or within the 30 days following the visit were reviewed. Based on the documented prescribing information, treatments were categorized as CDC recommended therapy (250-mg ceftriaxone intramuscular injection single dose PLUS 1-g azithromycin) or other regimen (i.e., nonceftriaxone, nonazithromycin regimens) (see footnote on Table 1). For the purpose of this analysis, ceftriaxone plus azithromycin (1 g, <1 g, >1 g, or unknown dose) were included in the categorization of CDC recommended therapy. We intentionally used this conservative inclusion of azithromycin dosing to allow for missing data and/or minor data entry errors regarding documentation of azithromycin treatment. All visits with other regimens were assessed for a pharyngeal TOC within 30 days following treatment. Though a TOC is recommended within 14 days, an additional 2 weeks following treatment were given to allow time for receipt of test results and contacting the patient. Hence, clinic data through August 31, 2018, were included to capture all relevant treatment and follow-up visits.

During the 2.5-year study period, a total of 413,524 STD clinic visits were made by 203,461 patients. Overall, there were 72,369 (35.6%) unique patients tested for pharyngeal gonorrhea at least once. The proportion of patients with 1 or more tests varied considerably by sex and sexual behavior (23.6% of women, 78.8% of the MSM, and 23.2% of the MSW). Overall, the median age of patients was 30 years (interquartile range, 25–38). The race/ethnicity distribution was 33.3% non-Hispanic (NH) black, 31.5% NH white, 14.8% Hispanics, 4.8% Asian, and the remaining were of other races or unknown race. Overall, 10.3% (n = 7457) of patients tested for pharyngeal GC were known to be persons living with HIV.

Of the 72,369 unique patients, 10.5% (n = 7625) were positive for 1 or more pharyngeal infections. Men who have sex with men accounted for 82.1% of patients with a pharyngeal infection and one third came from a single jurisdiction (New York City). Among those tested for pharyngeal GC, the proportion positive by race was 15% (n = 1545) in Hispanics, 12.1% (n = 2658) in NH whites, 10.9% (n = 366) in Asians, 10.4% (n = 1136) in other, and 8.3% (n = 1920) in NH blacks. One sixth of the patients testing positive were known to be persons living with HIV. The 7625 unique patients represented 8495 new pharyngeal gonococcal infections. Of these, 96.3% were associated with multiple anatomic site testing (Supplemental Table 1, http://links.lww.com/OLQ/A416); however, 48.8% of the pharyngeal infections did not have a gonococcal infection concurrently diagnosed at another anatomic site.

Treatment prescribed was documented for 7914 (93.2%) of positive pharyngeal tests (Table 1). Centers for Disease Control and Prevention recommended therapy of 250-mg ceftriaxone and 1-g azithromycin was prescribed for 76.4% (6047 of 7914) of infections, with an additional 9.8% (n = 775) treated with 250-mg ceftriaxone PLUS azithromycin (>1 g, <1 g, or unknown dosing) (Table 1). There were 1092 (13.8%) infections treated with other regimens. ATOC (subsequent visit within 30 days following therapy with other regimens and documentation of a pharyngeal gonorrhea test) followed for 93 (8.5%) diagnoses. The TOC rate varied by jurisdiction (0.0–15.1%) (Supplemental Table 2, http://links.lww.com/OLQ/A417) but did not appear more common by other regimen (Table 1). For the remaining

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infections, either no follow-up clinic visits were documented (n = 416, 38.1%), or a subsequent visit was noted but it was longer than 30 days from when the patient was treated with other regimens (n = 541, 49.5%), or a clinic visit occurred within 30 days after treatment but a pharyngeal gonorrhea test was not documented (n = 42, 3.6%). Of the 93 TOC visits, 4 (4.3%) yielded positive pharyngeal gonorrhea results. Three of those 4 patients returned, were treated with other regimens, and subsequently tested negative; 1 patient was retreated but did not return (Supplemental Table 3, http://links.lww.com/OLQ/A418).

Our multisite study of more than 250,000 patients attending SSuN STD clinics found that one third of patients were tested for pharyngeal gonorrhea, and testing occurred more commonly among MSM. Pharyngeal gonorrhea positivity among all clinic patients was 10.5%. Half of the positive testing visits were not accompanied by diagnosed infections at other anatomic sites and would have gone undetected if the pharyngeal specimen had not been collected. Consistent with earlier studies,[8,9] a relatively small percentage of positive testing visits were treated with other regimens, underscoring a high rate of adherence to recommended treatment in STD clinics. However, there were suboptimal return rates for patients treated with regimens other than ceftriaxone and azithromycin, which has important implications if TOC is used as a strategy for the control of emerging gonococcal antibiotic resistance.[10]

The concept of TOC for gonorrhea for cases treated with second-line or other regimens seem reasonable on the surface, but may be challenging in reality. Previous studies have reported that pharyngeal infections are more asymptomatic when compared with anogenital infections.[11,12] This highlights the need to reinforce to patients that despite the absence of symptoms, retesting is an important part of resistant gonorrhea control. Additionally, accommodating for routine TOC visits poses extra clinic burden and volume in retesting patients.[13] In order for this to be fully operationalized, clinics would need to have a systematic way of identifying these patients and providing consistent follow-up to bring them back.

Our study results have some notable limitations. First, patients may have had follow-up testing at a non-SSuN clinic, underestimating the proportion of patients who receive a TOC. Second, treatment records were based on a review of all treatments prescribed or provided in the 30 days following the positive testing visit, allowing for the possibility that some treatments were given for conditions other than the pharyngeal gonococcal infection, but considered as treatment for that infection. However, treatment records were reviewed for all possible combinations of medications commonly prescribed for gonorrhea. Finally, we are unable to comment on reasons for the suboptimal TOC rate, such as whether or not providers were aware of TOC recommendations and/or did not advise patients to come back, or whether patients did not follow guidance to return for a TOC.

Pharyngeal gonococcal infections may be an important driver of gonorrhea transmission within key populations. In the present study, almost 50% of the patients with pharyngeal infections did not have a gonococcal infection concurrently diagnosed at another anatomic site, emphasizing that extragenital testing is important. A suboptimal TOC rate among patients treated with nonrecommended regimens for a pharyngeal infection highlights the

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need to understand factors that contribute to poor compliance, especially if TOC is to be used as a means of identifying persons with persistent infections.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1.

Distribution of Antimicrobials Prescribed Among Pharyngeal Gonorrhea-Positive Testing Visits (n = 8495) and TOC at 17 STD Clinics, January 2016 to June 2018, SSuN

	Gonorrhea-Positive Testing Visits		TOC Visit	
	n	Column %	n	Column %
Regimens containing ceftriaxone 250 mg plus azithromycin				
Ceftriaxone 250 mg PLUS azithromycin 1 g	6047	71.2	—	—
Ceftriaxone 250 mg PLUS azithromycin (>1 g, <1 g, or UNK)	775	9.1	—	—
Other regimens				
Ceftriaxone (UNK or 250 mg) PLUS doxycycline (any dosage)	464	5.5	36	38.7
Gentamicin (UNK or 240 mg) PLUS doxycycline (any dosage) or Azithromycin (any dosage) or levofloxacin (any dose)	191	2.3	38	40.9
Other antimicrobials*	437	5.1	19	20.4
No treatment recorded	581	6.8	—	—
Total	8495	100.0	93	100.0

UNK, unknown.

*Includes cefixime plus doxycycline (any dosage) or cefixime plus azithromycin (any dosage), ceftriaxone (125 mg or UNK dosing) only, azithromycin (1 g, 2 g, UNK dosing) only, doxycycline (any dose) only, or azithromycin plus doxycycline only, and moxifloxacin (any dose).

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