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Routine Pharyngeal Gonorrhea Test-of-Cure: Is It An Effective Cephalosporin-Resistant Gonorrhea Control Strategy?

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Abstract

Background: Centers for Disease Control and Prevention recommends test-of-cure (TOC) for persons with pharyngeal gonorrhea (GC) 7–14 days after treatment. We investigated the yield and feasibility of routine pharyngeal GC TOC to detect treatment failures.

Methods: During May 2021–July 2022, four U.S. STD clinics implemented pharyngeal GC TOC. Sites collected demographic, clinical, and behavioral data on all treated pharyngeal GC and positive TOC cases. Cases were dispositioned with the suspected reason for positive TOC. To assess perceived feasibility, sites participated in qualitative interviews.

Results: During the study period, 1,968 pharyngeal GC infections were diagnosed. Among 1,829 treated cases, 97.3% (n=1,777) received ceftriaxone and 45.7% (n=836) returned for TOC, varying by site (range: 35.5%– 70.8%). Among those with TOC, 4.7% (n=39) were positive by NAAT. Of these, 48.7% had culture attempted; six positive TOC (15.4%) were also positive by culture. Most positive TOC (66.7%) were attributed to re-infection (n=13) or false-positive results (n=13). Six (15.4%) were treatment failures. Four failed recommended treatment and had a positive culture: two were susceptible to ceftriaxone and two did not have antimicrobial susceptibility results. Seven positive TOC (17.9%) had insufficient data to disposition. Sites perceived TOC to be feasible, though substantial resources were required.

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Conclusion: Routine pharyngeal GC TOC yielded 5% positivity, though treatment failure was rare (<1%), and no cases of cephalosporin-resistant GC were identified. Low TOC return rates, limited culture collection, and limited culture yield highlight challenges to determining the cause of a positive TOC and the limitations of TOC in identifying cephalosporin resistance.

Summary

We investigated the yield and feasibility of routine pharyngeal gonorrhea test-of-cure to detect treatment failures through a multi-site project.

Keywords

Neisseria gonorrhoeae; pharyngeal gonorrhea; test of cure; antimicrobial resistance

BACKGROUND

Neisseria gonorrhoeae has been designated an urgent antibiotic-resistance threat-level pathogen in the United States since 2013.^{1,2} Pharyngeal gonorrhea (GC) may facilitate acquisition or development of resistance mutations through genetic reassortment and plasmid uptake of resistance genes from other *Neisseria* species that colonize the pharynx.³⁻⁶ Combined with lower concentration of some antimicrobials at the pharynx, this creates an optimal setting for selection of resistance mutations due to subinhibitory drug concentrations.^{7,8}

Ceftriaxone is the only highly-effective single-dose regimen recommended for gonococcal treatment at the pharynx.⁹ Reports of ceftriaxone treatment failures internationally have primarily occurred at the pharynx.¹⁰ Quickly identifying and appropriately treating all suspected GC treatment failures should prevent transmission of resistant strains. Implementation of routine test-of-cure (TOC) is a potential strategy to identify and prevent the spread of antimicrobial-resistant gonorrhea. In 2021, the Centers for Disease Control and Prevention (CDC) recommended TOC for anyone diagnosed with pharyngeal GC 7 to 14 days after initial treatment, regardless of treatment regimen,⁹ to detect persistent asymptomatic infection, thereby preventing transmission, and to potentially identify antimicrobial resistance and reduce the risk of transmission of resistant strains.¹⁰ There are data gaps regarding the efficacy and feasibility of this strategy. During 2021–2022, National Association of County and City Health Officials (NACCHO), with support from the CDC, funded four U.S. local jurisdictions with public STD clinics to implement and assess pharyngeal GC TOC in routine clinical practice. We investigated the yield of routine pharyngeal GC TOC to detect treatment failures and antimicrobial resistance and the feasibility of implementing TOC for all pharyngeal GC infections.

METHODS

Study Design and Population

Between May 1, 2021–July 31, 2022, four health departments [San Francisco Department of Public Health (San Francisco, California); Maricopa County Department of Public Health (Phoenix, Arizona); Public Health Institute at Denver Health (Denver, Colorado); and DC

Health (Washington D.C.)) implemented pharyngeal GC TOC into routine clinical practice at public STD clinics. We conducted a cross-sectional analysis of all pharyngeal GC cases treated at the participating clinics during the study period. Pharyngeal GC episodes, including TOC and all associated follow up data, were included in the analysis if the initial treatment date occurred during the project period.

Clinical and Laboratory procedures

All patients treated for pharyngeal GC were advised to return in 10–14 days for TOC with a nucleic acid amplification test (NAAT). Strategies for TOC activities such as scheduling TOC visits, tracking patients, follow-up communications to encourage TOC completion, and TOC specimen collection varied by site; all sites employed additional dedicated TOC staff/navigator(s) to perform them (Table 1).¹¹ All sites offered in-clinic TOC by clinician specimen collection or self-collection; two sites also offered TOC via self-collected NAAT outside of the clinic (i.e., home specimen collection kit). Patients with a positive pharyngeal GC TOC were managed per CDC STI Treatment Guidelines and local protocols.^{9,11} Patients with positive TOC were asked to return to clinic for further evaluation including consideration for re-treatment (depending on clinical suspicion of false-positive test, re-infection, or treatment failure) and specimen collection for gonococcal culture; initial TOC culture was typically performed at time of repeat TOC NAAT and re-treatment. Antimicrobial susceptibility (AST) by Etest and/or agar dilution was performed by participating sites' local laboratories if *N. gonorrhoeae* was isolated from TOC culture; AST results were reported as minimum inhibitory concentrations (MIC) for anti-gonococcal antimicrobials.¹²

Quantitative Data Collection

Although implementation strategies varied, all sites collected line-listed, de-identified demographic and clinical data for treated pharyngeal GC cases using a standardized data-collection form. Sites assigned a unique identifier to the patient, allowing for longitudinal tracking of patients, and linked the patient's epidemiologic and clinical data to lab results. For TOC positive cases, additional data were collected including reported sexual activity (i.e., oral, genital, anal sex) between most recent treatment for pharyngeal gonorrhea and TOC, follow-up testing and treatment, and the final case disposition (i.e., the suspected reason for the positive TOC). The final case disposition for the positive pharyngeal GC TOC was determined by the site project staff based on chart reviews and often involved consultation with the clinic medical director.

Definitions

For male patients, we defined men who have sex with men (MSM) as males that reported only having male sex partners within the past 3 months; men who have sex with men and women (MSMW) were defined as males that reported having male and female sex partners within the past 3 months; and men who have sex with women only (MSW) were defined as males that reported only having female partners in the past 3 months. The TOC response rate was defined as the number of patients that had TOC performed within 1–6 weeks of GC treatment over the total number of patients treated for pharyngeal GC at the participating clinical site. For this analysis, TOC response rate was based on the first TOC performed

for a case (initial TOC); data on subsequent TOC visits (follow-up TOC) for patients who tested positive at initial TOC visit were not included. The final case dispositions for cases with positive TOC were classified as 1) reinfection, 2) false-positive due to residual genetic material, 3) treatment failure due to non-recommended regimen, 4) treatment failure to ceftriaxone without resistance ($\text{MIC} \leq 0.25 \mu\text{g/mL}$) and 5) treatment failure to ceftriaxone with resistance ($\text{MIC} > 0.25 \mu\text{g/mL}$; see Table 2 for final case disposition definitions). Cases with a positive TOC that did not return to clinic for further testing, treatment, or additional evaluation that could inform the suspected reason for the positive test were classified as “insufficient data to disposition.” If cases were dispositioned as “unknown” or “missing” by participating sites, additional review and consultation with CDC clinical project staff were conducted to determine the most likely final case disposition.

Qualitative data collection

To assess perceived feasibility of routine pharyngeal GC TOC implementation, a qualitative project evaluation was conducted with site representatives, including 1–2 staff per site (site project leads for all sites, clinical lead for two sites), that participated in two virtual one-hour qualitative interviews: a mid-project interview in December 2021 and an end-of-project interview in August 2022. A semi-structured interview guide was developed to explore the strengths and limitations of each site’s TOC implementation. Interviews were recorded and sent to a contractor for verbatim transcription. Qualitative data were also collected in final implementation progress reports that were submitted by each of the participating sites. The progress report included free response questions about sustainability of TOC implementation.

Data analysis

We calculated the frequencies of demographic, behavioral, and clinical characteristics of pharyngeal GC cases overall and stratified by pharyngeal GC TOC performed. Key outcomes included the TOC response rate calculated overall and by sites, the median [interquartile range (IQR)] time to TOC from GC treatment date, type of TOC diagnostic test performed, number/proportion of cases with positive pharyngeal GC TOC, and the final case disposition. These analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

Qualitative data from interview transcripts and progress reports were analyzed using inductive coding in NVivo (released in March 2020). Codes were generated for each interview or progress report question. Relationships among codes were examined to develop themes related to perceived feasibility of pharyngeal GC TOC implementation, drivers, and limitations to TOC implementation (including considerations among other STD clinics), and perceived sustainability of implementation.

Data were collected as public health program evaluation activities and were determined to be exempt from CDC Institutional Review Board review.

RESULTS

Characteristics of population

During the study period, 1,968 pharyngeal GC cases were diagnosed at the four clinical sites. Among those diagnosed, 1,829 cases (93%) were treated among 1,654 individual patients. Most patients had one episode of pharyngeal GC (n=1514; 92%); 7.3% (n=120) had 2 episodes and 1.2% (n=20) had ≥3 episodes during the study period.

Pharyngeal GC cases treated varied by site with almost half of treated cases (49%, n=888) reported by Maricopa County (Table 3). Across sites, the median age was 30 years (IQR: 25–36). Most cases were among men (84%) and, among men, 68% were among MSM. Approximately one-third of treated cases were reported as Non-Hispanic White and 39% as Hispanic. Overall, 8% of cases were among persons with HIV.

Almost half of treated pharyngeal GC cases had a prior history of GC (ever); among these, over half (57%, n=443) had ≥1 GC infections within the past 12 months. At the time of the first clinical evaluation for the present pharyngeal GC episode, 9.1% reported experiencing a symptom of pharyngeal GC (i.e., sore throat) and almost half of all treated cases (48.7%) had GC diagnosed at other anatomic sites at the same time. Most cases (n=1,777; 97.2%) received CDC recommended treatment (ceftriaxone 500mg IM or 1g IM once).*

In over half of treated pharyngeal GC cases (58%; n=1,061), staff made or attempted follow-up communication/contact to encourage TOC; 64.2% (n=681) of cases had a TOC reminder card provided and/or sent, 26.8% (n=284) received telephone call(s) from staff, and 8.2% (n=87) received both reminder telephone call(s) and text messages. Among those cases that had follow-up communication (n=1061), 39.7% had one contact, 23.6% had two contacts, and 36.8% had three or more contacts.

Test-of-cure completion

Among 1,829 treated pharyngeal GC cases, 836 (45.7%) had TOC completed. Completion rate varied by project site – from 35.5% in Maricopa County to 70.8% in Washington DC (Table 3). The median time to TOC from treatment date was 14 days (IQR 14–18). Just over half of asymptomatic patients returned for TOC while about 40% patients reporting any urogenital or extragenital gonococcal symptoms had TOC performed. Similarly, patients without concurrent GC infection(s) at other anatomic sites were more likely to return for pharyngeal GC TOC (47.2% vs. 38.4%). Among the 356 patients at the two sites that opted for self-collected NAAT outside of the clinic, approximately half completed TOC (n=199; 55.9%). Among cases with TOC performed (n=836), 95.6% had initial TOC performed using only NAAT and 4.2% had both NAAT and culture performed (Table 4). The NAAT type used most for TOC was Aptima Combo 2 assay (n=737; 88.2%; Hologic Inc., San Diego, CA, USA), followed by Roche cobas 8800 CT/NG assay (n=67; 7.9%; Roche Diagnostics, Indianapolis, IN, USA), and Cepheid Xpert® CT/NG assay (n=31; 3.7%; Cepheid, Sunnyvale, CA, USA). TOC positivity varied by NAAT type with Roche being

*CDC recommends ceftriaxone 500 mg intramuscularly in a single dose for the treatment of uncomplicated gonorrhea. For persons weighing ≥150 kg, 1 g ceftriaxone should be administered.

the highest at 7.5% (5/67), 4.3% (32/737) for Aptima, and 3.2% (1/31) for Cepheid. The five TOC positive cases using the Roche assay were dispositioned as false-positive results (making up 38.5% of all false-positive TOCs).

Cases with positive pharyngeal GC TOC

Among cases with TOC performed, 4.7% (n=39) had a positive TOC; all were positive by NAAT and 3 cases had both positive NAAT and culture at the initial TOC visit. Culture was performed at the re-treatment visit to further investigate 16 NAAT positive TOC cases that did not have culture performed at initial TOC; of these, thirteen (81.3%) were culture negative, and three (18.8%) were culture positive. Overall, among all TOC positive cases, six (15.4%) were both NAAT positive and culture positive. Among the 39 positive TOC cases, one-third (33.3%, n=13) were considered likely re-infection, one-third (33.3%, n=13) likely false-positive tests, 15.4% (n=6) were dispositioned as clinical treatment failures, and 17.9% (n=7) had insufficient data to disposition mostly due to loss-to-follow-up (Table 2). Among the six cases dispositioned as treatment failures, two were treated with a non-ceftriaxone regimen. Among the four ceftriaxone-receiving treatment failure cases, all had received ceftriaxone 500 mg intramuscular once as initial treatment, all had TOC performed ≥ 12 days from treatment and had culture performed, all of which were positive (Table 5). AST was performed for two cases, both of which were susceptible to ceftriaxone and cefixime. All four cases were re-treated with different anti-gonococcal regimens and were cured as evidenced by repeat TOC NAAT with negative results.

Qualitative Results

Feasibility of implementation. Interviewees reported TOC implementation was feasible, created minimal disruptions to clinical workflow, but required substantial staff investment. All sites worked with a multi-disciplinary team that included providers, clerical staff, and epidemiologists (staff size range: 3–16). At minimum, sites employed a clinical provider and ≥ 1 project staff member (e.g., program/research assistant) to conduct visit reminders and follow-ups. On average, clinicians needed 5–30 minutes to perform clinical TOC activities, including patient education, specimen collection, and dispensing test kits (where applicable), exclusive of staff time required for clerical tasks. Time varied by the site's testing strategy and case disposition, with activities taking up to one hour for a positive TOC. Interviewees reported that reminder calls were the most time-consuming activity, followed by patient education. Additionally, in-clinic testing options required more staffing capacity than home self-collection kits.

Drivers and limitations to implementation. Interviewees most frequently cited support from leadership and the clinical team, as well as flexible clinic culture to rapidly pivot, as key drivers for successful implementation. During the study period, some sites revised local protocols to recommend TOC ≥ 10 days post-treatment to decrease false-positive tests. Other facilitators included conducting patient education to improve the TOC completion rate, scheduling the TOC appointment at the time of the first test or treatment visit, adapting existing electronic health record infrastructure to capture data correctly and consistently, and having a laboratory at the clinic to reduce time to result. Although sites did not deem TOC as overly burdensome in practice (e.g., minimal changes to the existing

clinic workflow), they reported that many additional resources required could outweigh the benefits given their perceived low yield of detecting treatment failures. In addition, the complexity of evaluating a positive TOC to determine clinical significance was cited as a fundamental challenge, requiring additional staff time and testing to investigate.

Sustainability of implementation. All interviewees shared plans to continue pharyngeal GC TOC implementation in some capacity. Two sites planned to continue offering home self-collection kits only, while also automating or decreasing the number of follow-up calls to lessen implementation burden. The other two sites planned to move TOC to their express clinic to reduce burden on staff resources, noting these resources could be more effectively dedicated elsewhere because of the limited yield to detect treatment failures. The largest barriers to TOC sustainability were inadequate systems, resources, and staff capacity. Interviewees cited needing additional funding for testing and additional staff to perform case management, specimen collection, and reminder calls.

DISCUSSION

Among nearly 2,000 cases of pharyngeal GC across four jurisdictions that implemented routine pharyngeal GC TOC in STD clinics, we found that less than half of cases returned for TOC and of those, less than 5% had a positive TOC, <1% were treatment failures, and none were due to cephalosporin resistance. Completion rates varied across the four jurisdictions and implementation strategies, but overall, the program was considered feasible, albeit resource intensive. Our findings suggest that routine pharyngeal GC TOC implementation into clinical practice to detect treatment failures and cephalosporin resistance may be limited by low TOC response rates, limited culture completion, limited culture yield for positive TOCs, challenges interpreting positive TOC, and clinic resources and capacity.

This is the first multi-jurisdiction and largest study to-date evaluating the CDC recommendation for routine pharyngeal GC TOC to detect treatment failures.⁹ Our findings are consistent with multiple other studies in both international and U.S. clinical settings that have described suboptimal GC TOC completion rates (range: 8.5%–61%) and low TOC positivity (1%–8%) when evaluating persistence of pharyngeal GC infection after treatment.^{13–19} TOC via home collection did not increase TOC completion rate substantially compared to in-clinic TOC specimen collection, as had been expected. Moreover, the low overall TOC completion rate, high number of patient follow-up attempts, and qualitative findings from our study reflect the challenges and resource-intensive process required to facilitate TOC in clinics and suggests that patients may not find TOC acceptable. Fifteen percent (n=6) of the positive TOC cases were unable to be dispositioned because the patient did not return to clinic for additional evaluation. With implementation of pharyngeal TOC, most patients diagnosed with pharyngeal GC will have at least three clinic visits – initial pharyngeal test visit, treatment visit, and TOC visit; if a patient has a positive TOC that becomes five or more visits. TOC increases the burden that patients face and can cause distress and anxiety, particularly for those who have a positive TOC. Clinicians must be trained to counsel patients on the reasons for conducting a TOC, and the nuances of interpreting positive TOC NAAT results, particularly given the known low yield of

culture for detecting *N. gonorrhoeae* in pharyngeal specimens and, therefore, the potential for having to interpret TOC NAAT positive/culture negative scenarios.²⁰ As STI testing and treatment is increasingly performed outside of STD specialty clinics, TOC completion rates may be different in other clinical settings; additional investigations could be helpful to understand implementation strategies and challenges in those settings.^{21,22}

Although the 2021 CDC STI Treatment Guidelines recommend performing pharyngeal GC TOC 7–14 days after initial treatment using either culture or NAAT, local study protocols generally recommended TOC between 10–14 days after experiencing false-positives when TOC was performed earlier. Following the publication of the TOC recommendation, a study found that time-to-clearance of pharyngeal GC RNA-based NAAT for >95% of specimens did not occur until 12 days after treatment.²³ Although the median time from treatment to TOC across project sites was 14 days, our data are consistent with Barbee et al. as we found 4.7% positivity at a median of 14 days, though only one-third of the positive TOC cases were considered false-positive results.²³ The most used NAAT for pharyngeal GC TOC in this study was the Aptima Combo 2 assay, an RNA-based NAAT, though TOC positivity was highest for Roche, a DNA-based NAAT, compared to Aptima and Cepheid. As DNA-based NAATs may have a slower time to clearance compared to RNA-based NAATs and decreased specificity at the pharynx on some assay systems, the selection of NAAT platform used for TOC may have implications for pharyngeal GC TOC yield and interpretation.^{24,25} Additionally, false-positives can occur due to cross-reactivity with commensal *Neisseria* species; clinicians may consider testing on a different NAAT platform in cases of persistently positive NAAT and culture negative pharyngeal TOC cases.^{26,27}

Four positive TOC cases (<1% of all treated pharyngeal GC cases) were dispositioned as treatment failures to ceftriaxone without cephalosporin resistance; no treatment failures due to ceftriaxone-resistant GC were detected. Tonsillar concentrations of ceftriaxone are lower than blood concentrations, and also exhibit interpersonal variability.⁸ In this study and others, treatment failures at the pharynx with GC isolates with susceptible cephalosporin MICs are not uncommon, and are to some degree expected.¹⁸ The CDC and World Health Organization both recommend an efficacy threshold of >95%, which ceftriaxone 500 mg intramuscularly once appears to offer.¹⁰ Clinical treatment failures due to GC isolates with susceptible cephalosporin MICs based on current Clinical and Laboratory Standards Institute-established breakpoints highlight the challenges in treating pharyngeal gonorrhea and may warrant further discussion around the cephalosporin susceptibility breakpoints at the pharynx given the concern for lower concentration of ceftriaxone in tonsillar tissue. Although a formal cost effectiveness was not performed, given that each funded site received up to 100,000 dollars to support pharyngeal GC TOC implementation and only four treatment failures were detected across sites, the minimum program cost per case detected (approximately \$100,000 per treatment failure) in addition to clinics likely leveraging existing infrastructure, may exceed what would be considered a cost-effective program.²⁸

This analysis was subject to several limitations. First, these findings may not be nationally representative as this was limited to four geographic sites, in publicly funded STD clinics, two of which had previous experience implementing TOC.¹⁸ Variations in TOC implementation strategies across participating sites could have impacted pharyngeal GC

TOC performance compared to other clinical sites. Second, gonorrhea treatment failure due to ceftriaxone resistance has not been reported in the U.S., and only two known gonococcal cases have been reported with MICs of 1.0 µg/mL to ceftriaxone (three total with the mosaic *penA* 60.001 allele that confers decreased susceptibility to ceftriaxone). A larger sample size may have been required to identify such a rare event. If ceftriaxone-resistant GC remains less than 1 in 1000, which was approximately our TOC sample size, large scale implementation would likely be needed at the national scale to detect ceftriaxone resistance through pharyngeal TOC. Notably, the two known ceftriaxone resistant cases in the U.S. were not identified through TOC and neither resulted in a treatment failure.^{29,30} Moreover, to date defining a cephalosporin resistance breakpoint has been limited by lack of clinical outcomes stratified by MIC, and it is possible that MICs might vary by anatomical site, particularly for cephalosporins at the pharynx. Third, patients with positive TOC were not explicitly asked about kissing, a possible GC transmission mode; therefore, cases of reinfection may have been misclassified.³¹ Finally, as the project was implemented during 2021, clinics were experiencing challenges due to the COVID-19 pandemic, which may have contributed to lower TOC completion rates.

In conclusion, implementation of routine pharyngeal GC TOC was considered feasible for the four participating clinics; however, the yield for detecting treatment failures was low (<1% ceftriaxone clinical treatment failure), and the resources needed to achieve this outcome was high. Low TOC completion rates might be interpreted as a lack of patient acceptability, and almost half of positive TOC did not have culture attempted which is crucial to adjudicating the etiology of a positive TOC. Most positive TOC cases were ultimately determined to be reinfections or false-positive tests, yet the investigations required to make those determinations were resource intensive both for clinics and patients. Based on our findings, routine pharyngeal GC TOC implementation as a strategy for identifying antimicrobial resistant gonorrhea may warrant reconsideration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

CDC 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.

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Table 1.
Pharyngeal Gonorrhea Test-of-Cure (TOC) Implementation Strategies by Project Site *

TOC Implementation Strategies	DC Health and Wellness Center, Washington, D.C.	Public Health Institute at Denver Health, Denver, CO	Maricopa County Department of Public Health, Phoenix, AZ	San Francisco City Clinic, San Francisco, CA
Navigator/dedicated TOC Staff	X TOC Project Assistant	X TOC Project Assistant	X Medical Assistant	X TOC Project Assistant
In-clinic clinician-collected TOC	X	X	X	X
In-clinic self-collected TOC	X	X	X	X
Outside of the clinic self-collected TOC (i.e., home specimen collection kit)		X		X
Active follow-up calls/texts/ Electronic health record (EHR) messages	X	X	X	X
TOC EHR template/reports	X		X	X
REDCap database for TOC data entry/reports	X			
TOC financial incentive			X	
In-house laboratory			X	X
TOC patient education	X	X	X	X

* Adapted from NACCHO Pharyngeal Gonorrhea Test-of-Cure Final Report: <https://www.naccho.org/blog/articles/pharyngeal-gonorrhea-test-of-cure-toc-final-report-and-toolkit>

[†] Sites that participate in CDC's Strengthening the U.S. Response to Resistant Gonorrhea project and have implemented TOC for reduced susceptible gonorrhea

Table 2.

Final case dispositions among pharyngeal gonorrhea cases with positive test-of-cure (TOC; N=39)

Final Case Disposition		Definition	n (%)
Insufficient data to disposition		Patient with a positive pharyngeal GC TOC that did not return to clinic for further testing, treatment, or additional evaluation that could inform the suspected reason for the positive test	7 (17.9)
Re-infection		Patient received the recommended treatment and reported any interval sexual activity (i.e., oral, genital, anal sex) between the most recent treatment for pharyngeal gonorrhea and TOC	13 (33.3)
False positive due to residual genetic material		Patient received recommended treatment, patient reported no sexual exposure between treatment and TOC, and repeat TOC prior to or at the time of re-treatment was negative	13 (33.3)
Treatment failure	Non-recommended treatment *	Patient received an antimicrobial therapy other than ceftriaxone	2 (5.1)
	Recommended treatment without cephalosporin resistance	Patient received ceftriaxone, did not report interval sexual activity, TOC culture was positive, and the initial gonococcal isolate was susceptible to ceftriaxone (MIC ≤ 0.25 $\mu\text{g/mL}$)	4 (10.3)
	Recommended treatment with cephalosporin resistance	Patient received ceftriaxone; TOC culture was positive and initial isolate had elevated ceftriaxone MICs (MIC > 0.25 $\mu\text{g/mL}$)	0 (0)

MIC = minimum inhibitory concentration

* Recommended and non-recommended treatment classification was based on the CDC 2021 STI Treatment Guidelines

Table 3.

Demographic, behavioral, and clinical characteristics of pharyngeal gonorrhea cases treated at participating project sites, May 2021– July 2022

	All Treated Episodes	Test of Cure Performed	
		No	Yes
	(N=1,829)	(n=993)	(n=836)
	N (Col %)	n (Row %)	n (Row %)
Project clinic site			
Denver	302 (16.5)	104 (34.4)	198 (65.6)
Maricopa County	888 (48.6)	573 (64.5)	315 (35.5)
San Francisco	471 (25.8)	267 (56.7)	204 (43.3)
Washington D.C.	168 (9.2)	49 (29.2)	119 (70.8)
Age (years)			
Median (IQR)	30 (25, 36)	30 (24, 36)	30 (26, 37)
Sex			
Male	1543 (84.4)	830 (53.8)	713 (46.2)
Female	269 (14.7)	157 (58.4)	112 (41.6)
Sex partners among men [*] (n=1543)			
MSM	1045 (67.7)	529 (50.6)	516 (49.4)
MSMW	190 (12.3)	104 (54.7)	86 (45.3)
MSW	164 (10.6)	124 (75.6)	40 (24.4)
Unknown	144 (9.4)	73 (50.7)	71 (49.3)
Race and Hispanic Ethnicity			
Non-Hispanic American Indian or Alaska Native	22 (1.2)	16 (72.7)	6 (27.3)
Non-Hispanic Asian	75 (4.1)	35 (46.7)	40 (53.3)
Non-Hispanic Black or African American	315 (17.2)	189 (60.0)	126 (40.0)
Non-Hispanic Native Hawaiian or Other Pacific Islander	8 (0.4)	4 (50.0)	4 (50.0)
Non-Hispanic White	600 (32.8)	320 (53.3)	280 (46.7)
Hispanic	712 (38.9)	380 (53.4)	332 (46.6)
Non-Hispanic Other	18 (1.0)	10 (55.6)	8 (44.4)
Unknown	79 (4.3)	39 (49.4)	40 (50.6)
HIV status [†]			
Positive	217 (7.9)	124 (57.1)	93 (42.8)
Negative	1467 (80.2)	783 (53.4)	684 (46.6)
Unknown	145 (7.9)	86 (59.3)	59 (40.7)

	All Treated Episodes	Test of Cure Performed	
		No	Yes
	(N=1,829)	(n=993)	(n=836)
	N (Col %)	n (Row %)	n (Row %)
Prior history of gonorrhea ^{††}			
Yes	783 (42.8)	460 (58.7)	323 (41.3)
No	712 (38.9)	399 (56.0)	313 (44.0)
Unknown	334 (18.3)	134 (40.1)	200 (59.9)
Among those with history of gonorrhea (n=783): gonorrhea in the past year			
0 episodes	309 (39.5)	180 (58.3)	129 (41.7)
1 episode	310 (39.6)	176 (56.8)	134 (43.2)
2 episodes	90 (11.5)	58 (64.4)	32 (35.6)
3 or more episodes	43 (5.5)	26 (60.5)	17 (39.5)
Unknown	31 (4.0)	20 (64.5)	11 (35.5)
Urogenital and/or extragenital gonorrhea symptoms [¶]			
Yes	747 (40.8)	457 (61.2)	290 (38.8)
No	981 (53.6)	477 (48.6)	504 (51.4)
Unknown	101 (5.5)	59 (58.4)	42 (41.6)
Experienced symptom of pharyngeal gonorrhea (i.e., sore throat; n=747)			
Yes	166 (9.1)	83 (50.0)	83 (50.0)
No	1636 (89.4)	903 (55.2)	733 (44.8)
Unknown	27 (1.5)	7 (25.9)	20 (74.1)
Gonorrhea diagnosed at other anatomic sites [§]			
Yes	891 (48.7)	577 (61.6)	360 (38.4)
No	936 (51.2)	543 (52.8)	486 (47.2)
Unknown	2 (0.1)	2 (100)	0 (0)
Anatomic sites of diagnosed concurrent gonococcal infection(s) (n=891)			
Urogenital only	364 (40.9)	254 (69.8)	110 (30.2)
Rectal only	356 (40.0)	186 (52.2)	170 (47.8)
Urogenital and rectal	170 (19.1)	91 (53.5)	79 (46.5)
Unknown	1 (0.1)	1 (100)	0 (0)
Treatment prescribed for current pharyngeal gonorrhea episode			
Ceftriaxone 500mg IM ONCE	1762 (96.3)	948 (53.8)	814 (46.2)

	All Treated Episodes	Test of Cure Performed	
		No	Yes
	(N=1,829)	(n=993)	(n=836)
	N (Col %)	n (Row %)	n (Row %)
Ceftriaxone 1g IM ONCE	15 (0.8)	13 (86.7)	2 (13.3)
Gentamicin 240 mg intramuscularly once PLUS azithromycin 2 gm PO once	34 (1.9)	19 (55.9)	15 (44.1)
Azithromycin 2 g PO ONCE	9 (0.5)	8 (88.9)	1 (11.1)
Gentamicin 240 mg IM ONCE	3 (0.2)	1 (33.3)	2 (66.7)
Cefixime 800mg PO ONCE	1 (0.1)	1 (100)	0 (0)
Other treatment regimen	12 (0.7)	9 (75.0)	3 (25.0)
Unknown	5 (0.2)	3 (60.0)	2 (40.0)
Follow-up communication/contact from staff made or attempted ^{//}			
Yes	1061 (58.0)	594 (56.0)	467 (44.0)
No	309 (16.9)	248 (80.3)	61 (19.7)
Unknown	459 (25.1)	151 (32.9)	308 (67.1)
Number of follow-up contacts made or attempted by staff to encourage TOC completion (n=1061)			
One contact	421 (39.7)	201 (47.7)	220 (52.3)
Two contacts	250 (23.6)	120 (48.0)	130 (52.0)
Three or more contacts	390 (36.8)	273 (70.0)	117 (30.0)

MSM: men who have sex with men only; MSMW: men who have sex with men and women; MSW: men who have sex with women only

^{*} Sex partners among men was determined by patient's reported sex partners in the past 3 months.

^t Most current HIV status known at time of initial clinic visit for pharyngeal gonorrhea

^{tt} Any prior history of gonorrhea per clinical record, self-report, and/or per local/state surveillance system

[¶] Experienced symptoms of urogenital and/or extragenital gonorrhea at time of the first clinical evaluation for most recent pharyngeal gonorrhea episode

[§] Gonorrhea diagnosed at other anatomic site(s) at time of initial pharyngeal gonorrhea diagnosis

^{//} Follow-up communication/contact (e.g., telephone call, text message, email, electronic communication through electronic medical record) from staff made or attempted to encourage TOC completion

Table 4.

Type of Pharyngeal Gonorrhea Test-of-Cure (TOC) Performed and Results of Initial TOC Testing Among Gonococcal Cases with TOC Performed (n=836)

	All Initial TOC Performed (n=836)	Positive TOC Cases (n=39)
	n (%), Col	n (%), Col
Type of Initial TOC Performed		
NAAT only	801 (95.8)	38 (97.4)
Culture only	0 (0)	0 (0)
NAAT and culture	35 (4.2)	1 (2.6)
TOC specimen collection method		
In-clinic self-collected NAAT and/or culture	461 (55.1)	23 (59.0)
In-clinic clinician-collected NAAT and/or culture	187 (22.4)	8 (20.5)
Home testing kit	179 (21.4)	8 (20.5)
Unknown	9 (1.1)	0 (0)
Type of TOC NAAT Used		
Aptima Combo 2 assay	737 (88.2)	32 (82.0)
Roche cobas 8800 CT/NG assay	67 (7.9)	5 (12.8)
Cepheid Xpert® CT/NG assay	31 (3.7)	1 (2.6)
Unknown	1 (0.1)	1 (2.6)
Initial TOC NAAT results		
Negative	783 (93.7)	(0)
Positive	39 (4.7)	39 (100)
Indeterminant	10 (1.2)	0 (0)
Unknown	4 (0.4)	0 (0)
Initial TOC culture results		
Negative	32 (3.8)	1 (2.6)
Positive	3 (0.4)	3 (7.7)
Indeterminant	0 (0)	0 (0)
Not performed	793 (94.8)	33 (84.6)
Unknown	8 (1.0)	2 (5.1)
Time to TOC (Median, IQR)	14 (14–18)	14 (13–17)

NAAT= nucleic acid amplification test

Table 5.

Treatment failures after recommended treatment among pharyngeal gonorrhea cases with positive test-of-cure (TOC; n=4)

Case	Time between treatment and TOC (days)	TOC culture performed	Culture results	AST results	Follow Up	
					Re-treatment	Repeat TOC NAAT
1	14	Yes	Positive	Non-viable	CRO 1 g	Negative
2	14	Yes	Positive	Non-viable	GEN 240 mg plus AZI 2 g	Negative
3	21	Yes	Positive	CRO MIC 0.015 CFM MIC 0.015	CRO 1 g	Negative
4	12	Yes	Positive	CRO MIC 0.006 CFM MIC <0.016	CRO 1 g	Negative

AST= antimicrobial susceptibility testing; NAAT= nucleic acid amplification test; AZI= azithromycin; CFM=cefixime; CRO=ceftriaxone; GEN=gentamicin