Incidence and Treatment Outcomes of Pharyngeal Neisseria gonorrhoeae and Chlamydia trachomatis Infections in Men Who Have Sex with Men: A 13-Year Retrospective Cohort Study

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Background. This study investigated the incidence and treatment outcomes of pharyngeal Neisseria gonorrhoeae and Chlamydia trachomatis cases at a Canadian clinic that mainly serves men who have sex with men.

Methods. All patients with pharyngeal N. gonorrhoeae and C. trachomatis infections detected from 1 January 1995 through 31 December 2007 were identified. Original and test-of-cure N. gonorrhoeae culture isolates were compared using antibiotic susceptibility testing and N. gonorrhoeae multiantigen sequence typing.

Results. One hundred seventy-eight cases of pharyngeal N. gonorrhoeae infection and 97 cases of pharyngeal C. trachomatis infection were identified, primarily by culture methods. The mean incidence was 1.62 and 0.81 cases per 1000 visits per year for N. gonorrhoeae and C. trachomatis infection, respectively. Poisson regression modeling demonstrated a statistically significant surge of pharyngeal N. gonorrhoeae cases in 2007 after controlling for seasonal and long-term oscillation and long-term linear trends. Among patients with pharyngeal N. gonorrhoeae and C. trachomatis infection, 60.2% and 84.3%, respectively, would have been missed by relying on antibiotic susceptibility testing and N. gonorrhoeae multiantigen sequence typing. Nine percent of patients with pharyngeal N. gonorrhoeae and 4.3% of patients with pharyngeal C. trachomatis infection who underwent test-of-cure procedures had at least 1 positive result. Antibiograms were not different in 8 of 10 pretreatment and posttreatment N. gonorrhoeae isolate pairs. N. gonorrhoeae multiantigen sequence typing results were identical in 2 of these cases. Public health records documented abstinence in both individuals.

Conclusions. Nine percent of cases with pharyngeal N. gonorrhoeae and 4.3% of cases with pharyngeal C. trachomatis infection that underwent tests of cure had positive results. Available typing results suggest antibiotic treatment failure rather than reinfection. Specific antibiotic treatment regimens for pharyngeal N. gonorrhoeae and C. trachomatis infections need to be developed and formally evaluated.

Neisseria gonorrhoeae and Chlamydia trachomatis infections are a significant problem among men who have sex with men, because of high rates of unprotected sex [1]. The pharynx is a frequently overlooked reservoir for these pathogens. Pharyngeal N. gonorrhoeae and C. trachomatis infections are well documented in the literature, with a recent study reporting a prevalence of 9.2% for pharyngeal N. gonorrhoeae and 1.4% for pharyngeal C. trachomatis in a population of men who have sex with men [2]. Moreover, data in the literature have reported urethral N. gonorrhoeae infections associated with insertive oral sex [3] and pharyngeal N. gonorrhoeae associated with receptive oral sex [4], providing evidence that not only does N. gonorrhoeae colonize the pharynx, it also appears to be transmitted bidirectionally through oral-penile contact [4].

Effective antimicrobial therapy is required for the eradication of N. gonorrhoeae and C. trachomatis from
the pharynx; however, data documenting the efficacy of commonly used antimicrobial regimens are lacking. This retrospective cohort study documented the incidence of pharyngeal N. gonorrhoeae and C. trachomatis infections at a Canadian clinic for men who have sex with men and investigated treatment outcomes.

**METHODS**

**Data collection.** Clinic records from the Hassle Free Men’s Clinic in Toronto, Ontario, Canada, were used to identify all patients with pharyngeal N. gonorrhoeae and C. trachomatis infections detected from 1 January 1995 through 31 December 2007. This clinic serves a large population of men who have sex with men from Toronto and the surrounding area. Clinic medical records were used to extract the following data: the antibiotic regimen administered, test-of-cure results, and the presence of N. gonorrhoeae and/or C. trachomatis at other anatomical sites. Antibiotic susceptibility testing results were recorded for patients with pharyngeal N. gonorrhoeae infection. For individuals who did not receive antibiotic therapy, public health documentation of attempts to contact the individual were noted.

The clinic policy during the study period was to sample the pharynx, rectum, and urethra (or urine) for N. gonorrhoeae and C. trachomatis in patients presenting for sexually transmitted disease screening, regardless of the presence or absence of symptoms. It was also their policy to perform 2 tests of cure by culture in all cases of culture-positive pharyngeal N. gonorrhoeae infection. For individuals who did not receive antibiotic therapy, public health documentation of attempts to contact the individual were noted.

Cohort of patients with pharyngeal N. gonorrhoeae and C. trachomatis detected by molecular methods. In 2007, additional patients were recruited from a study that evaluated the performance of the ProbeTec and APTIMA Combo 2 assays (APTIMA; Gen-Probe) in detecting pharyngeal and rectal N. gonorrhoeae and C. trachomatis infections; this study was also conducted at the Hassle Free Men’s Clinic [5]. Pharyngeal and rectal specimens were obtained for N. gonorrhoeae and C. trachomatis testing by culture, ProbeTec, and APTIMA assays. Positive results of the APTIMA test were confirmed using the ACT and AGC assays (Gen-Probe). Tests of cure were performed using culture, ProbeTec, and APTIMA tests at 3 and 4 weeks after the completion of treatment.

For the purpose of analysis, a positive pharyngeal nucleic acid amplification test result was deemed a true-positive result if (1) a second assay result was positive or (2) the patient had a positive result for the same organism at another anatomical site [5]. Details pertaining to this study have been published elsewhere [5].

In this cohort of patients, 28 individuals had positive results for pharyngeal N. gonorrhoeae by ProbeTec, APTIMA, or both tests. Eighteen patients had N. gonorrhoeae detected by both assays. Two had positive results by the APTIMA test but negative results by the ProbeTec test, and both patients had positive confirmatory results by the AGC assay. Eight patients had positive results by the ProbeTec assay but negative results by the APTIMA assay. N. gonorrhoeae was detected in a rectal sample from 1 individual. The remaining 7 individuals had unconfirmed results and were not included in this study [5]. Therefore, 21 patients with confirmed pharyngeal N. gonorrhoeae infection from this 2007 cohort were included in this study.

Seven individuals from the cohort had positive results for pharyngeal C. trachomatis, and all were included in this study. Four had positive results for C. trachomatis by both ProbeTec and APTIMA assays. The remaining 3 had positive results by the APTIMA test but negative results by the ProbeTec test; the detection of C. trachomatis was confirmed by the ACT assay. Culture failed to detect any cases of pharyngeal N. gonorrhoeae and C. trachomatis infection in this cohort.

Statistical analysis. SAS statistical software, version 9.1 (SAS Institute), was used for statistical analysis. To assess the impact of the molecular techniques introduced in 2007, Poisson regression was used to investigate the relationship between the incidence of pharyngeal N. gonorrhoeae and C. trachomatis infection (measured as the number of cases per 1000 sexually transmitted disease program visits per month) and diagnosis in 2007. Initial models included the following variables: detection in 2007 (as a step function), a within-year oscillation term (modeled by incorporating sine and cosine terms into the model with use of a fast Fourier transform) [6], and a yearly term that described linear trends over time. However, visual inspection of trend data and evaluation of model goodness of fit and Akaike’s information criterion indicated that a long-term oscillation term with a 5-year period provided better fit. This term was added, giving rise to a second set of models. Because of the colinearity between the linear yearly terms and the long-term oscillation terms, the former was removed in the second set of models.

**Typing of pharyngeal N. gonorrhoeae isolates.** For individuals with pharyngeal N. gonorrhoeae infection and positive test-of-cure results, the original and the test-of-cure isolates...
were compared using antibiotic susceptibility testing results and, where possible, the *N. gonorrhoeae* multiantigen sequence typing (NG-MAST) procedure [7]. The Public Health Laboratory reported antibiotic susceptibility results for penicillin, ciprofloxacin, tetracycline, cefixime, ceftriaxone, spectinomycin, and erythromycin. The susceptibility results for a given antibiotic were considered to be “not different” if both isolates were reported susceptible or if the reported MICs were within 1 doubling dilution of the other.

The NG-MAST sequencing procedure involved sequencing highly polymorphic internal fragments within the *por* gene, which encodes an outer membrane protein, and the *tbpB* gene, which encodes the β-subunit of transferrin binding protein B [7]. The forward and reverse primers used to amplify the DNA fragments within the *tbpB* gene were 5′-CGTTGTCCAGGCGCGAAAC-3′ and 5′-TTTCATCGGTGCGCTCGCCTTG-3′, respectively. The forward and reverse primers for the *por* gene were 5′-CAATGAAAAATCCCTGATTG-3′ and 5′-TTTGCA-GATTGATTTGCTTG-3′, respectively [7]. After editing and trimming, the sequences were submitted to the NG-MAST database, where they were compared against all existing alleles and assigned a sequence type [7].

**RESULTS**

*Incidence.* In total, 178 cases of pharyngeal *N. gonorrhoeae* and 97 cases of pharyngeal *C. trachomatis* infection were identified. Figure 1 illustrates the number of pharyngeal *N. gonorrhoeae* and *C. trachomatis* infections diagnosed per 1000 sexually transmitted disease program visits from 1995 through 2007. The mean incidence of pharyngeal *N. gonorrhoeae* was 1.62 cases per 1000 sexually transmitted disease visits per year. The mean incidence of pharyngeal *C. trachomatis* was 0.81 cases per 1000 sexually transmitted disease visits per year.

Initial Poisson regression models demonstrated significant within-year oscillation of both pharyngeal *N. gonorrhoeae* (P = .001) and *C. trachomatis* (P = .002) incidence. A significant linear yearly increase in the incidence of pharyngeal *C. trachomatis* (incidence rate ratio [IRR], 1.20; 95% CI, 1.12–1.29; P < .001) but not *N. gonorrhoeae* (IRR, 1.02; 95% CI, 0.98–1.07; P = .34) was observed. After controlling for within-year oscillation and linear trends, a significant increase was seen in incidence of pharyngeal *N. gonorrhoeae* in 2007 (IRR, 1.64; 95% CI, 1.12–2.40; P = .01). This was not the case for pharyngeal *C. trachomatis* (IRR, 0.77; 95% CI, 0.44–1.35; P = .36).

We created a second pair of models that replaced the linear terms with long-term oscillation (with 5-year periodicity). Significant within-year oscillation was observed for both *N. gonorrhoeae* (P = .001) and *C. trachomatis* (P = .002). Pharyngeal *C. trachomatis* demonstrated significant long-term oscillation (P = .016). *N. gonorrhoeae* also exhibited a long-term oscillatory trend (P = .06). After controlling for oscillation on both short- and long-term time scales, a significant increase in incidence in 2007 was again seen for pharyngeal *N. gonorrhoeae* (IRR, 1.88; 95% CI, 1.21–2.94; P = .005) but not for *C. trachomatis* (IRR, 1.50; 95% CI, 0.69–3.25; P = .31). Model Akaike’s information criterion was lower for the second set of models.

**Urethral and rectal N. gonorrhoeae and C. trachomatis infections in patients with pharyngeal N. gonorrhoeae and C. trachomatis infections.** Seventy (39.8%) of the 176 individuals with pharyngeal *N. gonorrhoeae* who underwent urethral testing also had *N. gonorrhoeae* in the urethra or urine, whereas 35 (39.3%) of the 89 who underwent rectal testing had positive results for *N. gonorrhoeae* in the rectum (table 1). Twelve individuals tested positive for *N. gonorrhoeae* at all 3 sites. Among patients with pharyngeal *N. gonorrhoeae* infection, 13.6% had concomitant *C. trachomatis* infection at another site.

Fourteen (15.7%) of 89 individuals with pharyngeal *C. trachomatis* who were tested had positive results for *C. trachomatis* in urethra or urine, whereas 9 (21.4%) of 42 tested had positive results for *C. trachomatis* in the rectum. One individual was positive for *C. trachomatis* at all 3 sites. Among patients with pharyngeal *C. trachomatis* detected, 13.5% had concomitant *N. gonorrhoeae* infection at another site. There were 2 cases of

![Figure 1. Pharyngeal Neisseria gonorrhoeae (black bars) and Chlamydia trachomatis (gray bars) incidence by year, Hassle Free Men’s Clinic, Toronto, Ontario, Canada. STD, sexually transmitted disease.](image-url)
concomitant *N. gonorrhoeae* and *C. trachomatis* infection of the pharynx.

**Treatment and outcome.** Overall, 99.4% of patients with pharyngeal *N. gonorrhoeae* infection and 90.7% of patients with pharyngeal *C. trachomatis* infection received treatment. Most (95.5%) of the treated pharyngeal *N. gonorrhoeae* patients received single-dose oral cefixime. Treatment of pharyngeal *C. trachomatis* was split evenly between single-dose oral azithromycin, (1 g; 52.3%) and oral doxycycline (100 mg twice daily for 7 days; 47.7%). In all 9 individuals with pharyngeal *C. trachomatis* and the single individual with pharyngeal *N. gonorrhoeae* who did not receive antibiotic therapy, medical record review showed public health documentation of 3 attempts to contact the individual to schedule a return visit for antibiotic therapy.

Table 2 summarizes the individuals who had at least 1 positive test-of-cure result. Among the 122 individuals with pharyngeal *N. gonorrhoeae* infection who underwent test of cure, 11 (9.0%) had at least 1 positive result (patients 1–11; table 2). Ten of these individuals were treated initially with 400 mg of oral cefixime, and the remaining patient received 400 mg of oral ofloxacin. All *N. gonorrhoeae* culture isolates were susceptible to cefixime. The lone patient who was treated with ofloxacin was infected with a quinolone-susceptible strain. Nine of the 11 patients returned for a second course of treatment (5 with cefixime, 4 with ofloxacin) and returned subsequently for a second test of cure, in which 8 had negative results. The ninth individual (patient 10) had positive results on the second test of cure but negative results on a third test. He was originally treated with 400 mg of cefixime and received the same regimen after each positive test-of-cure result.

Antibiotic susceptibility profiles of the original and test-of-cure isolates were examined for patients with *N. gonorrhoeae* infection (patients 1–9 and 11; patient 10 tested positive by nucleic acid amplification test only). On the basis of the susceptibility status of 4 antibiotics (penicillin, ciprofloxacin, tetracycline, and erythromycin), 8 of the 10 isolate pairs had antibiotic susceptibility profiles that were “not different” according to the predefined criteria. All 20 isolates were susceptible to cefixime, ceftriaxone, and spectinomycin.

Original and test-of-cure isolates were available for patients 2 and 9. The NG-MAST results assigned sequence type 225 to both patient 2 isolates and sequence type 2493 to both patient 9 isolates. The antibiotic susceptibility profiles were “not different” for each pair.

Of the 70 patients with pharyngeal *C. trachomatis* with test-of-cure results available, 3 (4.3%) had positive results (patients 12–14). Patients 12 and 13 were initially treated with azithromycin. Both received a 7-day regimen of doxycycline after the positive test-of-cure result, and subsequent test-of-cure results were negative in both cases. Patient 14, initially treated with doxycycline, had 2 successive tests of cure that produced positive results and was retreated with the doxycycline regimen each time. A third test of cure produced negative results. Review of the medical records showed public health documentation that 13 of these 14 patients were abstaining from sexual activity at the time of the first test of cure.

The 2 individuals who repeatedly had positive test-of-cure results (patients 10 and 14) were both enrolled as participants in the 2007 study. Both individuals initially had positive results by both ProbeTec and APTIMA but had negative results by culture. Both individuals also had positive results for both tests on the first test of cure (3 weeks after treatment) and the second test of cure (4 weeks after treatment). Culture and molecular assays both yielded negative results for both individuals on the third test of cure.

**DISCUSSION**

*N. gonorrhoeae* and *C. trachomatis* were regularly isolated from pharyngeal specimens at the Hassle Free Men’s Clinic during the 13-year period examined. The incidence of both pharyngeal *N. gonorrhoeae* and *C. trachomatis* detection oscillated over time, a phenomenon that has not been described elsewhere.

The spike in incidence of pharyngeal *N. gonorrhoeae* infection in 2007 was likely related to superior detection provided by the molecular testing that was introduced through the clinic’s participation in a research study, which would be consistent with data emerging in other reports [5, 8]. Because only a small proportion of patients were enrolled in the study (*n* = 248)
in 2007 was not observed for pharyngeal
have increased the 2007 incidence even more. A similar spike
[5], it is likely that larger-scale use of molecular testing would
believe that this is significant and that it supports the practice
of testing for pharyngeal
in high-risk popula-
C. trachomatis
infections over time. It is unlikely to be related to changes in sampling, because no changes occurred in the screening practices at the study clinic during the period examined.

Historically, the relevance of
isolated from the
Nine percent of patients with pharyngeal
infection had positive test-of-cure
results at 15 days and 0 had positive results at 22 days after treatment with clarithromycin (400 mg/day, for 7 or 14 days).

We believe that this is significant and that it supports the practice of testing for pharyngeal
in high-risk populations. Although the Public Health Agency of Canada and the Centers for Disease Control and Prevention do not make specific recommendations for the treatment of individuals with pharyngeal
infection, they recommend that indivi-
dividuals with pharyngeal
infection receive treatment for
if the presence of the latter has not been excluded [13, 14]. Specific screening and treatment recommendations for pharyngeal
infection would help to resolve this inconsistency.

The necessity of performing pharyngeal testing has been questioned with the argument that individuals with pharyngeal infections will likely have a concomitant infection detected by routine urethral or urine testing. This study confirms results of other reports indicating that this is not the case [2, 5, 15]. In this cohort, relying on routine urethral and urine specimens would have missed 60.2% of pharyngeal infections and 84.3% of pharyngeal
infections, indicating that urine and urethral specimens cannot be relied on to incidentally detect pharyngeal infections. Nine percent of patients with pharyngeal
infection who underwent tests of cure had positive results. This number is higher than that reported by McMillan and Young [16] (1 [2.2%] of 45 cases) but similar to that reported by Sathia et al. [17] (6 [10.3%] of 58 cases). Among
patients who underwent tests of cure, 4.3% had positive results. This small number of patients makes interpretation difficult. Mikamo et al. [18] reported that 2 (3.8%) of 52 patients with pharyngeal
infection had positive test-of-cure results at 15 days and 0 had positive results at 22 days after treatment with clarithromycin (400 mg/day, for 7 or 14 days).

The antibiotic susceptibility profile of the original and test-of-cure isolates for the pharyngeal
infection were detected during the 13-year pe-
for7days

<table>
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<tr>
<th>Patient</th>
<th>Pathogen</th>
<th>Antibiotic therapy</th>
<th>TOC 1</th>
<th>TOC 2</th>
<th>Different susceptibility on TOC</th>
<th>Concurrent N. gonorrhoeae or C. trachomatis</th>
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<td>1</td>
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<td>Cefixime, 400 mg&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>No</td>
<td>Urethral C. trachomatis</td>
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<tr>
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<td>–</td>
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<tr>
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<td>N. gonorrhoeae</td>
<td>Cefixime, 400 mg&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>–</td>
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<td>ND</td>
<td>Yes</td>
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<tr>
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<td>+</td>
<td>–</td>
<td>No</td>
<td>Rectal N. gonorrhoeae</td>
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| 10      | N. gonorrhoeae | Cefixime, 400 mg<sup>a</sup> | +     | +     | NAAT only                     | Rectal N. gonorrhoeae, urethral N. gonor-
| 11      | N. gonorrhoeae | Cefixime, 400 mg<sup>a</sup> | +     | –     | No                            | No                                       |
| 12      | C. trachomatis | Azithromycin, 1 g    | –     | +     | –                             | No                                       |
| 13      | C. trachomatis | Azithromycin, 1 g    | –     | +     | –                             | No                                       |
| 14      | C. trachomatis | Doxycycline, 100 mg + for 7 days | +     | +     | NAAT only                     | Rectal N. gonorrhoeae, urethral N. gonor-

NOTE. –, negative; +, positive; NAAT, nucleic acid amplification test; ND, second course of treatment and second TOC not performed.

<sup>a</sup> Azithromycin (1 g) given empirically.

<sup>b</sup> Typed with N. gonorrhoeae multiantigen sequence typing.
“not different” in 8 of the 10 individuals who had positive test-of-cure results by culture. Although the ability of antibiotic susceptibility testing to discriminate between N. gonorrhoeae strains is limited, the lack of differences in the antibiotic susceptibility results supports treatment failure as a possible explanation for the positive test-of-cure results. In the 2 individuals whose isolates were tested with molecular typing, the NG-MAST results were identical in both cases. Public health personnel had documented that both individuals were abstaining from sexual activities at the time of the positive test-of-cure results, further supporting the explanation of treatment failure and diminishing the possibility of reinfection with the same strain from an infected partner. It has been suggested that treatment failure in such cases may be related to poor drug penetration into pharyngeal tissue [19].

Both individuals who had positive test-of-cure results detected by molecular testing had positive results on 2 successive tests of cure (patients 10 and 14). The test-of-cure results were positive by molecular testing only. In both individuals, the first test of cure was performed 3 weeks after completion of antibiotic therapy, which is consistent with current guidelines for the use of molecular testing for test of cure in the context of urethral and cervical N. gonorrhoeae infections [14]. However, the possibility that these results were related to detection of the nucleic acid of dead organisms needs to be entertained [5, 20]

This study has some limitations. Completeness and accuracy are frequently a concern in retrospective studies that involve health records. The Hassle Free Men’s Clinic, however, maintains written policies regarding screening, treatment, and follow-up. As a result, medical record documentation and patient treatment were remarkably systematic and complete.

Also, although the NG-MAST typing system provides excellent discrimination among N. gonorrhoeae strains, culture isolates were available for only 2 of the 11 individuals with positive pharyngeal N. gonorrhoeae test-of-cure results, leaving an incomplete picture.

This study demonstrated that N. gonorrhoeae and C. trachomatis are regularly detected in pharyngeal specimens of men who have sex with men and that infections will remain undetected as a consequence of the poor sensitivity of culture and failure to obtain appropriate specimens from this site. There was a significant failure rate for both pharyngeal N. gonorrhoeae and C. trachomatis infections that were treated with standard antibiotic regimens originally developed for treatment of male urethral and female cervical infections. These failure rates were higher than those associated with treatment of urethral and cervical infections (3% for 1 g of azithromycin and 2% for the 7-day regimen of doxycycline (100 mg twice daily), for treatment of C. trachomatis 2%–3% for 400 mg of cefixime for treatment of N. gonorrhoeae) [21–23]. These data suggest that specific antibiotic treatment regimens for pharyngeal N. gonorrhoeae and C. trachomatis need to be developed and formally evaluated.

Acknowledgments

We thank Allan Lau and Irene Martin at the National Microbiology Laboratory and Lynn Towns, Gary Breienz, and Dr. Frances Jamesion at the Public Health Laboratory, Ontario Agency for Health Protection and Promotion, for their assistance with the molecular typing in this study. We also thank Leo Mitterni and Elmer Bagares from the Hassle Free Men’s Clinic for their assistance with data collection.

Potential conflicts of interest. All authors: no conflicts.

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