Adherence to CDC Gonococcal Treatment Guidelines among Chicago Health Care Providers, 2011-2012

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Word Count: 3,347

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Key Words: Neisseria gonorrhoeae, CDC Treatment Guidelines, gonococcal infection, antimicrobial resistance, cephalosporins
Short Summary

Among Chicago providers, recommended treatment for urogenital gonorrhea improved over time yet remains sub-optimal. Addressing underreporting of treatment and differential treatment by patient characteristics and provider setting are essential for efficacious outcome.
Abstract (Word Count = 250)

Background: Expansion of antimicrobial resistance in *Neisseria gonorrhoeae* requires rapid adaptation of treatment guidelines and responsive provider practice. We evaluated patient factors associated with provider adherence to the CDC gonococcal treatment recommendations among Chicago providers during 2011-2012.

Methods: Laboratory confirmed cases of uncomplicated urogenital gonorrhea were classified via surveillance data as originating from Chicago Department of Public Health (CDPH) or non-CDPH providers. Recommended treatment was determined according to the CDC STD Treatment Guidelines: April – July 2012 (period 1); August – December 2012 (period 2, following August 2012 revision). Multivariable log-binomial regression identified factors associated with recommended treatment over time, stratified by provider type.

Results: April 2011 through December 2012, 16,646 laboratory confirmed gonorrhea cases were identified, of which 9,597 (57.7%) had treatment information: 2,169 CDPH cases, 7,428 non-CDPH cases. Documented recommended treatment increased for CDPH (period 1: 71.3%, period 2: 80.8%, p-value <0.01) and non-CDPH providers (period 1: 63.5%, period 2: 68.9%, p-value <0.01). Among CDPH cases, statistically significant factors associated with recommended treatment were male gender [adjusted prevalence rate ratio (aPRR) = 1.16], White vs. Black race [aPRR = 0.68], same day treatment [aPRR = 1.07], and period 2 [aPRR=1.11]. Among non-CDPH cases, statistically significant factors were: male gender [aPRR=1.10], Other vs. Black race [aPRR=0.91], same day treatment [aPRR=1.31], greater number of within-facility reported cases [aPRRs ranging 1.22 to 1.41], and ≥50% within-facility missing treatment data [aPRR=0.84].
Conclusions: Recommended treatment improved over time, yet remains sub-optimal. Efforts to reduce variability and improve provider adherence to recommended treatment is urgently needed.
Introduction

Gonorrhea is the second most commonly reported notifiable communicable disease in the United States with over 300,000 cases annually [1], and an estimated annual incidence of over 800,000 cases [2]. Gonorrhea is a major cause of pelvic inflammatory disease (PID), infertility, ectopic pregnancy, and chronic pelvic pain [3], and can facilitate the transmission and acquisition of HIV infection [4-6]. Over time, *N. gonorrhoeae* has developed decreasing susceptibility to the several classes of antibiotics thus reducing the options for treatment.

Since 1986, the Centers for Disease Control and Prevention (CDC) has conducted surveillance of antimicrobial resistance through the Gonococcal Isolate Surveillance Project (GISP) [7]. Increases in fluoroquinolone-resistant *Neisseria gonorrhoeae* led to changes in national guidelines that now limit the recommended treatment to a single class of drug, cephalosporins [8]. Currently, for uncomplicated gonorrhea CDC recommends combination therapy with ceftriaxone 250 mg intramuscularly and either azithromycin 1 g orally as a single dose or doxycycline 100 mg orally twice daily for 7 days [3]. If cefixime is used as an alternative agent, then the patient should return in 1 week for a test-of-cure at the site of infection [9]. Efficacious treatment and limiting the spread of resistance relies on surveillance to monitor treatment practices and providers’ adherence to treatment recommendations. We evaluated the trends in provider adherence to recommended treatment of gonorrhea according to CDC treatment guidelines and identified associated patient and provider factors among health care providers at private and public health clinics in Chicago, Illinois, from April 2011 through December 2012.

Methods
This study was determined to be exempt from human subjects review by Institutional Review Boards of the Chicago Department of Public Health (CDPH) and by the University of Illinois at Chicago. This was an analysis of retrospective data collected on laboratory confirmed gonorrhea cases reported to the CDPH from April 1, 2011 through December 31, 2012. We assessed treatment trends 16 months prior to the release of the CDC treatment guidelines (period 1: April 2011 through July 2012), and after the release of the August 2012 treatment updates (period 2: August through December 2012) [9].

According to the Illinois State law, medical providers are required to report gonorrhea cases to the CDPH Sexually Transmitted Disease (STD) surveillance unit [10]. Cases reported by CDPH clinics (93.4% from STD specialty clinics) were defined as CDPH providers, while cases reported by other providers (community health centers (CHC), hospitals, primary physicians, etc.) were defined as non-CDPH providers. The CDPH STD/HIV Division operates five high-volume STD specialty clinics located throughout the city, serving a varied clientele (with regard to gender, race, ethnicity, and sexual orientation). Combined, CDPH STD clinics recorded over 23,000 annual patient visits in 2011 and approximately 22,000 in 2012.

Gonorrhea and chlamydia are reported through a web-based surveillance system called Illinois National Electronic Disease Surveillance System (I-NEDSS). I-NEDSS contains positive results of laboratory tests and morbidity reports provided by healthcare providers. If the test result for gonorrhea was reported as “positive”, “detected”, or “reactive” the case was included in our analysis. Cases represented patients presenting with symptoms, suspected contact with an infected partner or for screening purposes, and submitted urine, urethral swab, or cervical swab
specimens for nucleic acid amplification testing (NAAT). In addition to test results and date of test, for each case we obtained data regarding gender, age, race/ethnicity, and provider source. For cases reported by CDPH clinics, treatment data were extracted from the CDPH Electronic Medical Record (EMR) and matched to data extracted from I-NEDSS by patient’s name, date of birth, and date of visit. For non-CDPH cases, all data were abstracted from I-NEDSS only.

Cases with treatment data were reviewed and categorized as recommended or non-recommended based on the following criteria: treatment received from April 2011 through July 2012 (period 1, baseline) was defined as recommended if cases received an intramuscular (IM) injection of ceftriaxone 250mg or oral cefixime 400mg plus Azithromycin 1g (single dose) or Doxycycline 100mg (twice a day for 7 days) [3]. For cases treated between August 2012 through December 2012 (period 2), recommended therapy was defined as the combination of the injectable ceftriaxone 250mg IM plus either azithromycin 1g (single dose) or doxycycline 100mg (twice a day for 7 days) [9]. Any other treatments were defined as non-recommended treatment for analysis of factors associated with recommended therapy. We provide descriptive information for alternative recommended and not recommended treatments. There were 23 cases in which doses of doxycycline or azithromycin were not specified and treatment was classified as not recommended due to inability to infer otherwise. Overall, 42% of cases had missing treatment information, and these cases were excluded from analysis.

Statistical Analysis

Data were analyzed using Stata/SE version 13.1 (StataCorp, College Station, TX). Categorical variables were summarized with frequency distributions. Data were stratified by non-CDPH or
CDPH providers for all analyses due to significant differences in the rate of outcome, distributions of patient demographics, and numerous provider settings within non-CDPH cases.

Chi-square test was used to test for statistical significance in bivariate comparisons.

Multivariable log binomial regression was performed to determine the patient factors associated with recommended treatment, expressed as a prevalence rate ratio (PRR). For analysis of CDPH cases, 95% confidence intervals (CI) were estimated using robust variance. For non-CDPH cases, cluster-based variance estimation was used to allow for intragroup (i.e., within-facility) correlation. The level of significance was set as p-value < 0.05 (two-sided).

Results

From April 2011 through December 2012, a total of 16,646 laboratory confirmed gonococcal cases were identified. Treatment information was available for 57.7% (9,597) of cases: 89.3% (2,169) of cases treated by CDPH providers and 52.2% (7,428) of cases treated by non-CDPH providers. Compared to those with available treatment data (Supplemental Table 1), missing data were more likely (p<0.01) to be female cases (46% vs. 38% males), and those of Other race (70% vs. 36-38% for Black, White, and Hispanic). Missing treatment information varied by age (p<0.01) though not with an obvious pattern, and increased over time (41% period 1 to 46% period 2, p<0.01). The percent of cases with missing data ranged from 30-97% for non-CDPH providers and was generally higher for those providers generating a lower volume of cases (Supplemental Figure 1). Of the 7,428 non-CDPH cases, 1,360 (18%) originated from federally qualified health centers (FQHC), 98% of which were community health centers.
Demographic characteristics of cases with treatment information are presented in Table 1. Cases reported by non-CDPH providers were most frequently aged 13-19 years (38.0% vs. 21.4% CDPH cases), and majority female (55.7%), while CDPH cases were primarily male (75.9%) and aged 20-24 years (36.2% CDPH cases vs. 32.8% non-CDPH). For both provider types, case race/ethnicity was most commonly non-Hispanic Black (75.8% non-CDPH cases vs. 88.7% CDPH cases). Hospitals (41.5%), CHCs (28.9%), and private practitioners (13.4%) were the most common practice setting for non-CDPH cases. Nearly one-fourth (24.3%) of gonorrhea cases originated from test facilities reporting <10 cases of gonorrhea over the observation period.

Trends in Recommended Treatment by Provider Type

Recommended treatment increased over time (Table 2) for both CDPH (period 1: 71.3%, period 2: 80.8%, p-value <0.01) and non-CDPH providers (period 1: 63.5%, period 2: 68.9%, p-value <0.01). Adherence to guidelines showed relatively stable increase over time at CDPH clinics, peaking at 88% in June 2012 (Figure 1). Recommended treatment among non-CDPH providers also increased steadily over time, with no obvious inflection point following the update in August 2012, and peaked in November 2012 at 74%. Among non-CDPH cases, the increase over time in recommended treatment was observed for most provider settings (Figure 2).

Patterns in Recommended and Non-Recommended Treatment Regimens

Among CDPH cases, recommended treatment was primarily dual therapy via ceftriaxone plus azithromycin or doxycycline (Table 2). As an acceptable alternative, azithromycin 2g as a single oral dose was provided infrequently, decreasing from 3.9% in period 1 to 0.2% (a single case) in period 2. Similarly, the use of dual therapy with cefixime plus azithromycin or doxycycline as a
recommended treatment in period 1 decreased from 1.8% to 0.4% (2 cases) as an acceptable alternative in period 2. These patterns were similar among non-CDPH cases, though acceptable alternative treatments were somewhat more common, used for 4% of cases over the observation period.

Non-recommended treatment among CDPH cases decreased from 24.9% of cases in period 1 to 18.5% in period 2. In period 1, inadequate treatments were primarily single therapy with ceftriaxone 250mg IM (14.3%), treatment for *C. trachomatis* only (7.3%), and single therapy with cefpodoxime 400mg orally (1.9%), and. Among non-CDPH cases, inadequate treatment in period 1 was due primarily to single therapy with ceftriaxone 250mg IM (26.1%), followed by ceftriaxone 125mg IM (6%), and treatment for *C. trachomatis* only (5.2%).

**Factors Associated with Recommended Treatment**

Among CDPH cases (Table 3), recommended treatment was highest for cases aged >50 years (76.2%) and lowest for cases aged 13-19 years (70.3%), though differences by age were not statistically significant. Recommended treatment was higher for male (76.0%) than female (65.1%) cases, and this remained statistically significant in adjusted analyses [aPRR = 1.16; 95% CI: 1.08 – 1.25]. Recommended treatment was highest for Non-Hispanic Black cases (74.5%) and Non-Hispanic Other cases (73.6%), and substantially lower for Non-Hispanic White cases (50.6%). In adjusted analyses, Non-Hispanic White cases remained 32% less likely than Non-Hispanic Black cases to receive recommended treatment [aPRR = 0.68; 95% CI: 0.55 – 0.84].

Same day treatment was associated with a small but significant increase in recommended
treatment \([aPRR = 1.07; 95\% \text{ CI: } 1.00 – 1.15]\). The increase in recommended treatment in period 2 compared to period 1 remained significant \([aPRR = 1.11; 95\% \text{ CI: } 1.05 – 1.17]\).

Among non-CDPH cases (Table 4), recommended treatment was highest for the 25-29 year-old age group (70.7%) and lowest for those aged 50 and older (60.9%), though differences by age were no longer significant in multivariable analysis. Overall, recommended treatment was just 57.9% for female cases compared to 73.8% for males, highest for Non-Hispanic Whites (70.6%), and lowest for Non-Hispanic Other cases (56.0%). In multivariable regression, males remained 10% more likely to be treated with recommended regimens \([aPRR = 1.10; 95\% \text{ CI: } 1.05 – 1.16]\). The likelihood of recommended treatment remained lower for Non-Hispanic Other cases compared to Non-Hispanic Black cases \([aPRR = 0.91; 95\% \text{ CI: } 0.84 – 0.98]\); other racial/ethnic comparisons were not significant. The likelihood of recommended treatment increased for cases reported by test facilities with at least 10 reported cases of gonorrhea and was 16% lower for those test facilities with \(\geq 50\%\) missing treatment data for reported cases \([aPRR = 0.84; 95\% \text{ CI: } 0.76 – 0.92]\). Compared to period 1, the increase in recommended treatment was not statistically significant.

**Discussion**

During a period of rapid change in guidelines, the proportion of cases with documented recommended treatment for uncomplicated urogenital gonorrhea increased substantially for cases originating from CDPH and non-CDPH providers. Though by the end of 2012 rates were similar, recommended treatment was generally higher for CDPH providers than for non-CDPH.
providers. We also identified patient demographic factors which were associated with treatment practices, and these differed for CDPH and non-CDPH providers.

Recommended treatment was higher for cases originating from CDPH providers than non-CDPH providers (73% vs. 65%, overall). This is not surprising given that 94% of CDPH cases originated in STD specialty clinics. It is of note, though, that recommended treatment was still sub-optimal for CDPH cases, largely as a result of single therapy. While a standard measure for evaluating STD treatment practices is lacking, Healthy People Initiative 2010 cites a goal of >90% of providers prescribe CDC recommended STD treatments as a target [11]. Using STD Surveillance Network data from 6 states, Kerani et al. report ceftriaxone usage ranging from 45% to 95% for treatment of gonorrhea cases [12]. In contrast to our findings, previous studies have reported higher levels of recommended treatment among public and non-public health clinics to CDC STD Treatment Guidelines [13-14]. The higher recommended treatment rates from studies of non-public providers may have been due to differences in distribution of sex, younger age distributions, or screening practices; or, as in the study by Magid et al. due to guideline-concordant electronic-order to facilitate recommended treatment [15].

Using an interrupted time series analysis approach, Dowell et al. identified a 21.5% decline in fluoroquinolone use within 2 weeks of released revisions in 5 U.S. cities: public health clinics reached almost complete recommended treatment (90-100%), while primary care facilities (8.6%) and emergency departments, urgent care clinics, and hospitals (2.7%) demonstrated substantially lower and more gradual responses to updated guidelines [16]. In our analysis, the provider setting encompassing ED, Urgent Care, and Immediate Care had the lowest rate of
recommended treatment. This is in keeping with findings by Lechtenberg et al. for California [13] and Dowell et al. nationally [16]. For EDs serving high risk populations and difficulty ensuring follow-up, a lower threshold for empiric treatment may be warranted [17]. Among the provider group comprised by CHCs and other public providers, those that were FQHCs had recommended treatment rates approximately half that of non-FQHCs (Figure 2) which could be partially explained by underreporting of treatment information. Our findings underline the need for stronger collaboration between local health departments and non-CDPH providers to assist these providers with improving their fulfillment to public health reporting requirements and adherence to CDC treatment recommendations.

In multivariable adjusted analyses, we did not observe any statistically significant association between age and recommended treatment. For CDPH and non-CDPH providers, male cases were more likely to receive recommended treatment. Men are more likely than women to have symptomatic urogenital gonococcal infection [18]. Because results of laboratory testing are available after the patient has completed the clinical encounter, asymptomatic infection or non-specific symptoms in women may be a barrier to recommended treatment. Indeed, same day treatment was associated with increased rate of recommended treatment, by 7% and 31% for CDPH and non-CDPH providers, respectively. Among CDPH cases, White cases were 32% less likely than Non-Hispanic Black cases to receive recommended treatment. This is in keeping with analysis of national surveillance data by Kerani et al. who found that Black patients were statistically significantly 4% more likely to be treated with ceftriaxone than White patients [12]. We observed treatment by race was differential for CDPH and non-CDPH cases; this may be due to increased clinician suspicion among Blacks, stemming from differential risk assessment,
presentation (screening vs. symptoms), or variability in clinician threshold for empiric treatment based on assumptions of who is at risk for gonorrhea. Efforts to reduce variability and improve provision of recommended treatment may include addressing clinicians’ variability in risk assessment, barriers to risk assessment, and recommendations for how to incorporate patient risk with treatment decisions. Of note, clinicians at CDPH STD clinics perform on-site Gram staining for men (and at the clinician’s discretion in women with high index of suspicion for gonorrhea), which allows administration of recommended treatment at the point of care. Comparing two time periods, Bartelsman et al. found same day treatment for women attending an STI clinic was 66% when routine Gram staining for all high risk patients was implemented compared to 46.5% when Gram staining only for high risk patients with urogenital complaint; the period with routine Gram staining was associated with reduced costs [19]. While Gram staining has much lower accuracy in women than men and is likely infeasible for most non-CDPH providers, the possibility may be worth exploring for providers working in hospital systems with on-site laboratories and high risk patient populations.

Based on our results, we need to verify the extent to which CDPH clients are not receiving recommended treatment, and whether this is due to errors in recording. Because we analyzed provider type at the group level, we cannot determine whether differential treatment occurs at the individual provider level. As such, we need to investigate patient barriers (e.g., follow-up) and individual-level provider reasons (e.g., treatment for other conditions, other medical factors, availability of recommended treatment) why cases are not receiving recommended therapy. While we could find no studies comparing acceptability of the routes of administration for gonorrhea, some clinicians may find it easier to convince patients to accept oral antibiotics than
intramuscular injection. As dual therapy including cefixime contributed to ~5% of non-CDSH treatments, whether assessment of treatment outcome at 1 week is being done needs to be evaluated. Integrating treatment recommendations in electronic systems that support treatment decisions will facilitate increased adherence to guidelines [15]. Additionally, and especially in settings where electronic assists are not possible, communications from local health departments may be effective. The evaluation by Dowell et al. found that in metropolitan areas where the public health departments used stronger communication methods (e.g., press release) and direct language (e.g., “no longer recommended” rather than “continued cautious use”) resulted in larger and more rapid declines in fluoroquinolone use [16]. The impact of interactive (e.g., webinars, hotline) or in-person communication (e.g., in-services, regional society meetings) should be evaluated. While such efforts may seem resource intensive, over the 21-month observation period, only 18 non-CDSH facilities each reported ≥100 laboratory confirmed cases of gonorrhea, accounting for 3,136 (42%) of all non-CDSH cases (including cases with missing data), with recommended treatment ranging from 26-93%. As we observed, the likelihood of recommended treatment was generally greater for test facilities reporting a greater number of gonorrhea cases. Targeting more intense support to a restricted number of high volume facilities with lower recommended treatment rates may be an efficient approach to improving adherence to guidelines.

Limitations

By using retrospective documentation rather than directly observed practice, we have incomplete reporting. This led to underrepresentation of cases of Other race (70% were missing treatment information), and nearly all cases from online-testing services, Veteran’s Administration (VA),
and outreach services (missing treatment data ranged from 81-97% in these settings). It is possible the missing data for VA and outreach services is extremely high due to lack of follow-up; conversely, the nearly complete missing data also suggests these providers face barriers to recording treatment. We observed that cases from facilities with a greater proportion of missing treatment data were less likely to receive recommended treatment. If cases with missing treatment data are less likely to receive recommended treatment, then our estimates may considerably overestimate non-CDPH provider adherence to guidelines, given the magnitude of missing treatment data. Data abstraction included electronic medical review of all cases reported by CDPH providers, which was not possible for non-CDPH cases. This differential ascertainment may have led to more complete and more accurate classification of treatment data for CDPH cases. Given the increasing utility and cost-effectiveness of online testing services, procedures need to be in place to follow-up and document treatment. Spielberg et al. conducted testing of self-collected samples for gonorrhea, chlamydia, and trichomoniasis submitted via mail, with internet-based provision of results, and integrated this with electronic medical records and electronic prescribing [20]. Though the initial costs of integrating results with electronic health records were high, investment in these approaches may be cost-effective as this testing strategy grows.

We focused our analysis on CDC recommended therapy for uncomplicated urogenital infection; therefore we cannot generalize results to treatment of complicated infection, or rectal or pharyngeal infections. Assessing adherence to recommended treatment for extragenital infections may have more importance for stemming antibiotic resistance emergence and spread, and should be a focus area for surveillance. Errors in clinician recording may lead to misclassification. For
example, not recording whether a treatment was given or not specifying the doses, lead to
classification as non-recommended treatment in this analysis. Additionally, clinical information
(such as patients’ allergies, pregnancy status, diagnosis of complicated infection, and previous
treatment outcomes) which could influence treatment decisions was not documented in I-
NEDSS. Although data were de-duplicated by patient name, date of birth, and date of visit, there
may still have been individuals with repeated observation of the same infection.

Conclusion
We observed substantial adherence to CDC urogenital gonococcal treatment recommendations
among public and non-public providers following guidelines revisions in August, 2012. The
increase in adherence for public and non-public providers within 4 months of guideline
dissemination is encouraging. Investigation of reasons for non-recommended treatment and
interventions and resources to improve guideline concordance, especially among non-public
health providers, is urgently needed.


Supplemental Figure 1. Percent of GC positive cases with missing treatment information by provider type.

The size of the bubble is proportionate to the number of observations originating from the provider type.

Figure 1. Proportion of Cases with Recommended Treatment Regimen Over Time, by CDPH vs. non-CDPH Provider Type.

Figure 2. Proportion of GC cases treated with a recommended treatment regimen, over time by non-CDPH provider setting.