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

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21   **Short Summary**

22   Among Chicago providers, recommended treatment for urogenital gonorrhea improved over time

23   yet remains sub-optimal. Addressing underreporting of treatment and differential treatment by

24   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].

3

47   **Conclusions:** Recommended treatment improved over time, yet remains sub-optimal. Efforts to

48   reduce variability and improve provider adherence to recommended treatment is urgently

49   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

73 This study was determined to be exempt from human subjects review by Institutional Review

74 Boards of the Chicago Department of Public Health (CDPH) and by the University of Illinois at

75 Chicago. This was an analysis of retrospective data collected on laboratory confirmed gonorrhea

76 cases reported to the CDPH from April 1, 2011 through December 31, 2012. We assessed

77 treatment trends 16 months prior to the release of the CDC treatment guidelines (period 1: April

78 2011 through July 2012), and after the release of the August 2012 treatment updates (period 2:

79 August through December 2012) [9].

80

81 According to the Illinois State law, medical providers are required to report gonorrhea cases to

82 the CDPH Sexually Transmitted Disease (STD) surveillance unit [10]. Cases reported by CDPH

83 clinics (93.4% from STD specialty clinics) were defined as CDPH providers, while cases

84 reported by other providers (community health centers (CHC), hospitals, primary physicians,

85 etc.) were defined as non-CDPH providers. The CDPH STD/HIV Division operates five high-

86 volume STD specialty clinics located throughout the city, serving a varied clientele (with regard

87 to gender, race, ethnicity, and sexual orientation). Combined, CDPH STD clinics recorded over

88 23,000 annual patient visits in 2011 and approximately 22,000 in 2012.

89

90 Gonorrhea and chlamydia are reported through a web-based surveillance system called Illinois

91 National Electronic Disease Surveillance System (I-NEDSS). I-NEDSS contains positive results

92 of laboratory tests and morbidity reports provided by healthcare providers. If the test result for

93 gonorrhea was reported as "positive", "detected", or "reactive" the case was included in our

94 analysis. Cases represented patients presenting with symptoms, suspected contact with an

95 infected partner or for screening purposes, and submitted urine, urethral swab, or cervical swab

96   specimens for nucleic acid amplification testing (NAAT). In addition to test results and date of

97   test, for each case we obtained data regarding gender, age, race/ethnicity, and provider source.

98   For cases reported by CDPH clinics, treatment data were extracted from the CDPH Electronic

99   Medical Record (EMR) and matched to data extracted from I-NEDSS by patient's name, date of

100   birth, and date of visit. For non-CDPH cases, all data were abstracted from I-NEDSS only.

101

102   Cases with treatment data were reviewed and categorized as recommended or non-recommended

103   based on the following criteria: treatment received from April 2011 through July 2012 (period 1,

104   baseline) was defined as recommended if cases received an intramuscular (IM) injection of

105   ceftriaxone 250mg or oral cefixime 400mg plus Azithromycin 1g (single dose) or Doxycycline

106   100mg (twice a day for 7 days) [3]. For cases treated between August 2012 through December

107   2012 (period 2), recommended therapy was defined as the combination of the injectable

108   ceftriaxone 250mg IM plus either azithromycin 1g (single dose) or doxycycline 100mg (twice a

109   day for 7 days) [9]. Any other treatments were defined as non-recommended treatment for

110   analysis of factors associated with recommended therapy. We provide descriptive information

111   for alternative recommended and not recommended treatments. There were 23 cases in which

112   doses of doxycycline or azithromycin were not specified and treatment was classified as not

113   recommended due to inability to infer otherwise. Overall, 42% of cases had missing treatment

114   information, and these cases were excluded from analysis.

115

116   *Statistical Analysis*

117   Data were analyzed using Stata/SE version 13.1 (StataCorp, College Station, TX). Categorical

118   variables were summarized with frequency distributions. Data were stratified by non-CDPH or

119 CDPH providers for all analyses due to significant differences in the rate of outcome,

120 distributions of patient demographics, and numerous provider settings within non-CDPH cases.

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

122 Multivariable log binomial regression was performed to determine the patient factors associated

123 with recommended treatment, expressed as a prevalence rate ratio (PRR). For analysis of CDPH

124 cases, 95% confidence intervals (CI) were estimated using robust variance. For non-CDPH

125 cases, cluster-based variance estimation was used to allow for intragroup (i.e., within-facility)

126 correlation. The level of significance was set as p-value < 0.05 (two-sided).

127

128 **Results**

129 From April 2011 through December 2012, a total of 16,646 laboratory confirmed gonococcal

130 cases were identified. Treatment information was available for 57.7% (9,597) of cases: 89.3%

131 (2,169) of cases treated by CDPH providers and 52.2% (7,428) of cases treated by non-CDPH

132 providers. Compared to those with available treatment data (Supplemental Table 1), missing data

133 were more likely (p<0.01) to be female cases (46% vs. 38% males), and those of Other race

134 (70% vs. 36-38% for Black, White, and Hispanic). Missing treatment information varied by age

135 (p<0.01) though not with an obvious pattern, and increased over time (41% period 1 to 46%

136 period 2, p<0.01). The percent of cases with missing data ranged from 30-97% for non-CDPH

137 providers and was generally higher for those providers generating a lower volume of cases

138 (Supplemental Figure 1). Of the 7,428 non-CDPH cases, 1,360 (18%) originated from federally

139 qualified health centers (FQHC), 98% of which were community health centers.

140

141 Demographic characteristics of cases with treatment information are presented in Table 1. Cases

142 reported by non-CDPH providers were most frequently aged 13-19 years (38.0% vs. 21.4%

143 CDPH cases), and majority female (55.7%), while CDPH cases were primarily male (75.9%) and

144 aged 20-24 years (36.2% CDPH cases vs. 32.8% non-CDPH). For both provider types, case

145 race/ethnicity was most commonly non-Hispanic Black (75.8% non-CDPH cases vs. 88.7%

146 CDPH cases). Hospitals (41.5%), CHCs (28.9%), and private practitioners (13.4%) were the

147 most common practice setting for non-CDPH cases. Nearly one-fourth (24.3%) of gonorrhea

148 cases originated from test facilities reporting <10 cases of gonorrhea over the observation period.

149

150 ***Trends in Recommended Treatment by Provider Type***

151 Recommended treatment increased over time (Table 2) for both CDPH (period 1: 71.3%, period

152 2: 80.8%, p-value <0.01) and non-CDPH providers (period 1: 63.5%, period 2: 68.9%, p-value

153 <0.01). Adherence to guidelines showed relatively stable increase over time at CDPH clinics,

154 peaking at 88% in June 2012 (Figure 1). Recommended treatment among non-CDPH providers

155 also increased steadily over time, with no obvious inflection point following the update in

156 August 2012, and peaked in November 2012 at 74%. Among non-CDPH cases, the increase over

157 time in recommended treatment was observed for most provider settings (Figure 2).

158

159 ***Patterns in Recommended and Non-Recommended Treatment Regimens***

160 Among CDPH cases, recommended treatment was primarily dual therapy via ceftriaxone plus

161 azithromycin or doxycycline (Table 2). As an acceptable alternative, azithromycin 2g as a single

162 oral dose was provided infrequently, decreasing from 3.9% in period 1 to 0.2% (a single case) in

163 period 2. Similarly, the use of dual therapy with cefixime plus azithromycin or doxycycline as a

9

164   recommended treatment in period 1 decreased from 1.8% to 0.4% (2 cases) as an acceptable

165   alternative in period 2. These patterns were similar among non-CDPH cases, though acceptable

166   alternative treatments were somewhat more common, used for 4% of cases over the observation

167   period.

168

169   Non-recommended treatment among CDPH cases decreased from 24.9% of cases in period 1 to

170   18.5% in period 2. In period 1, inadequate treatments were primarily single therapy with

171   ceftriaxone 250mg IM (14.3%), treatment for *C. trachomatis* only (7.3%), and single therapy

172   with cefpodoxime 400mg orally (1.9%), and. Among non-CDPH cases, inadequate treatment in

173   period 1 was due primarily to single therapy with ceftriaxone 250mg IM (26.1%), followed by

174   ceftriaxone 125mg IM (6%), and treatment for *C. trachomatis* only (5.2%).

175

176   ***Factors Associated with Recommended Treatment***

177   Among CDPH cases (Table 3), recommended treatment was highest for cases aged ≥50 years

178   (76.2%) and lowest for cases aged 13-19 years (70.3%), though differences by age were not

179   statistically significant. Recommended treatment was higher for male (76.0%) than female

180   (65.1%) cases, and this remained statistically significant in adjusted analyses [aPRR = 1.16; 95%

181   CI: 1.08 – 1.25]. Recommended treatment was highest for Non-Hispanic Black cases (74.5%)

182   and Non-Hispanic Other cases (73.6%), and substantially lower for Non-Hispanic White cases

183   (50.6%). In adjusted analyses, Non-Hispanic White cases remained 32% less likely than Non-

184   Hispanic Black cases to receive recommended treatment [aPRR = 0.68; 95% CI: 0.55 – 0.84].

185   Same day treatment was associated with a small but significant increase in recommended

186   treatment [aPRR = 1.07; 95% CI: 1.00 – 1.15]. The increase in recommended treatment in period

187   2 compared to period 1 remained significant [aPRR = 1.11; 95%: CI: 1.05 – 1.17].

188

189   Among non-CDPH cases (Table 4), recommended treatment was highest for the 25-29 year-old

190   age group (70.7%) and lowest for those aged 50 and older (60.9%), though differences by age

191   were no longer significant in multivariable analysis. Overall, recommended treatment was just

192   57.9% for female cases compared to 73.8% for males, highest for Non-Hispanic Whites (70.6%),

193   and lowest for Non-Hispanic Other cases (56.0%). In multivariable regression, males remained

194   10% more likely to be treated with recommended regimens [aPRR = 1.10; 95% CI: 1.05 – 1.16].

195   The likelihood of recommended treatment remained lower for Non-Hispanic Other cases

196   compared to Non-Hispanic Black cases [aPRR = 0.91; 95% CI: 0.84 – 0.98]; other racial/ethnic

197   comparisons were not significant. The likelihood of recommended treatment increased for cases

198   reported by test facilities with at least 10 reported cases of gonorrhea and was 16% lower for

199   those test facilities with ≥50% missing treatment data for reported cases [aPRR = 0.84; 95% CI:

200   0.76 – 0.92]. Compared to period 1, the increase in recommended treatment was not statistically

201   significant.

202

203   **Discussion**

204   During a period of rapid change in guidelines, the proportion of cases with documented

205   recommended treatment for uncomplicated urogenital gonorrhea increased substantially for cases

206   originating from CDPH and non-CDPH providers. Though by the end of 2012 rates were similar,

207   recommended treatment was generally higher for CDPH providers than for non-CDPH

11

208   providers. We also identified patient demographic factors which were associated with treatment

209   practices, and these differed for CDPH and non-CDPH providers.

210

211   Recommended treatment was higher for cases originating from CDPH providers than non-CDPH

212   providers (73% vs. 65%, overall). This is not surprising given that 94% of CDPH cases

213   originated in STD specialty clinics. It is of note, though, that recommended treatment was still

214   sub-optimal for CDPH cases, largely as a result of single therapy. While a standard measure for

215   evaluating STD treatment practices is lacking, Healthy People Initiative 2010 cites a goal of

216   >90% of providers prescribe CDC recommended STD treatments as a target [11]. Using STD

217   Surveillance Network data from 6 states, Kerani et al. report ceftriaxone usage ranging from 45%

218   to 95% for treatment of gonorrhea cases [12]. In contrast to our findings, previous studies have

219   reported higher levels of recommended treatment among public and non-public health clinics to

220   CDC STD Treatment Guidelines [13-14]. The higher recommended treatment rates from studies

221   of non-public providers may have been due to differences in distribution of sex, younger age

222   distributions, or screening practices; or, as in the study by Magid et al. due to guideline-

223   concordant electronic-order to facilitate recommended treatment [15].

224

225   Using an interrupted time series analysis approach, Dowell et al. identified a 21.5% decline in

226   fluoroquinolone use within 2 weeks of released revisions in 5 U.S. cities: public health clinics

227   reached almost complete recommended treatment (90-100%), while primary care facilities

228   (8.6%) and emergency departments, urgent care clinics, and hospitals (2.7%) demonstrated

229   substantially lower and more gradual responses to updated guidelines [16]. In our analysis, the

230   provider setting encompassing ED, Urgent Care, and Immediate Care had the lowest rate of

231 recommended treatment. This is in keeping with findings by Lechtenberg et al. for California

232 [13] and Dowell et al. nationally [16]. For EDs serving high risk populations and difficulty

233 ensuring follow-up, a lower threshold for empiric treatment may be warranted [17]. Among the

234 provider group comprised by CHCs and other public providers, those that were FQHCs had

235 recommended treatment rates approximately half that of non-FQHCs (Figure 2) which could be

236 partially explained by underreporting of treatment information. Our findings underline the need

237 for stronger collaboration between local health departments and non-CDPH providers to assist

238 these providers with improving their fulfillment to public health reporting requirements and

239 adherence to CDC treatment recommendations.

240

241 In multivariable adjusted analyses, we did not observe any statistically significant association

242 between age and recommended treatment. For CDPH and non-CDPH providers, male cases were

243 more likely to receive recommended treatment. Men are more likely than women to have

244 symptomatic urogenital gonocococcal infection [18]. Because results of laboratory testing are

245 available after the patient has completed the clinical encounter, asymptomatic infection or non-

246 specific symptoms in women may be a barrier to recommended treatment. Indeed, same day

247 treatment was associated with increased rate of recommended treatment, by 7% and 31% for

248 CDPH and non-CDPH providers, respectively. Among CDPH cases, White cases were 32% less

249 likely than Non-Hispanic Black cases to receive recommended treatment. This is in keeping with

250 analysis of national surveillance data by Kerani et al. who found that Black patients were

251 statistically significantly 4% more likely to be treated with ceftriaxone than White patients [12].

252 We observed treatment by race was differential for CDPH and non-CDPH cases; this may be due

253 to increased clinician suspicion among Blacks, stemming from differential risk assessment,

254   presentation (screening vs. symptoms), or variability in clinician threshold for empiric treatment

255   based on assumptions of who is at risk for gonorrhea. Efforts to reduce variability and improve

256   provision of recommended treatment may include addressing clinicians' variability in risk

257   assessment, barriers to risk assessment, and recommendations for how to incorporate patient risk

258   with treatment decisions. Of note, clinicians at CDPH STD clinics perform on-site Gram staining

259   for men (and at the clinician's discretion in women with high index of suspicion for gonorrhea),

260   which allows administration of recommended treatment at the point of care. Comparing two time

261   periods, Bartelsman et al. found same day treatment for women attending an STI clinic was 66%

262   when routine Gram staining for all high risk patients was implemented compared to 46.5% when

263   Gram staining only for high risk patients with urogenital complaint; the period with routine

264   Gram staining was associated with reduced costs [19]. While Gram staining has much lower

265   accuracy in women than men and is likely infeasible for most non-CDPH providers, the

266   possibility may be worth exploring for providers working in hospital systems with on-site

267   laboratories and high risk patient populations.

268

269   Based on our results, we need to verify the extent to which CDPH clients are not receiving

270   recommended treatment, and whether this is due to errors in recording. Because we analyzed

271   provider type at the group level, we cannot determine whether differential treatment occurs at the

272   individual provider level. As such, we need to investigate patient barriers (e.g., follow-up) and

273   individual-level provider reasons (e.g., treatment for other conditions, other medical factors,

274   availability of recommended treatment) why cases are not receiving recommended therapy.

275   While we could find no studies comparing acceptability of the routes of administration for

276   gonorrhea, some clinicians may find it easier to convince patients to accept oral antibiotics than

14

277   intramuscular injection. As dual therapy including cefixime contributed to ~5% of non-CDPH

278   treatments, whether assessment of treatment outcome at 1 week is being done needs to be

279   evaluated. Integrating treatment recommendations in electronic systems that support treatment

280   decisions will facilitate increased adherence to guidelines [15]. Additionally, and especially in

281   settings where electronic assists are not possible, communications from local health departments

282   may be effective. The evaluation by Dowell et al. found that in metropolitan areas where the

283   public health departments used stronger communication methods (e.g., press release) and direct

284   language (e.g., "no longer recommended" rather than "continued cautious use") resulted in larger

285   and more rapid declines in fluoroquinolone use [16]. The impact of interactive (e.g., webinars,

286   hotline) or in-person communication (e.g., in-services, regional society meetings) should be

287   evaluated. While such efforts may seem resource intensive, over the 21-month observation

288   period, only 18 non-CDPH facilities each reported $\geq$100 laboratory confirmed cases of

289   gonorrhea, accounting for 3,136 (42%) of all non-CDPH cases (including cases with missing

290   data), with recommended treatment ranging from 26-93%. As we observed, the likelihood of

291   recommended treatment was generally greater for test facilities reporting a greater number of

292   gonorrhea cases. Targeting more intense support to a restricted number of high volume facilities

293   with lower recommended treatment rates may be an efficient approach to improving adherence

294   to guidelines.

295

296   *Limitations*

297   By using retrospective documentation rather than directly observed practice, we have incomplete

298   reporting. This led to underrepresentation of cases of Other race (70% were missing treatment

299   information), and nearly all cases from online-testing services, Veteran's Administration (VA),

300 and outreach services (missing treatment data ranged from 81-97% in these settings). It is

301 possible the missing data for VA and outreach services is extremely high due to lack of follow-

302 up; conversely, the nearly complete missing data also suggests these providers face barriers to

303 recording treatment. We observed that cases from facilities with a greater proportion of missing

304 treatment data were less likely to receive recommended treatment. If cases with missing

305 treatment data are less likely to receive recommended treatment, then our estimates may

306 considerably overestimate non-CDPH provider adherence to guidelines, given the magnitude of

307 missing treatment data. Data abstraction included electronic medical review of all cases reported

308 by CDPH providers, which was not possible for non-CDPH cases. This differential

309 ascertainment may have led to more complete and more accurate classification of treatment data

310 for CDPH cases. Given the increasing utility and cost-effectiveness of online testing services,

311 procedures need to be in place to follow-up and document treatment. Spielberg et al. conducted

312 testing of self-collected samples for gonorrhea, chlamydia, and trichomoniasis submitted via

313 mail, with internet-based provision of results, and integrated this with electronic medical records

314 and electronic prescribing [20]. Though the initial costs of integrating results with electronic

315 health records were high, investment in these approaches may be cost-effective as this testing

316 strategy grows.

317

318 We focused our analysis on CDC recommended therapy for uncomplicated urogenital infection;

319 therefore we cannot generalize results to treatment of complicated infection, or rectal or

320 pharyngeal infections. Assessing adherence to recommended treatment for extragenital infections

321 may have more importance for stemming antibiotic resistance emergence and spread, and should

322 be a focus area for surveillance. Errors in clinician recording may lead to misclassification. For

323 example, not recording whether a treatment was given or not specifying the doses, lead to

324 classification as non-recommended treatment in this analysis. Additionally, clinical information

325 (such as patients' allergies, pregnancy status, diagnosis of complicated infection, and previous

326 treatment outcomes) which could influence treatment decisions was not documented in I-

327 NEDSS. Although data were de-duplicated by patient name, date of birth, and date of visit, there

328 may still have been individuals with repeated observation of the same infection.

329

330 **Conclusion**

331 We observed substantial adherence to CDC urogenital gonococcal treatment recommendations

332 among public and non-public providers following guidelines revisions in August, 2012. The

333 increase in adherence for public and non-public providers within 4 months of guideline

334 dissemination is encouraging. Investigation of reasons for non-recommended treatment and

335 interventions and resources to improve guideline concordance, especially among non-public

336 health providers, is urgently needed.

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

415

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

417

418

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

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421

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