A Retrospective Comparative Study of 2-Drug Oral and Intramuscular Cephalosporin Treatment Regimens for Pharyngeal Gonorrhea

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Background. The Centers for Disease Control and Prevention guidelines for pharyngeal gonorrhea treatment recommend dual therapy with intramuscular ceftriaxone and either azithromycin or doxycycline. Few clinical data exist to support this recommendation.

Methods. We conducted a retrospective analysis of patients diagnosed with pharyngeal gonorrhea during 1993–2011, at a sexually transmitted disease clinic in Seattle, Washington, and compared the proportion of repeat positive tests for pharyngeal gonorrhea 7–180 days following treatment among persons receiving different drug regimens. Associations of treatment regimens were assessed using relative risks through Poisson regression models with log link and robust standard errors.

Results. A total of 1440 cases of pharyngeal gonorrhea were diagnosed during the study period, 25% of which (n = 360) underwent retesting. Among retested patients, the risk of repeat positive test was lowest among persons receiving an oral cephalosporin and azithromycin (7%, reference group), and highest among those receiving an oral cephalosporin alone (30%; relative risk [RR], 3.98; 95% confidence interval [CI], 1.70–9.36) or in combination with doxycycline (33%; RR, 4.18; 95% CI, 1.64–10.7). The risk of repeat test positivity did not significantly differ between persons treated with an oral cephalosporin and azithromycin and those treated with ceftriaxone alone (9.1%; RR, 0.81; 95% CI, .18–3.60) or ceftriaxone combined with azithromycin or doxycycline (11.3%; RR, 1.20; 95% CI, .43–3.33).

Conclusions. In this retrospective study, dual therapy with an oral third-generation cephalosporin and azithromycin was comparable to ceftriaxone-based regimens in the treatment of pharyngeal gonorrhea. Combination oral therapy with doxycycline was associated with an elevated risk of persistent or recurrent infection.

Keywords. gonorrhea; pharyngeal gonorrhea; antimicrobial resistance; treatment; sexually transmitted disease.

Current Centers for Disease Control and Prevention (CDC) treatment guidelines for pharyngeal gonorrhea recommend a single intramuscular 250-mg dose of ceftriaxone in combination with either a single 1-g dose of azithromycin or doxycycline 100 mg orally twice daily for 7 days [1, 2]. However, to our knowledge, only 1 clinical study has evaluated the value of adding a second agent to ceftriaxone in the treatment of pharyngeal gonorrhea [3]. In the absence of strong data, the CDC's decision to recommend that pharyngeal infections be treated with 2 drugs was based largely on the well-established difficulty of eradicating *Neisseria gonorrhoeae* from the oropharynx [4–6], and experience with other infections in which 2 active agents of different antimicrobial classes are clinically superior to 1 agent and are thought to diminish the risk of selection for drug resistance [7–9].

Pharyngeal gonococcal infections are common in men who have sex with men (MSM) and in at least

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some populations of women [10–17]. Moreover, the oropharynx is thought to serve as an anatomic reservoir of infection that facilitates the gonococcus' acquisition of genes conferring antimicrobial resistance [6, 18] and promotes sustained gonococcal transmission in the population [19, 20]. Antimicrobial-resistant *N. gonorrhoeae*, particularly the increasing proportion of isolates with decreased susceptibility to third-generation cephalosporins, is now a major global public health concern [7, 21]. Better data on gonorrhea treatment, including the treatment of pharyngeal infections, is needed.

Using data collected over a period of 18 years, we assessed the efficacy of different regimens in treating pharyngeal gonorrhea. In particular, we were interested in testing the hypothesis that dual therapy with an oral cephalosporin and azithromycin is comparable to treatment with ceftriaxone, and superior to treatment with an oral cephalosporin alone or in combination with doxycycline, an idea supported by a previous observational study [3].

METHODS

Study Population and Data Collection

The study population included all patients who tested positive for pharyngeal gonorrhea at the Public Health–Seattle & King County (PHSKC) Sexually Transmitted Disease (STD) clinic between 1 January 1993 and 19 September 2011. All data were collected as part of routine medical care and recorded in the clinic's electronic database. The study was initially approved by the University of Washington Institutional Review Board (IRB) and, on subsequent IRB review for renewal, was determined not to constitute human subjects research and consequently did not require ongoing IRB approval.

Clinical and Laboratory Procedures

Clinicians used standardized forms to record sexual histories and exam findings on all persons seen in the clinic. Anatomic site–specific STD screening was performed based on self-reported sexual history. The clinic's recommended protocol throughout the study period was to test all MSM for pharyngeal gonorrhea if they reported performing fellatio in the past year. Protocols for testing heterosexual men and women were not well defined prior to 2010, and testing practices were largely based on clinician discretion. After 2010, our clinic protocol recommended against routine pharyngeal screening in women. Throughout the study period, clinic policy did not recommend returning for pharyngeal tests of cure.

We used culture to screen for pharyngeal gonorrhea between 1993 and October 2010; thereafter we used a nucleic acid amplification test (NAAT), the Aptima Combo 2 (Gen-Probe Diagnostics, San Diego, California). Clinicians smeared specimens taken for *N. gonorrhoeae* culture directly onto Thayer-Martin agar and then placed inoculated agar plates into a candle (CO_2) jar following completion of each patient visit. Culture plates were transported to the PHSKC laboratory daily. *Neisseria gonorrhoeae* was identified by Gram stain and standard biochemical tests; culture-positive specimens were subsequently forwarded to the Neisseria Reference Laboratory for preservation at −70°C.

Clinic policy recommended a single 400-mg dose of oral cefixime as the first-line agent for treating uncomplicated genital tract or rectal gonorrhea between 1993 and 2002, and again between 2008 and 2009. Between 2002 and 2008, cefixime was unavailable in the United States, and thus the clinic used a single 400-mg oral dose of cefpodoxime as standard therapy for uncomplicated anogenital gonorrhea. In 2009, a ceftriaxone 250 mg intramuscular dose was adopted as the standard treatment for all gonococcal infections. Until 2011, all persons treated for gonorrhea were also treated for chlamydia with azithromycin or doxycycline unless the patient had negative test results for chlamydial infection at the time of treatment. Throughout the study period, clinic policy was to treat diagnosed pharyngeal gonorrhea with ceftriaxone, 125 mg intramuscularly until 2009 and 250 mg intramuscularly thereafter. However, patients who were treated with an oral cephalosporin at the time of their initial testing were not routinely asked to return to the clinic for additional treatment with ceftriaxone.

Definition of Variables

We defined MSM as men who reported having sex with another man in the previous 12 months. When data on sex partner gender were missing and patients had prior visits to the clinic, we used information from previous clinic visits to define sexual orientation. All tests for pharyngeal gonococcal infection (either culture or NAAT) performed 7–180 days following known treatment with an agent active against *N. gonorrhoeae* were deemed repeat testing, regardless of the intent of the test. We defined any positive test (NAAT or culture) at the pharynx between 7 and 180 days following treatment as a repeat positive test. Patients were considered as having received dual therapy if they received 2 drugs with some activity against *N. gonorrhoeae* from different pharmacologic classes within a 1-week period. This included 48 cases in which patients received a second active drug within 1 week of their initial treatment; we defined the treatment date in these instances as the date the patient received the first drug. Dual-therapy treatment regimens consisted of 1 of 3 oral or injectable third-generation cephalosporins (cefixime, cefpodoxime, or ceftriaxone), and either azithromycin or doxycycline as the second agent.

Statistical Analysis

We calculated the percentage of repeat positive tests as the number of positive repeat tests divided by all repeat testing

obtained, stratified by treatment regimen and time from treatment date. Since our outcome variables of interest were common, we used Poisson regression models with log link and robust standard errors [22] to estimate relative risks of association. For our main study outcome, the association of repeat test positivity with treatment regimen, we created a multivariate model to control for the following confounders: year of diagnosis, sexual orientation, number of sex partners in the 2 months prior to diagnosis, age and time between treatment and repeat test. All analyses were conducted using Stata software, version 9.2 or higher (StataCorp, College Station, Texas). An α of .05 was considered significant.

RESULTS

Study Population

The clinic diagnosed a total of 1274 individuals with 1440 cases of pharyngeal gonorrhea during the study period; 1215 (84%) cases occurred in MSM, 165 (12%) in women, and 60 (4%) in heterosexual men. Medical records documented that 1410 (98%) cases were treated within 30 days of diagnosis, with 1005 (70%) receiving treatment on the same day as diagnosis.

The mean age of patients diagnosed with pharyngeal gonorrhea was 32 years and the majority of cases occurred in white patients (Table 1). Most pharyngeal gonococcal infections were asymptomatic (>90%), and 34% of patients with pharyngeal infections were diagnosed with concurrent urogenital infections. More than 90% of cases (1343/1440) were diagnosed using culture, with only 97 cases (6.7%) being diagnosed by NAAT ($P < .001$). More than half of all cases were diagnosed after 2005.

A total of 360 (25%) cases underwent repeat pharyngeal gonococcal testing (culture or NAAT) within 180 days of the initial treatment date (Table 1); the median time from treatment to repeat test was 58.5 days (SD, 51.6 days; interquartile range, 21–111 days). The proportion of persons who had a repeat test did not significantly vary by treatment regimen, age, or year of diagnosis, although more than half of all repeat testing occurred after 2005. Compared to women, repeat testing was more common among MSM (relative risk [RR], 2.18; 95% confidence interval [CI], 1.23–3.86) and heterosexual men (RR, 1.60; 95% CI, .86–2.97). Concurrent diagnosis with urogenital gonorrhea was associated with a decreased likelihood of having repeat pharyngeal testing (RR, 0.70; 95% CI, .58–.84).

Association of Different Treatment Regimens With Repeated Pharyngeal Infection

The proportion of persons with a repeat positive test was lowest in persons receiving an oral cephalosporin and azithromycin (7.0%) or ceftriaxone alone (9.1%), and highest in persons treated with oral cephalosporins alone (29.8%) or oral cephalosporins with doxycycline (33.3%) (Table 2). Adjusting for time from treatment to follow-up testing, year of diagnosis, sexual orientation, number of sexual partners in the 2 months prior to diagnosis, and age, treatment with oral cephalosporins alone or in combination with doxycycline was significantly associated with having a repeat positive test compared to treatment with an oral cephalosporin and azithromycin. There was no significant difference in the risk of positive repeat follow-up testing between persons treated with an oral cephalosporin and azithromycin and those treated with a ceftriaxone-based regimen or azithromycin alone, although only 15 retested patients received only azithromycin. Repeat test positivity was higher in persons treated with cefpodoxime monotherapy than cefixime monotherapy (33.4% vs 20.8%; RR, 1.75; 95% CI, .70–4.3) and in persons treated with cefpodoxime and azithromycin compared to cefixime and azithromycin (7.7% vs 6.0%; RR, 1.28; 95% CI, .32–5.1), although neither of these differences was statistically significant.

The patterns of repeatedly positive tests observed in our primary analysis were also observed when we restricted the analysis to persons who retested between 7 and 90 days following treatment. In this subgroup, only 5 of 74 (6.8%, reference) patients treated with an oral cephalosporin and azithromycin had a repeat positive test, compared to 11 of 27 (40.7%; RR, 6.49; 95% CI, 2.08–20.3) treated with an oral cephalosporin and doxycycline, and 14 of 35 (40%; RR, 5.59; 95% CI, 1.96–15.9) treated with an oral cephalosporin alone. There was no statistically significant difference between combination therapy with an oral cephalosporin and azithromycin and either ceftriaxone alone (11.5% [3/26] positive repeat tests; RR, 1.43; 95% CI, .48–4.23), or ceftriaxone dual therapy (12.2% [5/41] positive repeat tests; RR, 1.46; 95% CI, .32–6.64).

DISCUSSION

Evaluating treatment outcomes among persons with pharyngeal gonorrhea seen in a single STD clinic between 1993 and 2011, we found that dual therapy with an oral third-generation cephalosporin and azithromycin appeared to be comparable to treatment with intramuscular ceftriaxone, either alone or in combination with azithromycin, and superior to treatment with either an oral third-generation cephalosporin alone or in combination with doxycycline.

Literature on the treatment of pharyngeal gonorrhea is limited. Few randomized trials evaluating treatments for *N. gonorrhoeae* infections have included data comparing different therapies for pharyngeal gonorrhea, and no randomized controlled trials have been undertaken with the explicit objective of comparing different therapies for gonococcal infections of the pharynx. Most observational studies have assessed only

Table 1. Characteristics of the Study Population

Characteristic	Cases of Pharyngeal Gonorrhea, No. (%)	Cases With a Repeat Test ≥7 and ≤180 d After Treatment, No. (%)	Cases of Repeat Test Positivity, No. (%)
Total cases	1440	360 (25)	54 (15)
Male sex	1275 (88.5)	322 (89.4)	49 (90.7)
MSM	1215 (84.4)	314 (87.2)	47 (87.0)
Age, mean (SD)	32 (10.4)	31 (8.5)	28.5 (7.1)
Race[a]			
Black	172 (11.9)	36 (10.0)	5 (9.3)
White	979 (68.0)	257 (71.4)	40 (74.1)
Asian	58 (4.0)	16 (4.4)	. . .
Hispanic	68 (4.7)	19 (5.3)	3 (5.5)
Native American	27 (1.9)	8 (2.2)	2 (3.7)
Unknown	54 (3.8)	13 (3.6)	2 (3.7)
Symptoms at diagnosis	136 (9.4)	41 (11.4)	4 (7.4)
Concurrent genital tract infection with gonorrhea	487 (33.8)	101 (28.1)	13 (24.1)
No. of sex partners in previous 2 mo, mean (SD)	5.1 (13.4)	4.6 (9.3)	4.8 (6.1)
Time period			
1993–1995	113 (7.8)	20 (5.6)	3 (5.6)
1996–1998	109 (7.6)	19 (5.3)	6 (11.1)
1999–2001	140 (9.7)	27 (7.5)	5 (9.3)
2002–2004	233 (16.2)	55 (15.3)	6 (11.1)
2005–2007	341 (23.7)	92 (25.6)	18 (33.3)
2008–Sept 2011	504 (35.0)	147 (40.8)	16 (29.6)
Testing method[b]			
Culture	1339 (93.0)	343 (95.3)	53 (98.1)
NAAT	107 (7.4)	21 (5.8)	1 (1.9)
Treatment regimen			
Ceftriaxone alone	118 (8.3)	44 (12.2)	4 (7.4)
Cefixime alone	93 (6.5)	24 (6.7)	5 (9.3)
Cefpodoxime alone	119 (8.4)	33 (9.2)	12 (22.2)
Azithromycin alone	76 (5.3)	15 (4.2)	2 (3.7)
Ceftriaxone + azithromycin	238 (16.7)	60 (16.7)	7 (13.0)
Ceftriaxone + doxycycline	11 (0.8)	2(0.6)	. . .
Cefixime + azithromycin	182 (12.8)	50 (13.9)	3 (5.6)
Cefixime + doxycycline	180 (12.6)	31 (8.6)	9 (16.7)
Cefpodoxime + azithromycin	272 (19.1)	65 (18.1)	5 (9.3)
Cefpodoxime + doxycycline	35 (2.5)	11 (3.1)	5 (9.3)
Fluoroquinolone	72 (5.1)	23 (6.4)	2 (3.7)
Doxycycline alone	30 (2.1)	2 (0.6)	. . .

Abbreviations: MSM, men who have sex with men; NAAT, nucleic acid amplification test; SD, standard deviation.

[a] Numbers do not add up to 100% owing to missing data.

[b] Concurrent testing by both NAAT and culture for antimicrobial surveillance purposes was possible.

single-drug regimens, and we are aware of only 1 clinical study that evaluated dual-drug therapy, the currently recommended standard of care in the United States. That retrospective study assessed 88 patients with pharyngeal gonorrhea treated in the United Kingdom between 2004 and 2007 and found that all 24 persons treated with cefixime and azithromycin had negative tests of cure, compared to 25 (81%) of 31 treated with cefixime alone or in combination with doxycycline, and 30 (91%) of 33 treated with a ceftriaxone-containing regimen [3]. Our findings largely agree with this prior study, and suggest that, at least among gonococci found in Seattle over the last 18 years, dual therapy with cefixime and

Table 2. Repeat Test Positivity by Treatment Regimen and Timing of Repeat Test

Treatment Regimen	7–45 d	46–90 d	91–180 d	Total, 7–180 d	Relative Risk (95% CI)	Adjusted[a] Relative Risk (95% CI)	*P* Value
Combination therapy with ceftriaxone	2/22 (9.1)	3/19 (15.8)	2/21 (9.5)	7/62 (11.3)	1.62 (.62–4.27)	1.20 (.43–3.33)	.731
Ceftriaxone + azithromycin	2/21 (9.5)	3/19 (15.8)	2/20 (10.0)	7/60 (11.7)			
Ceftriaxone + doxycycline	0/1 (0)	. . .	0/1 (0)	0/2 (0)			
Combination therapy with oral cephalosporins + azithromycin	3/44 (6.8)	2/30 (6.7)	3/41 (7.3)	8/115 (7.0)	Reference group[b]	Reference group[b]	. . .
Cefixime + azithromycin	2/24 (8.3)	0/11 (0)	1/15 (6.7)	3/50 (6.0)			
Cefpodoxime + azithromycin	1/20 (5.0)	2/19 (10.5)	2/26 (7.7)	5/65 (7.7)			
Combination therapy with oral cephalosporins + doxycycline	7/16 (43.8)	4/11 (36.4)	3/15 (20.0)	14/42 (33.3)	4.79 (2.16–10.6)	4.18 (1.64–10.7)	.003
Cefixime + doxycycline	5/12 (42.7)	3/8 (37.5)	1/11 (9.1)	9/31 (29.0)			
Cefpodoxime + doxycycline	2/4 (50.0)	1/3 (33.3)	2/4 (20.0)	5/11 (45.5)			
Oral cephalosporin monotherapy	12/24 (50.0)	2/11 (18.2)	3/22 (13.6)	17/57 (29.8)	4.29 (1.97–9.35)	3.98 (1.70–9.36)	.002
Cefixime	4/15 (26.7)	1/6 (16.7)	0/3 (0)	5/24 (20.8)			
Cefpodoxime	8/9 (88.9)	1/5 (20.0)	3/19 (15.8)	12/33 (33.4)			
Ceftriaxone monotherapy	3/18 (16.7)	0/8 (0)	1/18 (5.6)	4/44 (9.1)	1.31 (.41–4.13)	0.81 (.18–3.60)	.786
Azithromycin (1 or 2 g) monotherapy	1/8 (12.5)	0/4 (0)	1/3 (33.3)	2/15 (13.3)			
Fluoroquinolone (± azithromycin)	2/7 (28.6)	0/6 (0)	0/10 (0)	2/23 (8.7)			
Doxycycline monotherapy	. . .	0/1 (0)	0/1 (0)	0/2 (0)			
Total repeat tests (n = 360)							

Data are presented as No. (%).

Abbreviation: CI, confidence interval.

[a] Adjusted for time between treatment and repeat test, calendar year, number of sexual partners in the 2 months prior to diagnosis, sexual orientation, and age.

[b] Persons receiving an oral cephalosporin plus azithromycin.

azithromycin is a highly effective treatment for pharyngeal gonorrhea and comparable to ceftriaxone.

Pharmacokinetic/pharmacodynamic data also suggest that cefixime and azithromycin should be effective in treating pharyngeal gonorrhea caused by the vast majority of *N. gonorrhoeae* found in the United States in 2010–2011. Although the Clinical and Laboratory Standards Institute (CLSI) has not defined a breakpoint for cephalosporin resistance, CLSI uses a minimum inhibitory concentration (MIC) of ≥0.5 μg/mL to define decreased susceptibility for cefixime and ceftriaxone [2]. The European Committee on Antimicrobial Susceptibility Testing defines resistance, however, as a cefixime MIC ≥0.25 μg/mL [23], and some recent data suggest that treatment failures may occur more frequently in infections with gonococcal isolates having cefixime MIC ≥0.12 μg/mL [24]. Based on the CLSI definition, at present, the overwhelming majority of gonococcal isolates in the United States are fully susceptible to both cefixime (99.9%) and azithromycin (99.7%) [2]. In Seattle, where this study was undertaken, no cefixime resistant isolates were identified between 2009 and 2011, though approximately 3% of isolates in MSM and 1% of isolates in heterosexuals had cefixime "alert value" MICs of 0.25 μg/mL (Gonococcal Isolates Surveillance Project [GISP], unpublished data). Moran and Levine posited that an effective antimicrobial for pharyngeal gonorrhea should achieve a total plasma concentration 4 times above the MIC_{90} (the MIC required to inhibit growth of 90% of organisms) for at least 20 hours [4]. If this is correct, a single 400-mg dose of cefixime should be efficacious in treating pharyngeal infections caused by *N. gonorrhoeae* isolates with an MIC of ≤0.06 μg/mL [25, 26]—97% of all isolates in the United States tested through GISP in 2010 [27]—although some authorities have suggested that higher plasma levels of cephalosporins are required due to the drug classes' high level of protein binding [25]. Very limited data exist on the efficacy of azithromycin 1 g for pharyngeal infections [28], but the 2-g dose appears to be highly effective [29, 30]. Additionally, at least 1 in vitro study found that cefixime and azithromycin were synergistic against *N. gonorrhoeae*, particularly among isolates with high cefixime MICs (0.5 μg/mL) [31], although data on this point are conflicting [32, 33].

Doxycycline did not appear to improve treatment outcomes for pharyngeal gonorrhea in our study. Small studies

conducted in the 1980s reported that tetracyclines were effective in treating pharyngeal gonorrhea [19, 34]. However, >20% of gonococcal isolates in the United States are now resistant to tetracyclines [1, 2]. On the basis of our findings and the current antimicrobial susceptibility profile of *N. gonorrhoeae* isolates from the United States, we believe that azithromycin, and not doxycycline, should be used in conjunction with a cephalosporin to treat infections caused by *N. gonorrhoeae*, and we have incorporated this into our clinic and local STD treatment guidelines.

Our findings, which are based on observational data, not a randomized trial, are subject to a number of limitations. First, only 25% of persons diagnosed with pharyngeal gonorrhea in our clinic underwent repeat testing within 6 months of diagnosis, and it is possible that the association we observed between treatment regimen and repeat positive testing reflects bias or confounding. Almost all pharyngeal infections in our clinic were asymptomatic, and we did not observe an association between treatment regimen and the likelihood of returning for repeat testing, suggesting that receipt of a particular regimen did not clearly prompt higher levels of follow-up testing. On multivariate analysis, the association of treatment regimen with repeat test positivity persisted even after controlling for baseline sexual behavior, time from treatment to repeat testing, calendar year, sexual orientation, and age. Despite this, we cannot exclude the possibility of residual confounding as an explanation for our findings. Second, because of our limited sample size, we elected to group persons receiving cefixime and cefpodoxime together in our primary analysis comparing different treatment regimens. Cefixime is more active against *N. gonorrhoeae* than cefpodoxime and, because we combined outcomes from the 2 drugs, our analysis may overestimate treatment failures associated with cefixime treatment. Third, some of the infections ascertained were likely reinfections, not treatment failures. Although we did not have data on patients' sexual behavior following treatment and before repeat testing, and some repeatedly positive tests almost certainly resulted from reinfections, we do not believe that receipt of specific treatment regimens would directly influence patients' risk behaviors following treatment and thereby explain our findings. Reinfections likely inflated our estimates of treatment failures overall, and thus should have biased our results against the observed finding of differential treatment efficacy. Of note, our findings did not change when we restricted our analysis to 7–90 days. Last, we did not have antimicrobial susceptibility data on the *N. gonorrhoeae* isolates associated with treatment failures among our patients, and we cannot say how effective any currently used antimicrobial regimen might be in treating gonococci with higher MICs than those seen in Seattle during the study period.

In summary, our findings suggest that dual, single-dose oral therapy with cefixime and azithromycin is an effective treatment for pharyngeal gonorrhea caused by *N. gonorrhoeae* with antimicrobial susceptibility patterns that have been commonly observed in the United States to date. Although more-resistant gonococci currently remain uncommon in the United States, *N. gonorrhoeae* with decreased susceptibility to oral cephalosporins is now common in Asia [35] and many European countries [36]. We strongly agree with the current CDC recommendation that clinicians use ceftriaxone and azithromycin as the first-line therapy in treating all gonococcal infections, including pharyngeal gonorrhea, which is common and often undiagnosed in persons with urogenital or rectal infections [17, 37]. However, in some instances, such as with expedited partner therapy, clinicians will continue to need a completely oral regimen. Although our study does not provide the certitude of findings from a randomized trial, it should provide practitioners with some reassurance that, at least at present in the United States, treatment with cefixime and azithromycin remains a reasonable alternative regimen, even for pharyngeal gonorrhea. Doxycycline does not appear to improve the efficacy of cefixime in treating pharyngeal gonorrhea, and we believe that dual therapy with cefixime and doxycycline should not be used routinely to treat gonorrhea.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Workowski KA, Berman S. Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep **2010**; 59(RR-12):1–110.
2. Update to CDC's sexually transmitted diseases treatment guidelines, 2010: oral cephalosporins no longer a recommended treatment for gonococcal infections. MMWR Morb Mortal Wkly Rep **2012**; 61:590–4.
3. Sathia L, Ellis B, Phillip S, Winston A, Smith A. Pharyngeal gonorrhoea—is dual therapy the way forward? Int J STD AIDS **2007**; 18:647–8.
4. Moran JS, Levine WC. Drugs of choice for the treatment of uncomplicated gonococcal infections. Clin Infect Dis **1995**; 20(suppl 1):S47–65.

5. Moran JS. Treating uncomplicated *Neisseria gonorrhoeae* infections: is the anatomic site of infection important? Sex Transm Dis **1995**; 22:39–47.
6. Weinstock H, Workowski KA. Pharyngeal gonorrhea: an important reservoir of infection? Clin Infect Dis **2009**; 49:1798–800.
7. Workowski KA, Berman SM, Douglas JM Jr. Emerging antimicrobial resistance in *Neisseria gonorrhoeae*: urgent need to strengthen prevention strategies. Ann Intern Med **2008**; 148:606–13.
8. Whiley DM, Goire N, Lahra MM, et al. The ticking time bomb: escalating antibiotic resistance in *Neisseria gonorrhoeae* is a public health disaster in waiting. J Antimicrob Chemother **2012**; 67:2059–61.
9. Shlaes DM, Gerding DN, John JF Jr, et al. Society for Healthcare Epidemiology of America and Infectious Diseases Society of America Joint Committee on the Prevention of Antimicrobial Resistance: guidelines for the prevention of antimicrobial resistance in hospitals. Clin Infect Dis **1997**; 25:584–99.
10. Wiesner PJ, Tronca E, Bonin P, Pedersen AH, Holmes KK. Clinical spectrum of pharyngeal gonococcal infection. N Engl J Med **1973**; 288:181–5.
11. Bro-Jorgensen A, Jensen T. Gonococcal pharyngeal infections: report of 110 cases. Br J Vener Dis **1973**; 49:491–9.
12. Tice AW Jr, Rodriguez VL. Pharyngeal gonorrhea. JAMA **1981**; 246:2717–9.
13. Ahmed-Jushuf IH, Bradley MG, Rao PM. Oropharyngeal carriage of *Neisseria gonorrhoeae* and its response to treatment in patients with anogenital infection. Genitourin Med **1988**; 64:64–5.
14. Kinghorn G. Pharyngeal gonorrhoea: a silent cause for concern. Sex Transm Infect **2010**; 86:413–4.
15. Peters RP, Nijsten N, Mutsaers J, Jansen CL, Morre SA, van Leeuwen AP. Screening of oropharynx and anorectum increases prevalence of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infection in female STD clinic visitors. Sex Transm Dis **2011**; 38:783–7.
16. Giannini CM, Kim HK, Mortensen J, Mortensen J, Marsolo K, Huppert J. Culture of non-genital sites increases the detection of gonorrhea in women. J Pediatr Adolesc Gynecol **2010**; 23:246–52.
17. Kent CK, Chaw JK, Wong W, et al. Prevalence of rectal, urethral, and pharyngeal chlamydia and gonorrhea detected in 2 clinical settings among men who have sex with men: San Francisco, California, 2003. Clin Infect Dis **2005**; 41:67–74.
18. Stoltey JE, Barry PM. The use of cephalosporins for gonorrhea: an update on the rising problem of resistance. Expert Opin Pharmacother **2012**; 13:1411–20.
19. Hutt DM, Judson FN. Epidemiology and treatment of oropharyngeal gonorrhea. Ann Intern Med **1986**; 104:655–8.
20. Bernstein KT, Stephens SC, Barry PM, et al. *Chlamydia trachomatis* and *Neisseria gonorrhoeae* transmission from the oropharynx to the urethra among men who have sex with men. Clin Infect Dis **2009**; 49:1793–7.
21. Bolan GA, Sparling PF, Wasserheit JN. The emerging threat of untreatable gonococcal infection. N Engl J Med **2012**; 366:485–7.
22. Zou G. A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol **2004**; 159:702–6.
23. European Committee on Antimicrobial Susceptibility Testing . Clinical breakpoint tables v. 3.0. Available at: http://www.eucast.org/clinical_breakpoints/. Accessed 9 January 2013.
24. Allen VG, Mitterni L, Seah C, et al. *Neisseria gonorrhoeae* treatment failure and susceptibility to cefixime in Toronto, Canada. JAMA **2013**; 309:163–70.
25. Chisholm SA, Mouton JW, Lewis DA, Nichols T, Ison CA, Livermore DM. Cephalosporin MIC creep among gonococci: time for a pharmacodynamic rethink? J Antimicrob Chemother **2010**; 65:2141–8.
26. Lupin Pharmaceuticals. SUPRAX (package insert). Baltimore, MD: Lupin Pharmaceuticals, Inc. Available at: http://www.lupinpharmaceuticals.com/pdf/09/SUPRAX%20Common%20PI%20.pdf. Accessed 20 February 2013.
27. Centers for Disease Control and Prevention. Sexually transmitted disease surveillance, 2010. Atlanta, GA: US Department of Health and Human Services, **2011**. Available at: http://www.cdc.gov/std/stats10/default.htm. Accessed 20 February 2013.
28. Waugh MA. Open study of the safety and efficacy of a single oral dose of azithromycin for the treatment of uncomplicated gonorrhoea in men and women. J Antimicrob Chemother **1993**; 31(suppl E):193–8.
29. Handsfield HH, Dalu ZA, Martin DH, Douglas JM Jr, McCarty JM, Schlossberg D. Multicenter trial of single-dose azithromycin vs. ceftriaxone in the treatment of uncomplicated gonorrhea. Azithromycin Gonorrhea Study Group. Sex Transm Dis **1994**; 21:107–11.
30. Dan M, Poch F, Amitai Z, Gefen D, Shohat T. Pharyngeal gonorrhea in female sex workers: response to a single 2-g dose of azithromycin. Sex Transm Dis **2006**; 33:512–5.
31. Furuya R, Nakayama H, Kanayama A, et al. In vitro synergistic effects of double combinations of beta-lactams and azithromycin against clinical isolates of *Neisseria gonorrhoeae*. J Infect Chemother **2006**; 12:172–6.
32. Pereira R, Cole MJ, Ison CA. Combination therapy for gonorrhoea: in vitro synergy testing. J Antimicrob Chemother **2013**; 68:640–3.
33. Unemo M, Nicholas RA. Emergence of multidrug-resistant, extensively drug-resistant and untreatable gonorrhea. Future Microbiol **2012**; 7:1401–22.
34. Jordan WC. Clinical trial of doxycycline in the treatment of anorectal and oropharyngeal gonorrhea. J Natl Med Assoc **1985**; 77:1020–1.
35. Lahra MM. Surveillance of antibiotic resistance in *Neisseria gonorrhoeae* in the WHO Western Pacific and South East Asian Regions, 2010. Commun Dis Intell **2012**; 36:95–100.
36. Van de Laar M, Spiteri G. Increasing trends of gonorrhoea and syphilis and the threat of drug-resistant gonorrhoea in Europe. Euro Surveill **2012**; 17. pii:20225.
37. Morris SR, Klausner JD, Buchbinder SP, et al. Prevalence and incidence of pharyngeal gonorrhea in a longitudinal sample of men who have sex with men: the EXPLORE study. Clin Infect Dis **2006**; 43:1284–9.