The Efficacy and Safety of Gentamicin Plus Azithromycin and Gemifloxacin Plus Azithromycin as Treatment of Uncomplicated Gonorrhea

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(See the Editorial Commentary by Rice on pages 1092–4.)

Background. Ceftriaxone is the foundation of currently recommended gonorrhea treatment. There is an urgent need for backup treatment options for patients with cephalosporin allergy or infections due to suspected cephalosporin-resistant *Neisseria gonorrhoeae*. We evaluated the efficacy and tolerability of 2 combinations of existing non-cephalosporin antimicrobials for treatment of patients with urogenital gonorrhea.

Methods. We conducted a randomized, multisite, open-label, noncomparative trial in 5 outpatient sexually transmitted disease clinic sites in Alabama, California, Maryland, and Pennsylvania. Patients aged 15–60 years diagnosed with uncomplicated urogenital gonorrhea were randomly assigned to either gentamicin 240 mg intramuscularly plus azithromycin 2 g orally, or gemifloxacin 320 mg orally plus azithromycin 2 g orally. The primary outcome was microbiological cure of urogenital infections (negative follow-up culture) at 10–17 days after treatment among 401 participants in the per protocol population.

Results. Microbiological cure was achieved by 100% (lower 1-sided exact 95% confidence interval [CI] bound, 98.5%) of 202 evaluable participants receiving gentamicin/azithromycin, and 99.5% (lower 1-sided exact 95% CI bound, 97.6%) of 199 evaluable participants receiving gemifloxacin/azithromycin. Gentamicin/azithromycin cured 10 of 10 pharyngeal infections and 1 of 1 rectal infection; gemifloxacin/azithromycin cured 15 of 15 pharyngeal and 5 of 5 rectal infections. Gastrointestinal adverse events were common in both arms.

Conclusions. Gentamicin/azithromycin and gemifloxacin/azithromycin were highly effective for treatment of urogenital gonorrhea. Gastrointestinal adverse events may limit routine use. These non-cephalosporin-based regimens may be useful alternative options for patients who cannot be treated with cephalosporin antimicrobials. Additional treatment options for gonorrhea are needed.

Clinical Trials Registration. NCT00926796.

Keywords. *Neisseria gonorrhoeae*; gonorrhea treatment; azithromycin; gentamicin; gemifloxacin.
The public health burden of *Neisseria gonorrhoeae* infections is substantial. Untreated or inadequately treated gonorrhea can cause epididymitis, pelvic inflammatory disease (PID), chronic pelvic pain, ectopic pregnancy, and tubal infertility [1, 2]. In resource-limited settings, childhood blindness from gonococcal ophthalmia neonatorum occurs in children born to infected mothers. Worldwide, approximately 106.1 million gonococcal infections are estimated to occur annually [3]. In the United States, gonorrhea is the second most commonly reported notifiable infection: 334,826 cases were reported in 2012 [4]. Many gonococcal infections go undetected or unreported; the Centers for Disease Control and Prevention (CDC) estimate that >800,000 infections occur annually in the United States among 15- to 49-year-olds [5]. The annual total direct medical cost of gonorrhea is estimated to be US$162.1 million [6].

Effective control and prevention of gonorrhea relies on prompt and effective antimicrobial therapy. However, since the introduction of antimicrobials in the 1930s, *N. gonorrhoeae* has progressively developed resistance to each class used for treatment, including sulfonamides, penicillins, tetracyclines, and second-generation fluoroquinolones such as ciprofloxacin [7–10]. By 2007, cephalosporin antimicrobials were the only remaining agents recommended by the CDC for empiric treatment of gonorrhea, and no new treatment options were on the horizon [10]. However, descriptions of patients with gonorrhea unsuccessfully treated with oral cephalosporins were already being reported from East Asia [11–13], and multiple countries reported increasing cephalosporin minimum inhibitory concentrations (MICs) [14].

To support public health preparedness and address the emerging threat of cephalosporin-resistant gonococcal infections, the CDC recognized that clinical efficacy and safety data on alternative therapeutic regimens for gonorrhea were urgently needed. Because no new antimicrobial treatment agents with robust efficacy data were available when this trial was designed, existing antimicrobials that were not recommended for treatment of gonorrhea were evaluated for use in combination therapy. Azithromycin monotherapy is effective for gonorrhea treatment but has not been recommended for routine use because of the ease with which *N. gonorrhoeae* can develop macrolide resistance [15–17]. Gentamicin, an injectable aminoglycoside that binds to the 30S ribosomal subunit and inhibits protein synthesis, has not been recommended in the United States for treatment of gonorrhea, but it has been used successfully in other countries for gonorrhea treatment, including Malawi [18]. It is chemically similar to spectinomycin (which is efficacious but not available in the United States [16]), widely available in the United States, and relatively inexpensive. Gemifloxacin, an oral fourth-generation fluoroquinolone, had not undergone clinical study for gonorrhea, but demonstrated in vitro activity against ciprofloxacin-resistant *N. gonorrhoeae* [19]. In vitro synergy testing of azithromycin and gemifloxacin suggested that gemifloxacin may have promise as an agent in combination therapy (CDC, unpublished data). In this trial, we evaluated the efficacy and tolerability of azithromycin plus either gentamicin or gemifloxacin for treatment of uncomplicated urogenital gonorrhea.

**METHODS**

**Study Design**

This study was a multicenter, randomized, open-label, noncomparative trial involving men and women with uncomplicated urogenital gonorrhea. Enrollment was conducted from May 2010 through November 2012. Study follow-up was completed in November 2012. The study was registered at ClinicalTrials.gov (NCT00926796).

The final protocol was approved by investigational review boards at each clinical site and the CDC. Participants provided written consent. The trial was monitored by an independent safety monitoring committee (SMC), which convened semiannually. Following the SMC meeting held in August 2012, the SMC recommended halting trial enrollment because continued participant accrual to targeted enrollment of 500 infected participants would be highly unlikely to alter the results.

**Setting and Participants**

Participant enrollment occurred in outpatient sexually transmitted disease (STD) clinics in Birmingham, Alabama; San Francisco and Los Angeles, California; Pittsburgh, Pennsylvania; and Baltimore, Maryland.

Patients were initially eligible for inclusion if they (1) were suspected to be infected with urethral or cervical *N. gonorrhoeae* (defined as untreated urethral or cervical *N. gonorrhoeae* identified by Gram stain demonstrating gram-negative intracellular diplococci, laboratory testing at a previous visit indicating gonorrhea, or untreated patients reporting anal, oral, or vaginal sexual contact in the past 60 days with someone diagnosed with gonorrhea), and (2) were willing to abstain from sexual intercourse or use condoms until follow-up was complete. Pregnancy tests were completed for all women; pregnant women were not enrolled.

Major exclusion criteria were age <15 years or >60 years, having a history of renal insufficiency, hepatic insufficiency, cardiac arrhythmia, neuromuscular disorders, rheumatoid arthritis, or tendon disorders; prior receipt of kidney, lung, or heart transplants; pregnancy or lactation; allergy or prior adverse reaction to macrolides, aminoglycosides, or fluoroquinolones; concomitant infection requiring systemic antimicrobial therapy (besides chlamydia); receipt of systemic or intravaginal antimicrobials within 30 days of study enrollment, or current use of corticosteroids, immunosuppressive therapy, or cardiac antiarrhythmic medication; and clinically diagnosed abdominal pain related to PID, testicular pain, epididymitis, disseminated gonococcal
infection, or genital ulcer disease. Women diagnosed with bacterial vaginosis (BV) at enrollment were enrolled if they were willing to defer BV treatment until the follow-up visit. Women who did not wish to defer BV treatment were withdrawn from the study and treated in accordance with local clinic protocols.

At enrollment, clinical information and culture specimens were collected, and participants were treated according to the randomized assignment. Participants later found to have negative enrollment cervical or urethral cultures for N. gonorrhoeae were deemed ineligible and were discontinued from the study.

Randomization and Interventions
Using a permuted blocked randomization scheme with stratification by study site and allocation by numbered envelopes, participants were randomly assigned treatment in a 1:1 ratio to treatment with either gentamicin 240 mg intramuscularly (or 5 mg/kg if ≤45 kg) plus azithromycin 2 g orally, or gemifloxacin 320 mg plus azithromycin 2 g given simultaneously as single oral doses. For those who received gentamicin 240 mg, 2 separate 3-mL injections of 40 mg/mL solution were administered. Azithromycin was provided as four 500-mg tablets. A small snack was provided prior to medication administration. Participants were observed for at least 30 minutes after medication administration and were instructed to return to the clinic or contact the study coordinator immediately if vomiting occurred within 30 minutes of departing the clinic. Those who vomited within 1 hour were discontinued from the study, re-treated per the local clinic standard of care, and asked to return in 10–17 days for evaluation. Participants who vomited within 1 hour were not included in the PP analysis. For each treatment group, we calculated the proportion of participants with urogenital gonorrhea who achieved microbiological cure and the exact binomial lower 1-sided 95% CI bound of ≥95% and allowed for a 10% dropout rate. The target sample size was 250 infected participants per group.

The primary analysis used the per protocol (PP) population, which comprised all infected participants who (1) satisfied inclusion and exclusion criteria, (2) were randomized and treated, (3) returned for follow-up within 10–17 days, and (4) had an evaluable follow-up culture result. Participants who vomited within 1 hour were not included in the PP analysis. For each treatment group, we calculated the proportion of participants with urogenital gonorrhea who achieved microbiological cure and the exact binomial lower 1-sided 95% CI bound. Sensitivity analyses of microbiological efficacy were conducted using the modified intent-to-treat (mITT) population, which included all infected participants who satisfied inclusion and exclusion criteria and were randomized and treated. For the purposes of the mITT analyses, participants who were lost to follow up, vomited within 1 hour of drug administration, or whose follow-up culture results were not evaluable were considered to have failed treatment. We calculated the frequency of adverse events (AEs) among patients in the PP population and the safety population (all patients who received at least 1 dose of study medication, including those who vomited within 1 hour of drug administration). All analyses were performed using SAS version 9.3 (SAS Institute, Cary, North Carolina).

Role of the Funding Source
The study was designed by the investigators, the CDC, and the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health; sponsored by NIAID; and funded by NIAID and the CDC.
RESULTS

Participants

Of 664 participants with suspected gonorrhea, 614 were randomized (491 men, 121 women, and 2 participants with sex data missing), and 603 received study medication (Figure 1). Of those randomized and treated, 305 received gentamicin/azithromycin and 298 received gemifloxacin/azithromycin. One hundred nine individuals were found to be ineligible after randomization and treatment, of which 117 were due to negative enrollment cultures (58 were men and 59 were women).

Most participants were men, and approximately one-third of participants self-identified as men who have sex with men (MSM) (Table 1). Nearly half of the participants were enrolled in San Francisco. Of 401 participants, 152 (38%) reported sex between the initial and follow-up study visit, and 61 reported sex without a condom.

Efficacy

In the PP analysis, microbiological cure was achieved by 100% of participants with urogenital gonorrhea treated with gentamicin and azithromycin (lower 1-sided exact 95% CI bound, 98.5%) and by 99.5% (lower 1-sided exact 95% CI bound, 97.6%) of participants treated with gemifloxacin/azithromycin. One heterosexual male participant treated with gemifloxacin/azithromycin had N. gonorrhoeae isolated from a urethral swab collected at a follow-up visit. The MICs of this participant’s pretherapy isolates of gemifloxacin, ciprofloxacin, and azithromycin were 0.004, 0.002, and 0.25 µg/mL, respectively (Supplementary Table 1). The posttherapy isolate was not available for susceptibility testing. He reported having vaginal sex without a condom between visits. All 25 participants with pharyngeal gonorrhea (15 received gemifloxacin/azithromycin and 10 received gentamicin/azithromycin) and 6 participants with rectal gonorrhea (5 received gemifloxacin/azithromycin, 1 received gentamicin/azithromycin) were microbiologically cured.

The mITT sensitivity analysis, which considers participants who vomited within 1 hour and those lost to follow-up as failing treatment, demonstrated gentamicin/azithromycin efficacy of 83.8% (lower 1-sided 95% CI bound, 80.0%) and gemifloxacin/azithromycin efficacy of 84.4% (lower 1-sided 95% CI bound, 80.5%) (Supplementary Table 2).
The most commonly reported AEs were mild to moderate gastrointestinal conditions. Among 202 PP participants in the gentamicin/azithromycin arm, 27.7% reported nausea, 18.8% reported diarrhea, and 7.4% reported vomiting (Table 2). Among 199 PP participants in the gemifloxacin/azithromycin arm, 25.7% reported nausea, 12.6% reported diarrhea, and 7.6% reported vomiting (Table 2).
Table 3. Antimicrobial Susceptibility of Pretreatment Neisseria gonorrhoeae Isolates Collected From Participants in the Per Protocol Analysis (n = 421) a

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>MIC 50, µg/mL</th>
<th>MIC 90, µg/mL</th>
<th>Range, µg/mL</th>
<th>Percentage at or Above MIC Breakpoint</th>
<th>MIC Breakpoint for Resistance or Elevated MICs, µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin</td>
<td>0.25</td>
<td>0.5</td>
<td>0.03–16</td>
<td>0.5</td>
<td>≥2.0</td>
</tr>
<tr>
<td>Cefixime</td>
<td>0.015</td>
<td>0.06</td>
<td>0.001–1.0</td>
<td>1.4</td>
<td>≥0.25</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>0.008</td>
<td>0.03</td>
<td>0.001–0.125</td>
<td>1.2</td>
<td>≥0.125</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>0.004</td>
<td>8.0</td>
<td>0.002–32.0</td>
<td>24.5</td>
<td>≥1.0</td>
</tr>
<tr>
<td>Gemifloxacin</td>
<td>0.004</td>
<td>2</td>
<td>0.001–8.0</td>
<td>17.1</td>
<td>≥1.0</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>4</td>
<td>8</td>
<td>0.002–16</td>
<td>0</td>
<td>≥32.0</td>
</tr>
<tr>
<td>Penicillin</td>
<td>0.5</td>
<td>4</td>
<td>0.004–64</td>
<td>23.0</td>
<td>≥2.0</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>0.5</td>
<td>16</td>
<td>0.03–32</td>
<td>24.2</td>
<td>≥2.0</td>
</tr>
</tbody>
</table>

Abbreviations: MIC, minimum inhibitory concentration; MIC 50, minimum inhibitory concentration required to inhibit growth of 50% of organisms; MIC 90, minimum inhibitory concentration required to inhibit growth of 90% of organisms.

* Three hundred ninety-six participants provided a total of 421 isolates (participants with genital and extragenital infections may have contributed >1 pretreatment isolate).

arm, 37.2% reported nausea, 23.1% reported diarrhea, and 5% reported vomiting. No serious AEs occurred.

Among all 305 participants who received gentamicin/azithromycin (safety analysis), nearly 26% of 305 participants experienced nausea and 17% reported diarrhea (Supplementary Table 3A); 10 (3.3%) participants vomited within 1 hour of gentamicin/azithromycin administration (Figure 1). Among all 298 gemifloxacin/azithromycin recipients, 40% experienced nausea and 22% reported diarrhea (Supplementary Table 3B); 23 (7.7%) vomited within 1 hour of gemifloxacin/azithromycin administration (Figure 1).

Antimicrobial Susceptibility

From 396 PP participants, 421 pretreatment N. gonorrhoeae isolates were available for antimicrobial susceptibility testing (participants with pharyngeal or rectal infections may have contributed >1 pretreatment isolate). Elevated azithromycin MICs (≥2.0 µg/mL) were detected in 0.5% of isolates, and elevated gemifloxacin MICs (≥1.0 µg/mL) were detected in 17.1% of isolates (Table 3). Previous studies found gemifloxacin MICs to be 4-fold lower than ciprofloxacin MICs [19, 23, 24]. In contrast, our study found that gemifloxacin MICs of most isolates were the same as or 1–2 dilutions lower than the ciprofloxacin MICs. None of the isolates were resistant to gentamicin.

DISCUSSION

Neisseria gonorrhoeae has acquired resistance to each antimicrobial recommended for treatment. As this trial was being conducted, gathering evidence pointed to emergence of gonococcal cephalosporin resistance. Multiple reports from Europe and recently, Toronto, Canada, described patients with gonorrhea who were unsuccessfully treated with oral cephalosporins [25–27]. Ceftriaxone-resistant isolates were identified in Japan and Europe [28–30]. Cefixime MICs increased in the United States, particularly in the western states and among MSM; in response, the CDC updated its STD treatment guidelines in 2012 to recommend dual therapy with ceftriaxone 250 mg as a single intramuscular dose plus either azithromycin 1 g orally or doxycycline 100 mg orally twice daily for a week as the only first-line treatment for gonorrhea [31]. In 2013, CDC named N. gonorrhoeae as one of 3 “urgent” antimicrobial threats [32]. Additional gonorrhea treatment options are needed.

This trial provides clinical data on 2 therapeutic options that may be useful for patients who cannot be treated with currently recommended ceftriaxone-based therapy, due to infection with ceftriaxone-resistant strains or severe cephalosporin allergy. Among participants included in the primary analysis, all urethral gonococcal infections were successfully treated with gentamicin/azithromycin, and nearly all urethral infections treated with gemifloxacin/azithromycin were cured. All of the rectal and pharyngeal gonococcal infections were cured, but only a small number of these nongenital infections were studied. Gastrointestinal AEs, especially mild nausea and diarrhea, were common. Some participants vomited within 1 hour of study drug administration, and those participants were not included in the primary analysis.

It is not entirely surprising that both combinations demonstrated excellent efficacy. As previously noted, azithromycin has demonstrated excellent efficacy as monotherapy [17], and gentamicin and gemifloxacin are active against N. gonorrhoeae. Prior to this trial, however, we lacked clinical efficacy and, importantly, safety data on the combination of these agents.

Although these combinations exhibited excellent efficacy, the burden of adverse events is likely to limit the routine use of these combinations. A substantial proportion of participants in both arms reported mild nausea, diarrhea, and vomiting,
and 5% of all patients who received study drugs vomited within 1 hour. These results probably reflect the known tolerability profile of azithromycin 2 g administered orally [33]. A larger proportion of participants who received gemifloxacin/azithromycin seem to have experienced gastrointestinal AEs than participants who received gentamicin/azithromycin. This may reflect the additive contribution of gemifloxacin, which is associated with nausea, diarrhea, vomiting, and abdominal pain [34]. If prescribing either of these regimens, it might be prudent for clinicians to monitor the patient for vomiting after administration, so as to ensure adequate therapy.

Although inpatient gentamicin therapy is often limited because of potential nephro- or ototoxicity, the risk of toxicity has appeared low among healthy patients with normal renal function who received single-dose gentamicin treatment for gonorrhea [35–38]. Further investigation of the risk of nephro- or ototoxicity in young adults receiving single-dose gentamicin therapy might be useful, however. Clinicians must exercise caution when considering the use of these combinations for pregnant women: although azithromycin has been assigned to pregnancy class B by the US Food and Drug Administration, gemifloxacin has been assigned to pregnancy class C and gentamicin to pregnancy class D [33, 34, 39].

Published in vitro gemifloxacin susceptibility data indicate that gemifloxacin is active against N. gonorrhoeae, including isolates with ciprofloxacin resistance or mutations in gyrA and parC, possibly due to stronger inhibitory activity than other fluoroquinolones [19, 23, 24]. Although a gemifloxacin resistance MIC breakpoint has not been defined and the clinical relevance of the gemifloxacin MIC breakpoint used in this trial is unclear, it is nevertheless worrisome that a large percentage of isolates in this trial exhibited elevated gemifloxacin MICs. Many isolates exhibited gemifloxacin MICs that were the same as or only 1–2 dilutions lower than the ciprofloxacin MICs. Surveillance of gemifloxacin MICs and efforts to define the MIC associated with resistance may be warranted.

This study has several limitations. Because the design only included combination therapies, we are unable to define the efficacy of individual antimicrobials included in the regimens, and we are unable to clearly define the benefit of adding a second antimicrobial. A theoretical basis exists for using 2 antimicrobials to potentially delay emergence and spread of resistance, and combination therapy has been recommended for routine clinical care of gonorrhea since 2010 [16, 31]. However, the evaluation of newly developed antimicrobials should begin with the study of single agents, rather than antimicrobial combinations, so that efficacy and tolerability can initially be determined for each new drug. The study was not designed to provide the appropriate statistical power to obtain precise estimates of efficacy for pharyngeal and rectal gonococcal infections. Nonetheless, the results suggest that the studied treatments may be efficacious for extragenital infections. Enrollment of women proved challenging during the study, and many enrolled women were deemed ineligible because of negative baseline cultures. The relative underrepresentation of women might limit generalizability. These findings may not be applicable to patients aged >60 years or to those with significant comorbid medical conditions.

In summary, the results of this trial indicate that the combinations of azithromycin plus gentamicin or gemifloxacin exhibit excellent efficacy for treatment of uncomplicated urogenital gonorrhea. Cephalosporin resistance in N. gonorrhoeae is expected to emerge, and these combinations may be helpful for patients infected with ceftriaxone-resistant gonococci or patients with severe cephalosporin allergy. This trial provides much-needed data in the short term, but additional treatment options for gonorrhea are urgently needed.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyrighted. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Author contributions. R. D. K. and P. C. M. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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References


APPENDIX

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