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Management of Gonorrhea in Adolescents and Adults in the United States

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Abstract

Gonorrhea is the second most commonly reported notifiable disease in the United States and is associated with serious health sequelae, including pelvic inflammatory disease, infertility, and ectopic pregnancy. Treatment for gonorrhea has been complicated by antimicrobial resistance. *Neisseria gonorrhoeae* has developed resistance to each of the antimicrobials that were previously recommended as first-line treatment regimens, and current treatment options are severely limited. This article summarizes the key questions and data that were discussed at the Sexually Transmitted Diseases (STD) Treatment Guidelines Expert Consultation meeting in April 2013, and the rationale for the 2015 Centers for Disease Control and Prevention STD treatment guidelines for gonococcal infections in adolescents and adults. Key issues addressed include whether to change the dosage of ceftriaxone and azithromycin used in the recommended dual treatment regimen, whether to continue to list dual treatment with cefixime and azithromycin as an alternative treatment regimen, and management of gonococcal infections in persons with severe cephalosporin allergy or suspected treatment failure.

Keywords

gonorrhea; *Neisseria gonorrhoeae*; drug therapy

Gonorrhea, a sexually transmitted infection, is the second most commonly reported notifiable disease in the United States [1], with a total of 333 004 new cases reported to the Centers of Disease Control and Prevention (CDC) in 2013 [2]. However, because many infections are never diagnosed or reported, the true burden of gonococcal infection is likely significantly higher. It is estimated that >800 000 new gonococcal infections occur in the United States each year [3]. Although the national gonorrhea rate has declined substantially from its peak in 1975 (464.1 cases per 100 000 population) and reached an all-time low in

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2009 (98.1 cases per 100 000), the rate subsequently increased each year during 2010–2012, and plateaued at 106.1 cases per 100 000 population in 2013 [2]. High gonorrhea rates continue to be observed in certain demographic groups and geographic areas. In particular, adolescents aged 15–19 years (337.5 cases per 100 000 population), young adults aged 20–24 years (500.5 cases per 100 000 population), non-Hispanic blacks (426.6 cases per 100 000 population), and residents of the Southern United States (128.6 cases per 100 000 population) bear the highest burden of disease [2].

Timely and effective treatment is an essential component of gonorrhea control programs. It reduces transmission in the community by shortening the duration of infection and decreases the risk of serious health sequelae, including pelvic inflammatory disease, infertility, and ectopic pregnancy [4]. Unfortunately, treatment for gonorrhea has been complicated by antimicrobial resistance. *Neisseria gonorrhoeae* has progressively developed resistance to each of the antimicrobials that were previously recommended as first-line treatment regimens, and current treatment options are severely limited [5]. In 2013, the CDC hosted a meeting with expert consultants to review the most recent data on gonococcal antimicrobial susceptibility, review the most recent data on treatment effectiveness, and make recommendations for the management of gonorrhea in adolescents and adults in the United States. This paper summarizes the evidence discussed at the meeting and the rationale for the 2015 CDC Sexually Transmitted Diseases (STD) treatment guidelines for gonococcal infections in adolescents and adults.

METHODS

The CDC hosted a STD Treatment Guidelines Expert Consultation meeting in April 2013, where >60 experts in the fields of STD, infectious disease, epidemiology, and medicine discussed the latest developments in STD clinical and preventive services. In preparation for the meeting, 9 key questions on the management of gonococcal infections were developed based on input solicited from partners at state and local health departments and expert consultants. To address the key questions, a PubMed search for relevant articles published since 2008 (previous treatment guidelines meeting) through 9 March 2013 was conducted using the search terms “(gonorrhea or gonorrhoeae or gonorrrhoea or gonococcus or gonococcal) AND (treatment or therapy or resistance or antibiotics or failure)” and was restricted to abstracts or articles written in English. References listed in the retrieved articles were also searched for other relevant articles and abstracts. Additional data on national or regional gonococcal susceptibility were obtained from reports published on the websites of internationally recognized public health agencies and directly from the US Gonococcal Isolate Surveillance Project (GISP). GISP is a sentinel surveillance system, located in 25–30 cities throughout the United States, that monitors gonococcal antimicrobial susceptibility among urethral isolates obtained from men with urethritis [6]. Relevant data from these articles and reports were reviewed, summarized, and presented to a group of expert consultants at the April 2013 meeting. Preliminary answers to the 9 key questions and proposed recommendations were drafted based on available evidence or, when data were insufficient, expert opinion. Below is a list of key questions discussed, a summary of the data available for each question, and an overview of the discussion and recommendations resulting from each question.

In July 2013, the results of a clinical trial evaluating 2 new dual treatment regimens for gonorrhea were presented at an international conference and subsequently published [7, 8]. In September 2013, a subset of the expert consultants met to discuss the data from the trial, and amended the proposed recommendations based on the new evidence. These data and revised recommendations are included in the following discussion.

RESULTS AND DISCUSSION

Key Question 1. Are There Any Data to Suggest That There Should Be a Change in the Recommended Dosage of Ceftriaxone or Azithromycin for the Treatment of Uncomplicated Urethral, Cervical, or Rectal Gonococcal Infections?

At the time of the 2013 guidelines meeting, the CDC recommendation for treatment of uncomplicated gonococcal infection of the cervix, urethra, and rectum was dual treatment with ceftriaxone 250 mg intramuscularly as a single dose and either azithromycin 1 g orally as a single dose or doxycycline 100 mg orally twice daily for 7 days; azithromycin was preferred over doxycycline as the second antimicrobial, owing to the high prevalence of tetracycline resistance among gonococcal isolates in the United States [2, 9]. However, other countries have recommended higher doses of ceftriaxone and/or azithromycin than those recommended by the CDC [10–12].

Ceftriaxone Clinical Effectiveness Data—The CDC has traditionally used the criteria of ≥95% effectiveness, and a lower 95% confidence interval (CI) bound of ≥95% effectiveness, for recommended treatment regimens [13, 14]. According to summed data from clinical trials published in the 1980s and early 1990s, the effectiveness of ceftriaxone 250 mg for uncomplicated urethral, cervical, and rectal gonococcal infections is 99.2% (95% CI, 98.8%–99.5%) (Table 1) [21]. There are no new clinical trial data on the efficacy of ceftriaxone 250 mg. A literature review identified 2 recent studies assessing the clinical effectiveness of ceftriaxone at higher doses: one evaluated ceftriaxone 500 mg and one evaluated ceftriaxone 1 g. The evaluation of ceftriaxone 500 mg reported a cure rate of 90% in 100 patients with urethral or cervical infection [16]. However, this study did not use standard bacteriologic criteria to confirm gonococcal infection and treatment failure, and these results should be interpreted with caution. The evaluation of ceftriaxone 1 g demonstrated a cure rate of 100% in 48 patients with urethral or cervical gonococcal infection [17].

Ceftriaxone Susceptibility Data—In general, for an antimicrobial to meet the ≥95% clinical effectiveness criterion, ≥95% of gonococcal infections must be susceptible to the antimicrobial. Accordingly, although the correlation between in vitro resistance and clinical treatment failure is imperfect, in the past the CDC has changed treatment guidelines when the prevalence of resistance to a recommended antimicrobial reached ≥5% in the population [14]. The in vitro minimum inhibitory concentration (MIC) breakpoints that correspond to cefixime and ceftriaxone resistance have not been defined, but the Clinical and Laboratory Standards Institute (CLSI) defines decreased susceptibility to ceftriaxone as an MIC ≥0.5 μg/mL [23]. The proportion of GISP isolates with decreased susceptibility to ceftriaxone has remained <0.1% (Table 2). While increases in cephalosporin MICs were observed

worldwide during 2000–2010 [9, 24–26], ceftriaxone MICs in the United States during 2011–2013 were similar to ceftriaxone MICs during 1987–2000, when the majority of the ceftriaxone clinical trials were conducted (Table 2).

Worldwide, a total of 4 isolates with very high ceftriaxone MICs (MICs 1–4 μg/mL) have been identified (Table 3) [33, 37, 38, 42, 43]. The first of these was associated with a pharyngeal infection and ceftriaxone 1 g treatment failure. The other 3 were associated with urethral or rectal infections that were treated with antimicrobials other than ceftriaxone. No other isolates with ceftriaxone MICs in this range or higher have been reported.

Case Reports of Ceftriaxone Treatment Failures—There have been no reported cases of ceftriaxone treatment failure for urethral, cervical, or rectal infection, and no reported cases of ceftriaxone treatment failure at any anatomic site in the United States (Table 3). While ceftriaxone treatment failure for pharyngeal infection has been reported at MICs as low as 0.016 μg/mL [36], pharyngeal infection is known to be more difficult to eradicate, and treatment failure at this site does not necessarily indicate antimicrobial resistance [22].

Pharmacokinetic Estimates of Ceftriaxone Effectiveness—A pharmacodynamic modeling study published in 2010 predicted that treatment failures with ceftriaxone 250 mg would be likely at ceftriaxone MICs of 0.125–0.25 μg/mL [44]. However, clinical data on the ceftriaxone MIC breakpoint that is correlated with treatment failure for urethral, cervical, or rectal infection are lacking.

Rationale for Dual Treatment—Prior to the 2010 STD treatment guidelines, administration of a second antimicrobial was recommended for patients with gonococcal infection to provide treatment for *Chlamydia trachomatis* infection, which frequently co-occurred with gonococcal infection [45]. Since the publication of the 2010 treatment guidelines, dual treatment that included either azithromycin or doxycycline has been recommended for all patients with gonococcal infection, regardless of the presence of chlamydial coinfection [46]. The primary rationale for recommending dual treatment is that it may enhance treatment effectiveness and prevent further transmission of a resistant organism. In addition, coadministration of 2 antimicrobials with different mechanisms of action may also hinder the development of resistance.

Recent recommendations have stated that azithromycin was preferred over doxycycline as the second antimicrobial owing to the high prevalence of tetracycline resistance among gonococcal isolates in the United States [9,47]. In 2013, 23.7% of GISP isolates were resistant to tetracycline [2].

Azithromycin Clinical Effectiveness Data—Based on summed data from clinical trials, monotherapy with azithromycin 1 g cures 97.6% of uncomplicated gonococcal infections of the urethra, cervix, or rectum (95% CI, 95.7%–98.9%), and monotherapy with azithromycin 2 g cures 99.2% of these infections (95% CI, 97.3%–99.9%) (Table 1) [14]. For urethral and cervical infections, a more recent review estimated that the clinical effectiveness of azithromycin 1 g was 96.5% (95% CI, 94.3%–97.6%) if retrospective

studies were excluded and 97.0% (95% CI, 95.2%–97.9%) if retrospective studies were included [15]. The same review estimated that azithromycin 2 g cured 99.0% (95% CI, 97.5%–99.6%) of urethral or cervical infections.

Azithromycin Susceptibility Data—Azithromycin MICs among US GISP isolates appear to have slightly increased from the early 1990s, when the majority of azithromycin clinical studies were conducted, to 2011–2013 (Table 4). However, interpretation of these data is complicated by the use of a new media formulation beginning in 2005, which may have resulted in a one-dilution increase in azithromycin MIC results [48].

The MIC breakpoint that defines resistance or that correlates with clinical treatment failure has not been defined for azithromycin, and CLSI has not established an MIC breakpoint that defines decreased susceptibility to azithromycin. In GISP, isolates with azithromycin MICs ≥2 μg/mL are considered to have elevated MICs [6]. The percentage of GISP isolates with elevated azithromycin MICs has remained <1% (Table 4). However, of concern, sporadic cases of high-level azithromycin resistance (MICs ≥256 μg/mL) have been identified in the United Kingdom, Italy, Argentina, Hong Kong, and the United States [49–54].

Case Reports of Azithromycin Treatment Failures—There have been multiple reports of azithromycin treatment failures since the 1990s, but these are infrequently associated with higher azithromycin MICs and so do not necessarily indicate failure due to antimicrobial resistance [32,55–60]. Urethral and cervical infection treatment failures have been associated with pretreatment azithromycin MICs of 0.06–0.5 μg/mL following treatment with azithromycin 1 g and MICs of 0.25–1 μg/mL following treatment with azithromycin 2 g.

Other Considerations for Azithromycin Dosing—Other considerations for azithromycin include the ease with which *N. gonorrhoeae* develops resistance to macrolides when given as monotherapy. Most recently, a case report documented the rapid emergence of resistance (MIC increased from 1 μg/mL to 8 μg/mL) following a single 2-g dose of azithromycin [60].

In addition, when considering increasing the dual treatment dose of azithromycin from 1 g to 2 g as part of a dual treatment regimen, a tradeoff exists between the possible benefit of increasing the cure rate and the risk of increasing the frequency or severity of adverse effects. Depending on formulation, studies using azithromycin 2 g as a single dose report vomiting in 0.7%–7.0% of patients and gastrointestinal symptoms in up to 24.4%–35.3% [61–63]. In comparison, azithromycin 1 g as a single dose is generally associated with fewer and milder gastrointestinal symptoms, and studies using a 1-g dose report any adverse effect in <10% of patients [55, 56, 59].

Recommendations—The available clinical data indicate that ceftriaxone 250 mg is effective in approximately 99% of uncomplicated urethral, cervical, and rectal gonococcal infections. There are no clinical data to support the administration of ceftriaxone at higher doses than 250 mg. Therefore, dual treatment for gonorrhea that includes ceftriaxone at the

250-mg dose is recommended for the treatment of uncomplicated urethral, cervical, and rectal gonococcal infections.

When azithromycin 1 g is given as part of a dual treatment regimen with ceftriaxone, development and subsequent transmission of azithromycin resistance is unlikely. Therefore, based on the effectiveness of azithromycin 1 g and the increased adverse effects associated with the 2 g dose, azithromycin 1 g should be used when given as part of a dual treatment regimen with ceftriaxone.

Last, given the prevalence of tetracycline resistance among US GISP isolates, doxycycline is no longer recommended for use as the second antimicrobial for treatment of gonococcal infections. The recommended regimen for uncomplicated urethral, cervical, or rectal gonococcal infection is dual treatment with ceftriaxone 250 mg intramuscularly as a single dose and azithromycin 1 g orally as a single dose.

Key Question 2. Should Cefixime or Any Oral Cephalosporin Continue to Be Recommended as an Alternative Treatment for Urethral, Cervical, or Rectal Gonococcal Infections?

In 2012, CDC treatment guidelines were updated so that cefixime was no longer recommended as first-line treatment for gonorrhea [9]. This change was made based on observations that the overall percentage of GISP isolates with elevated cefixime MICs (MIC ≥0.25 μg/mL) had increased from 0.1% in 2006 to 1.5% during January–August 2011. Of particular concern was that the percentage of isolates with elevated cefixime MICs in the West increased from 0.2% to 3.2%, and the percentage among gay, bisexual, and other men who have sex with men (collectively referred to as MSM) in the West increased from 0.1% to 4.5%. Although the cefixime MIC breakpoints that correlate with clinical treatment failure have not been defined, there was concern that this pattern indicated early stages of the development of clinically significant gonococcal resistance to cefixime, and the rising cefixime MICs would soon result in declining effectiveness of cefixime. Additionally, there was concern that, as cefixime became less effective, its use might hasten the development of resistance to ceftriaxone. Although cefixime was no longer included as part of the recommended treatment regimen, CDC continued to list dual treatment with cefixime 400 mg orally as a single dose and either azithromycin 1 g orally as a single dose or doxycycline 100 mg orally twice daily for 7 days as an alternative regimen for gonococcal infections of the urethra, cervix, or rectum when ceftriaxone is not available.

Cefixime Clinical Effectiveness Data—Based on summed data from clinical trials published in the 1980s and 1990s, the effectiveness of cefixime 400 mg for urethral, cervical, and rectal gonococcal infections is 97.5% (95% CI, 95.4%–98.8%) [14]. The only recent data on cefixime effectiveness come from a retrospective analysis of gonococcal infections at any anatomic site (urethral, cervical, rectal, or pharyngeal) that were treated with a variety of cefixime-based regimens (cefixime 400 mg or 800 mg; some patients also received either azithromycin or doxycycline) (Table 1) [20]. Overall, in this analysis cefixime-based regimens cured 93.2% of gonococcal infections among patients who returned for test of cure, but cefixime effectiveness varied depending on cefixime MIC.

Among patients who returned for test of cure, cefixime-based regimens successfully cured 98.1% of infections associated with a cefixime MIC <0.12 μg/mL, but only 75.0% of infections associated with a cefixime MIC ≥0.12 μg/mL (relative risk of treatment failure, 13.1 [95% CI, 2.9–59.7]). The authors also performed a secondary analysis to account for possible bias resulting from limiting the analysis to patients who returned for test of cure. If all patients who were treated were included in the analysis and it was assumed that no treatment failures occurred among those who did not return for tests of cure, cefixime-based regimens cured 99.1% of infections associated with a cefixime MIC <0.12 μg/mL, and 88.1% of infections associated with a cefixime MIC ≥0.12 μg/mL (relative risk of treatment failure 13.8 [95% CI, 2.9–64.5]).

Cefixime Susceptibility Data—The MIC breakpoint that corresponds to cefixime resistance and treatment failure has not been defined, but CLSI defines decreased susceptibility to cefixime as a cefixime MIC ≥0.5 μg/mL [23]. The proportion of US GISP isolates with decreased susceptibility to cefixime (MIC ≥0.5 μg/mL) has remained ≤0.1% (Table 5). In contrast, the proportion of GISP isolates with elevated cefixime MICs (MIC ≥0.25 μg/mL) has increased from 0.1% during 2001–2005 to 0.9% during 2011–2013. The proportion of isolates with MICs ≥0.125 μg/mL, the MIC threshold associated with increased risk of treatment failure [20], increased from 0.7% during 2001–2005 to 2.7% in 2011–2013.

Case Reports of Cefixime Treatment Failures—Globally, cefixime treatment failures following treatment with cefixime 400 mg have generally been associated with cefixime MICs of 0.12–4 μg/mL [20, 30–34] (Table 3). However, at least one study has reported cefixime treatment failures at MICs as low as ≤0.03 μg/mL [20].

Recommendation—Clinical data from a recent retrospective analysis and from documented cefixime treatment failures suggest that gonococcal infections with cefixime MICs ≥0.125 μg/mL are associated with a higher risk of treatment failure compared to those with MICs <0.125 μg/mL. Given the increase in cefixime MICs observed in the last decade, ceftriaxone is clearly preferable to cefixime for the treatment of gonococcal infections. However, there are no data to suggest that the clinical effectiveness of dual treatment with cefixime and azithromycin for urethral, cervical, and rectal gonococcal infections is <95% in the United States. Recognizing that there are circumstances where ceftriaxone is not available or where an injection is not possible, and that treatment with a cefixime-based dual treatment regimen is preferable to no treatment, dual treatment with cefixime 400 mg orally as a single dose and azithromycin 1 g orally as a single dose will continue to be an alternative regimen for the treatment of uncomplicated urethral, cervical, and rectal gonococcal infections when ceftriaxone is not available.

Key Question 3. Should Dual Treatment With Cefixime and Azithromycin Be Recommended for Expedited Partner Therapy (EPT)? Are There Any Data to Support Use of Azithromycin 2 g Over Azithromycin 1 g in Combination With Cefixime for EPT?

The 2012 update to CDC gonorrhea treatment guidelines recommended that EPT be considered for heterosexual partners of a patient with gonorrhea if they cannot be linked to

evaluation and treatment in a timely fashion. In this scenario, EPT using dual treatment with cefixime 400 mg orally as a single dose and azithromycin 1 g orally as a single dose would be delivered to the partner by the patient, a disease investigation specialist, or through a collaborating pharmacy. The legal status of EPT varies by state. EPT has been shown to reduce the rate of reinfection among index patients and increase rates of partner treatment in clinical trials [64]. However, EPT requires an oral regimen, and given recent concerns about the continued effectiveness of cefixime, some have questioned whether the advantages of EPT outweigh the potential increased risk of treatment failures associated with a cefixime-based dual treatment regimen.

In practice, EPT must be prescribed without knowing the partner's complete history of sexual exposure, and there are no population data or estimates of the proportion of partners that are infected at different anatomic sites. It is therefore important to consider the effectiveness of an EPT regimen for urethral, cervical, and rectal infections, as well as pharyngeal infections. The previous question addressed the data on cefixime effectiveness for urethral, cervical, and rectal infections and concluded that dual treatment with cefixime and azithromycin should continue to be listed as an alternative treatment regimen in situations when ceftriaxone is not available (see Key Question 2). For pharyngeal infections, older summed clinical trials data estimate that monotherapy with cefixime 400 mg cures 92.3% (95% CI, 74.9%–95.7%), while ceftriaxone 250 mg cures 99.0% (95% CI, 94.4%–100%) of gonococcal infections of the pharynx (Table 6) [21]. More recent data on the effectiveness of cefixime for pharyngeal infections, and all data on the effectiveness of dual treatment regimens for pharyngeal infections, are limited to retrospective studies among the relatively small subset of persons who returned for test of cure. However, some retrospective data suggest that the effectiveness of dual treatment with an oral cephalosporin (either cefixime 400 mg or cefpodoxime 400 mg) in combination with azithromycin 1 g (93.0%) is comparable to the effectiveness of ceftriaxone 125–250 mg monotherapy (90.9%) or dual treatment with ceftriaxone 125–250 mg and either azithromycin 1 g or doxycycline (88.7%) [65].

Data on the comparative effectiveness of azithromycin 1 g vs azithromycin 2 g as monotherapy, as well as their potential adverse effects, are reviewed elsewhere (see Key Question 1 for urethral, cervical, and rectal infections, and Key Question 7 for pharyngeal infections). There are no data comparing the effectiveness of dual treatment with cefixime and azithromycin 1 g vs dual treatment with cefixime and azithromycin 2 g for gonococcal infections at any anatomic site (Tables 1 and 6).

Recommendation—EPT increases rates of partner treatment and reduces reinfections among index patients. Although there are concerns about the effectiveness of cefixime-based regimens for the potential treatment of pharyngeal infection when used as EPT, these are outweighed by concerns that failure to use EPT will result in fewer partners receiving treatment. Based on these considerations, as well as the data presented in Key Question 2 that support continued use of dual treatment with cefixime and azithromycin as an alternative regimen for urethral, cervical, and rectal infections in settings where ceftriaxone is not available, dual treatment with cefixime 400 mg orally as a single dose and azithromycin 1 g orally as a single dose will continue to be recommended for EPT.

Key Question 4. Are There Any Other Drugs or Drug Regimens Besides Those Listed in the 2012 Update to the Treatment Guidelines That Can Be Recommended as First-line or Alternative Treatment for Gonorrhea?

At the time of the guidelines meeting, a literature search of studies published since 2008 did not identify any clinical trials for novel gonorrhea treatment regimens (Table 1). A systematic review of previously published clinical trials of gentamicin calculated that intramuscular gentamicin 240 mg or 280 mg had a pooled cure rate of 91.5% (95% CI, 88.1%–94.0%) [18] for urethral or cervical infection, lower than the CDC clinical effectiveness criterion. In addition, 2 studies assessed the clinical effectiveness of intramuscular spectinomycin 2 g for urogenital infection, and reported cure rates of 94% and 96.7% [16,19]. These data are consistent with older summed clinical trials data which estimate that the clinical effectiveness of spectinomycin is 98.2% (95% CI, 97.6%–99.9%) for urethral, cervical, and rectal gonococcal infections [21]. However, spectinomycin has poor efficacy against pharyngeal infection (51.8% [95% CI, 38.7%–64.9%]) (Table 6) [21], and is not currently available in the United States.

Following the guidelines meeting, the results of a clinical trial evaluating 2 new dual treatment regimens (dual treatment with gemifloxacin 320 mg orally as a single dose and azithromycin 2 g orally as a single dose, or dual treatment with gentamicin 240 mg intramuscularly as a single dose and azithromycin 2 g orally as a single dose) were published [8]. For urethral and cervical infections, this trial demonstrated that dual treatment with gemifloxacin and azithromycin cured 99.5% of infections (lower 95% CI bound, 97.6%) and dual treatment with gentamicin and azithromycin cured 100% of infections (lower 95% CI, bound 98.5%). Dual treatment with gemifloxacin and azithromycin also cured 15 of 15 pharyngeal and 5 of 5 rectal infections; dual treatment with gentamicin and azithromycin cured 10 of 10 pharyngeal and 1 of 1 rectal infections. Gastrointestinal adverse events were common with both regimens. Overall, 7.7% of patients given dual treatment with gemifloxacin and azithromycin and 3.3% of patients given dual treatment with gentamicin and azithromycin vomited within 1 hour of medication administration, necessitating retreatment with a different regimen.

Since 2008, there have been many published studies of in vitro activity of various agents against *N. gonorrhoeae*. Few agents have showed enough promise to warrant clinical trials. Notable agents tested in vitro include solithromycin [69, 70], delafloxacin and other novel quinolones [71–75], ertapenem [76], and novel carbapenems [77]. Of these, only solithromycin and delafloxacin have progressed to phase 3 clinical trials (ClincalTrials.gov identifiers and , respectively).

Recommendation—Based on data that became available after the treatment guidelines meeting, 2 new dual treatment regimens (dual treatment with gemifloxacin 320 mg orally as a single dose and azithromycin 2 g orally as a single dose, or dual treatment with gentamicin 240 mg intramuscularly as a single dose and azithromycin 2 g orally as a single dose) may be considered as alternative treatment options, but gastrointestinal adverse events may limit their use. Because of limited data on the effectiveness of these regimens for rectal and pharyngeal infections, and because of the frequency of gastrointestinal adverse events

associated with these regimens, dual treatment with cefixime 400 mg orally as a single dose and azithromycin 1 g orally as a single dose is the preferred alternative regimen for urethral, cervical, and rectal infections if ceftriaxone is not available and the patient is not allergic to cephalosporins.

Key Question 5. What Regimen Should Be Recommended for Persons Who Fail Treatment With the Recommended Regimen (Dual Treatment With Ceftriaxone 250 mg and Azithromycin 1 g)?

Few ceftriaxone treatment failures have been identified worldwide (Table 3). Therefore, only minimal clinical experience is available to guide treatment recommendations for treatment failures following the recommended regimen. All documented ceftriaxone treatment failures have been pharyngeal infections, and have successfully resolved with either repeated or higher doses of ceftriaxone, dual treatment with ceftriaxone 250 mg and azithromycin 1 g, or single-dose azithromycin 2 g [36–41]. Urethral or rectal infections associated with high ceftriaxone MICs (1–2 μg/mL) resolved after treatment with either gentamicin, a course of levofloxacin followed by a multiday course of azithromycin, or a course of doxycycline.

When available, antimicrobial susceptibility results may guide treatment decisions. Other regimens recently demonstrated to have high clinical effectiveness, such as dual treatment with gemifloxacin and azithromycin or dual treatment with gentamicin and azithromycin (see Key Question 4) [8], may be of use in the management of ceftriaxone treatment failures.

Recommendation—Because the majority of suspected treatment failures are actually reinfections, persons with suspected treatment failure following treatment with the recommended regimen (dual treatment with ceftriaxone 250 mg intramuscularly as a single dose and azithromycin 1 g orally as a single dose) should usually be re-treated with the same regimen. However, in situations with a higher likelihood of treatment failure than reinfection, clinicians should (1) culture relevant clinical specimens and obtain antimicrobial susceptibility testing of any *N. gonorrhoeae* isolates, and advise the laboratory to retain the isolate(s) for possible further testing; (2) consult an infectious disease specialist, an STD/HIV Prevention Training Center clinical expert, the local or state health department, or CDC for advice on obtaining cultures, obtaining antimicrobial susceptibility testing, and treatment; and (3) report the case to CDC via the state or local health department. Clinicians may consider treating these patients with either dual treatment with gemifloxacin 320 mg orally as a single dose and azithromycin 2 g orally as a single dose, or dual treatment with gentamicin 250 mg intramuscularly as a single dose and azithromycin 2 g orally as a single dose. Clinicians should also obtain a test of cure at the relevant anatomic site 7–14 days after retreatment. Culture is the recommended test for test of cure, preferably with simultaneous nucleic acid amplification test (NAAT). Antimicrobial susceptibility testing should be performed if *N. gonorrhoeae* is isolated. All sex partners from the preceding 60 days should be evaluated promptly with culture and presumptively treated with the same regimen as the patient.

Key Question 6. What Regimens Should Be Recommended for the Treatment of Uncomplicated Urethral, Cervical, or Rectal Infection in Persons With Severe Cephalosporin Allergy?

At the time of the treatment guidelines meeting, the only available treatment option for patients with severe cephalosporin allergy that met CDC clinical effectiveness criteria was monotherapy with azithromycin 2 g [9, 46]. Following the treatment guidelines meeting, the results of a clinical trial demonstrating the effectiveness of dual treatment with gemifloxacin 320 mg orally as a single dose and azithromycin 2 g orally as a single dose or dual treatment with gentamicin 240 mg intramuscularly as a single dose and azithromycin 2 g orally as a single dose were published (see Key Question 4) [8].

Recommendation—Given new data on the clinical effectiveness of 2 new dual treatment regimens (see Key Question 4) and the theoretical benefit of dual treatment using antimicrobials with different mechanisms of action (see Key Question 1), azithromycin 2 g is no longer recommended as an alternative regimen for persons with severe cephalosporin allergy. Dual treatment with gemifloxacin 320 mg orally as a single dose and azithromycin 2 g orally as a single dose, or dual treatment with gentamicin 240 mg intramuscularly as a single dose and azithromycin 2 g orally as a single dose are potential therapeutic options for these patients.

Key Question 7. Are Current Recommendations Sufficient for Pharyngeal Gonococcal Infection?

At the time of the guidelines meeting, the current (2012) recommendation for uncomplicated gonococcal infections of the pharynx was dual treatment with ceftriaxone 250 mg intramuscularly as a single dose and either azithromycin 1 g orally as a single dose or doxycycline 100 mg orally twice daily for 7 days [9]. Azithromycin was preferred over doxycycline as the second antimicrobial because of the high prevalence of tetracycline resistance among GISP isolates. There were no alternative regimens listed for treatment of pharyngeal infection.

Clinical Effectiveness Data—Gonococcal infections of the pharynx are more difficult to eradicate than infections of the urethra, cervix, or rectum [29], and few antimicrobial regimens reliably cure >90% of gonococcal pharyngeal infections (Table 6). According to summed data from clinical trials published in the 1980s and 1990s, ceftriaxone 250 mg eradicates 99.0% (95% CI, 94.4%–100%) of pharyngeal infections [21]. Prospective clinical trials data on azithromycin effectiveness for pharyngeal infections are particularly sparse. Older summed clinical trials data have estimated that the clinical effectiveness of azithromycin 1 g is 100% (95% CI, 29.2%–100%) and the effectiveness of azithromycin 2 g is 100% (95% CI, 82.3%–100%), but these estimates were based on only 3 and 19 infections, respectively [13, 21]. A more recent systematic review found that azithromycin 1 g cured 100% (7/7) and azithromycin 2 g cured 97.5% (39/40) of pharyngeal infections [15].

Review of the literature published since 2008 identified just 2 new prospective clinical trials with data on pharyngeal infections. A clinical trial of ceftriaxone 1 g demonstrated 100% effectiveness in 25 of 25 patients [17]. In a second trial, dual treatment with gemifloxacin

320 mg and azithromycin 2 g cured 100% (15/15) of pharyngeal infections and dual treatment with gentamicin 240 mg and azithromycin 2 g cured 100% (10/10) pharyngeal infections [8]. Unfortunately, gastrointestinal adverse events were commonly associated with both dual treatment regimens, potentially limiting their routine use (see Key Question 4).

Several retrospective analyses have attempted to describe the effectiveness of various regimens for the treatment of gonococcal infections of the pharynx [65,67,68] (Table 6). Overall, dual treatment regimens that include either ceftriaxone or cefixime and azithromycin compare favorably to other regimens evaluated in these analyses. However, interpretation of these data is complicated by limitations associated with retrospective studies; data were restricted to the subset of patients who returned for test of cure, and there were relatively small numbers of infections evaluated for some treatment regimens. In addition, most of these analyses did not report whether patients had been reexposed between treatment and test of cure, so it is possible some apparent treatment failures in these studies were actually reinfections.

Case Reports of Ceftriaxone Treatment Failure—Pharyngeal infection treatment failures following treatment with ceftriaxone 250–500 mg monotherapy have been reported from Australia [36, 40], Sweden [39], and Slovenia [41], and were associated with ceftriaxone MICs 0.03–0.25 μg/mL (Table 3). In addition, a pharyngeal infection treatment failure following treatment with ceftriaxone 1 g monotherapy was documented in Japan in 2009 and was associated with ceftriaxone MICs of 2–4 μg/mL [37, 38].

Recommendation—There are insufficient data to suggest that any treatment regimen for gonococcal infections of the pharynx is more effective than dual treatment with ceftriaxone 250 mg and azithromycin 1 g. There are no data comparing the effectiveness of azithromycin 1 g vs 2 g when used in combination with ceftriaxone for treatment of pharyngeal infections. Although newer dual treatment regimens (ie, dual treatment with gemifloxacin and azithromycin or dual treatment with gentamicin and azithromycin) appear promising, there are insufficient data on the effectiveness of these regimens for pharyngeal infections, and the adverse effects associated with these regimens may limit their use in practice. Therefore, dual treatment with ceftriaxone 250 mg intramuscularly as a single dose and azithromycin 1 g orally as a single dose is the recommended regimen for uncomplicated infections of the pharynx.

Key Question 8. Are Current Treatment Recommendations Sufficient for Disseminated Gonococcal Infection?

At the time of the guidelines meeting, the recommended treatment regimen for disseminated gonococcal infection (DGI) without evidence of meningitis or endocarditis was ceftriaxone 1 g given intramuscularly or intravenously every 24 hours [46]. This regimen was to be continued for 24–48 hours after clinical improvement begins, at which time therapy could be switched to oral cefixime 400 mg twice daily to complete at least 1 week of antimicrobial therapy.

There are no recent studies published on the treatment of DGI. No treatment failures have been reported following treatment with the above regimens.

Recommendation—Given the absence of data on the topic, DGI recommendations are based on expert opinion. Owing to growing concerns over gonococcal antimicrobial resistance, all persons with suspected DGI should have relevant clinical specimens collected for gonococcal culture, and if positive, gonococcal antimicrobial susceptibility testing. Treatment for DGI should be guided by the results of antimicrobial susceptibility testing. Pending antimicrobial susceptibility results, treatment decisions should be made on the basis of clinical presentation. The duration of treatment for DGI has not been systematically studied and should be determined in consultation with an infectious disease specialist.

For DGI without meningitis or endocarditis, the recommended treatment is ceftriaxone 1 g intramuscularly or intravenously every 24 hours plus azithromycin 1 g orally as a single dose. Clinicians may consider switching to an oral agent 24–48 hours after substantial improvement, but choice of oral antimicrobial should be guided by the results of antimicrobial susceptibility testing. The total duration of antimicrobial treatment should be at least 7 days.

For gonococcal meningitis or endocarditis, the recommended treatment is ceftriaxone 1–2 g intravenously every 12–24 hours and azithromycin 1 g orally in a single dose. Parenteral treatment for meningitis should be continued for 10–14 days. Parenteral treatment for endocarditis should be continued for at least 4 weeks.

Key Question 9. Should a Test of Cure Be Performed After Treatment for Gonococcal Infection? If so, Then What Test Should Be Used for Test of Cure and How Soon After Treatment Should Test of Cure Be Performed?

In the 2012 update to the gonorrhea treatment guidelines, test of cure was recommended for (1) persons treated with an alternative regimen and (2) persons with suspected treatment failure following treatment with the recommended regimen [9]. For persons treated with an alternative regimen, test of cure using culture or NAAT was recommended 1 week after completion of treatment. For patients with suspected treatment failure, culture and antimicrobial susceptibility testing was recommended to document persistent infection and guide therapy, and test of cure was recommended 1 week after completion of retreatment.

Use of Culture Versus NAAT for Test of Cure—The use of culture for test of cure facilitates antimicrobial susceptibility testing. However, the sensitivity of NAATs for detection of *N. gonorrhoeae* is superior to culture [78–84]. In practice, gonococcal culture is not readily available, and it is likely that NAATs will be used for test of cure in most settings.

Timing of Test of Cure—Test of cure using NAATs is complicated by the fact that residual nucleic acid from nonviable bacteria can be detected by NAATs for a period of time after successful treatment. There are few data on the duration of persistent *N. gonorrhoeae* nucleic acid after successful treatment. One study, using a ligase chain reaction (LCR) test that is no longer marketed in the United States, found the median time to a negative urine LCR test was 1 day for men and 2 days for women [85]. In this study, >90% of tests were negative on day 5 after treatment, but 18% of patients continued to have intermittent shedding of gonococcal nucleic acids after their first negative test. A second study, using an

in-house *porA* pseudogene polymerase chain reaction test, asked persons with urogenital gonorrhea to return for test of cure 4–7 days after treatment and found that 84% (16/19) of those who returned during this interval had a negative test [86]. Of patients with positive tests of cure, 2 had a negative test when they returned on day 11, and one did not return until day 19, at which time his test was negative. The third and most recent study with data on test of cure evaluated the APTIMA Combo 2 Assay and evaluated MSM who returned for test of cure 3–21 days after treatment [87]. In this study, tests of cure were positive in no (0/95) urethral infections, 7.4% (10/135) of rectal infections, and 5.2% (7/134) of pharyngeal infections. All positive rectal tests of cure were among persons who were tested within 14 days of treatment; all positive pharyngeal tests of cure were among persons who were tested within 10 days of treatment. Together, these results suggest that residual DNA typically clears from the urogenital site within 7 days, but may persist for longer at extragenital sites.

Recommendation—Culture or NAAT can be used for test of cure. In practice, it is likely that NAATs will be used for test of cure in most settings. If a NAAT test of cure is positive, every effort should be made to obtain confirmatory culture before retreatment, and all positive test of cure cultures should undergo antimicrobial susceptibility testing.

Given the evidence that dual treatment with the alternative treatment regimen (cefixime 400 mg and azithromycin 1 g) is most likely ≥95% effective for treatment of urethral, cervical, or rectal infections (see Key Question 2) as well as concerns about a low positive predictive value of NAAT tests of cure, routine test of cure for persons diagnosed with urogenital or rectal gonorrhea who are treated with the alternative regimen is not recommended. However, because of concerns over cefixime's effectiveness at the pharyngeal site (see Key Question 3), test of cure is recommended for persons diagnosed with pharyngeal infection who are treated with the alternative regimen. Test of cure is also recommended for persons with suspected treatment failure at any anatomic site of infection.

Based on the limited data on appropriate timing of test of cure using NAATs, test of cure should be performed 14 days after treatment in the setting of pharyngeal infections treated with the alternative regimen and 7–14 days after retreatment in the setting of suspected treatment failure.

RESEARCH PRIORITIES

Further research is needed to inform future recommendations for the optimal management of gonorrhea. Research priorities identified at the 2013 meeting included (1) evaluation of novel oral antimicrobials or novel combinations of antimicrobials for treatment of gonorrhea; (2) pharmacokinetic models for ceftriaxone and azithromycin in the treatment of gonorrhea at urethral, cervical, rectal, and pharyngeal sites; and (3) evaluation of transport media for gonococcal culture, to facilitate access to gonococcal culture and antimicrobial susceptibility testing.

SUMMARY

Dual treatment with ceftriaxone 250 mg intramuscularly as a single dose and azithromycin 1 g orally as a single dose is recommended for the treatment of uncomplicated gonorrhea of the urethra, cervix, rectum, or pharynx. For urethral, cervical, and rectal infections, dual treatment with cefixime 400 mg orally as a single dose and azithromycin 1 g orally as a single dose may be used as an alternative regimen when ceftriaxone is not available. Owing to the high prevalence of tetracycline resistance in the United States, doxycycline is no longer recommended as a second antimicrobial in either the first-line or alternative dual treatment regimen. Test of cure will continue to be recommended for persons with pharyngeal infection who receive an alternative treatment regimen, but is no longer recommended for persons with urethral, cervical, or rectal infection who are treated with the alternative regimen. Based on recent data demonstrating the effectiveness of 2 new dual treatment regimens (dual treatment with either gemifloxacin 320 mg orally as a single dose and azithromycin 2 g orally as a single dose, or dual treatment with gentamicin 240 mg intramuscularly as a single dose and azithromycin 2 g orally as a single dose), these regimens may be considered for persons with cephalosporin allergy or for those persons who fail treatment following the recommended regimen. Monotherapy with azithromycin 2 g orally as a single dose is no longer recommended for patients with cephalosporin allergy. Further research to identify new antimicrobials or new combinations of antimicrobials for the treatment of gonorrhea, particularly oral regimens, is urgently needed.

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Table 1.

Clinical Effectiveness Data for the Treatment of Uncomplicated Gonococcal Infections of the Urethra, Cervix, or Rectum

Antimicrobial Regimen, Reference	Geographic Location, Year of Study	Anatomic Site of Infection	Study Design	Percentage (no./No.) Cured
New (published in 2008 or later) studies evaluating single drug regimens				
Azithromycin				
1 g PO[15]	Multiple	Urethra or cervix	Systematic review and meta-analysis of clinical studies	Excluding retrospective data: 96.5% (520/539); 95% CI, 94.3%–97.6% Including retrospective data: 97.0% (688/709); 95% CI, 95.2%–97.9%
2g PO [15]	Multiple	Urethra or cervix	Systematic review and meta-analysis of clinical studies	99.0% (392/396); 95% CI, 97.5%–99.6%
1–2gPO[15]	Multiple	Rectum	Systematic review and meta-analysis of clinical studies	97.1% (34/35)
Ceftriaxone				
500 mg IM [16]	Saudi Arabia, 2003–2004	Urethra or cervix	Randomized clinical trial	90% (90/100)[a]
1 g IV [17]	Japan, 2004–2006	Urethra or cervix	Clinical trial	100% (48/48)
Ciprofloxacin				
500 mg PO [16]	Saudi Arabia, 2003–2004	Urethra or cervix	Randomized clinical trial	80% (80/100)[a]
Gentamicin				
240 mg or 280 mg IM [18]	Multiple	Urethra or cervix	Systematic review and meta-analysis of clinical studies	91.5%; 95% CI, 88.1%–94.0%
Spectinomycin				
2g IM [16]	Saudi Arabia, 2003–2004	Urethra or cervix	Randomized clinical trial	94% (94/100)[a]
2glM[19]	Japan, 2004–2006	Urethra	Clinical trial	96.7% (203/210)
New(published in 2008 or later) studies evaluating combination drug regimens				
Cefixime ± doxycycline or azithromycin				
Cefixime 400 mg or 800 mg PO ± doxycycline or azithromycin PO [20]	Canada, 2010–2011	Urethra, cervix, rectum, or pharynx	Retrospective analysis	Overall: 93.2% (124/133); If MIC ≥0.12 μg/mL: 75% (21/28); If MIC<0.12μg/mL: 98.1% (103/105)
Gemifloxacin + azithromycin				
Gemifloxacin 320 mg PO + azithromycin 2 g PO [8]	United States, 2010–2012	Urethra or cervix	Randomized clinical trial	99.5% (198/199); lower 1-sided exact CI bound 97.6%
Gemifloxacin 320 mg PO + azithromycin 2 g PO [8]	United States, 2010–2012	Rectum	Randomized clinical trial	100% (5/5)

Antimicrobial Regimen, Reference	Geographic Location, Year of Study	Anatomic Site of Infection	Study Design	Percentage (no./No.) Cured
Gentamicin + azithromycin				
Gentamicin 240 mg IM + azithromycin 2 g PO [8]	United States, 2010–2012	Urethra or cervix	Randomized clinical trial	100% (202/202); lower 1-sided exact CI bound 98.5%
Gentamicin 240 mg IM + azithromycin 2 g PO [8]	United States, 2010–2012	Rectum	Randomized clinical trial	100% (1/1)
Older(published prior to 2008) summed clinical trials data on selected antimicrobials				
Azithromycin				
1 g PO[14]	Multiple	Urethra, cervix, or rectum	Systematic review and meta-analysis of clinical trials	97.6% (411/421); 95% CI, 95.7%–98.9%
2g PO[14]	Multiple	Urethra, cervix, or rectum	Systematic review and meta-analysis of clinical trials	99.2% (262/264); 95% CI, 97.3%–99.9%
Cefixime				
400 mg PO [14]	Multiple	Urethra, cervix, or rectum	Systematic review and meta-analysis of clinical trials	97.5% (386/396); 95% CI, 95.4%–98.8%
800 mg PO [14]	Multiple	Urethra, cervix, or rectum	Systematic review and meta-analysis of clinical trials	98.0% (241/246); 95% CI, 95.3%–99.3%
Ceftriaxone				
125mglM[21]	Multiple	Urethra, cervix, or rectum	Systematic review and meta-analysis of clinical trials	98.9%; 95% CI, 97.9%–99.8%
250 mg IM [21, 13]	Multiple	Urethra, cervix, or rectum	Systematic review and meta-analysis of clinical trials	99.2% (2248/2267); CI, 98.8%–99.5%

Abbreviations: CI, confidence interval; IM, intramuscularly; IV, intravenously; MIC, minimum inhibitory concentration; PO, orally.

[a]Failure defined as persistence of symptoms with presence of gram-negative diplococci and pus on day 5 following treatment; no comment on evaluation for reexposure.

Table 2.

Ceftriaxone Minimum Inhibitory Concentrations in the Gonococcal Isolate Surveillance Project, United States, 1987–2013

Time Period	MIC_{50}, µg/mL	MIC_{90}, µg/mL	Maximum MIC, µg/mL	% With MIC ≥0.125 µg/mL	% With MIC ≥0.5 µg/mL
1987–1990	0.004	0.015	0.5	0.6	<0.1
1991–1995	0.004	0.015	0.5	0.5	<0.1
1996–2000	0.004	0.015	0.5	0.3	<0.1
2001–2005	0.004	0.015	0.25	0.1	0
2006–2010	0.008	0.015	0.25	0.2	0
2011–2013	0.008	0.015	0.5	0.2	<0.1

Source: Gonococcal Isolate Surveillance Project, unpublished data.

Abbreviations: MIC_{50}, minimum concentration needed to inhibit 50% of isolates; MIC_{90}, minimum concentration needed to inhibit 90% of isolates.

Table 3.

Cefixime Treatment Failures, Ceftriaxone Treatment Failures, and Additional Reports of High-Level Cefixime or Ceftriaxone Resistance

Year Identified, Reference	Country (Sample)	Failed Regimen	Anatomic Site	Resolution	Cefixime MIC, μg/mL	Ceftriaxone MIC, μg/mL
Cefixime treatment failures						
1999–2001 [27]	Japan (n = 8)	Cefixime 200 mg PO × 2, 6 h apart	Urethra	Cured with ceftriaxone or spectinomycin, doses not specified	0.125 (n = 5) 0.25 (n = 3)	Not reported
2002–2003 [28]	Japan (n =4)	Cefixime 200 mg PO twice daily × 3 d	Urethra	Cured with ceftriaxone 1 g IV × 1 (n = 3) or lost to follow-up (n = 1)	0.5 (n = 2) 1 (n = 2)	0.125 (n = 2) 0.25 (n = 1) 0.25–0.5 (n = 1)
1995–2007 [29]	Canada (n = 10)[a]	Cefixime 400 mg PO × 1 plus azithromycin 1 g PO × 1 (n = 5); Cefixime 400 mg PO × 1 (n = 2); Cefixime 800 mg PO × 1 (n = 3)	Pharynx	Cured with 2nd course cefixime (n =4), ofloxacin (n =4), 3rd course of cefixime (n = 1), or lost to follow-up (n= 1)	"Susceptible" (not defined)	"Susceptible" (not defined)
Not reported [30]	United Kingdom (n = 1)	Cefixime 400 mg PO × 1 plus azithromycin 1 g PO × 1	Urethra	Cured with ceftriaxone 500 mg IM × 1	≥0.25	≤0.12
2010 [31]	Norway (n = 2)	Cefixime 400 mg PO × 1	Urethra	Cured with ceftriaxone 500 mg IM × 1	0.25–0.5 (n = 1) 0.5 (n = 1)	0.125
2010 [32]	United Kingdom (n = 2)	Cefixime 400 mg PO × 1 (n = 1); Cefixime 400 mg PO × 1 plus doxycycline 100 mg PO twice daily × 7d(n = 1)	Urethra	Cured with ceftriaxone 250 mg IM × 1	0.19 (n = 1) 0.25 (n = 1)	0.047–0.064 (n = 1) 0.064 (n = 1)
2010 [33]	France (n = 1)	Cefixime 200 mg PO × 2, 6 h apart	Urethra	Cured with gentamicin 160 mg IM × 1	4	1–2
2011 [34]	Austria (n = 1)	Cefixime 400 mg PO daily × 7 d, then cefixime 400 mg PO daily × 14 d	Urethra	Cured with azithromycin 2 g PO × 1	1	0.5
2010–2011 [20]	Canada (n = 7)	Cefixime 400 mg PO × 1 plus doxycycline 100 mg PO twice daily × 7d (n=4)[b]; Cefixime 400 mg PO × 1 (n = 3)[c]	Urethra (n = 4); Pharynx (n = 1); Rectum (n = 2)	Cured with ceftriaxone 250 mg IM × 1 (n = 4) or cefixime 800 mg PO × 1 (n = 3)	≤0.03 (n = 1) 0.06 (n = 1) 0.06–0.12 (n = 1) 0.12 (n=4)	≤0.03 (n = 1) ≤0.03–0.06 (n = 2) 0.06 (n = 3) 0.06–0.12 (n = 1)
2010–2011 [20]	Canada (n = 2)	Cefixime 800 mg PO × 1 plus azithromycin 1 g PO × 1 (n = 1); Cefixime 800 mg PO × 1 (n = 1)[d]	Pharynx (n = 1); Rectum (n = 1)	Cured with ceftriaxone 250 mg IM × 1	0.06–0.12 (n = 1) 0.12 (n = 1)	≤0.03–0.06 (n = 2)
2012 [35]	South Africa (n = 1)	2 courses of cefixime 400 mg PO × 1	Urethra	Retreated with ceftriaxone 2 g IV × 1, but lost to follow-up	0.25	0.064
Ceftriaxone treatment failures:						
2007 [36]	Australia (n = 2)	Ceftriaxone 250 mg IM × 1	Pharynx	Retreated with azithromycin 1 g PO × 1, then ceftriaxone 500 mg IM × 1, but no repeat test of cure (n = 1); cured with ceftriaxone 1 g IM × 1 (n = 1)	Not reported	0.016 (n = 1) 0.03 (n = 1)

Year Identified, Reference	Country (Sample)	Failed Regimen	Anatomic Site	Resolution	Cefixime MIC, µg/mL	Ceftriaxone MIC, µg/mL
2009 [37, 38]	Japan (n = 1)	Ceftriaxone 1 g IV × 1	Pharynx	Retreated with 2nd dose of ceftriaxone (dose not specified); test of cure 2–3 mo later was negative	8	2–4
2010 [39]	Sweden (n = 1)	Ceftriaxone 250 mg IM × 1, then ceftriaxone 500 mg IM × 1	Pharynx	Cured with ceftriaxone 1 g IV × 1	0.5	0.125–0.25
2010 [40]	Australia (n = 1)	Ceftriaxone 500 mg IM × 1	Pharynx	Cured with azithromycin 2 g PO × 1	Not reported	0.03–0.06
2011 [41]	Slovenia (n = 1)	Ceftriaxone 250 mg IM × 1	Pharynx	Received doxycycline 100 mg PO twice daily × 7 d, then retreated with ceftriaxone 250 mg IM plus azithromycin 1 g PO × 1; test of cure 4–5 mo later was negative	0.25	0.125
Additional reports of high-level cefixime or ceftriaxone resistance:						
2011 [42, 43]	Spain (n = 2)		Urethra (n = 1) Rectum (n = 1)	Treated with doxycycline 100 mg PO twice daily × 7 d, symptoms resolved, but no test of cure performed (n = 1); Cured with levofloxacin 500 mg PO daily × 7 d, followed by azithromycin 500 mg PO daily × 3 d (n = 1)	1.5	1.5

Abbreviations: IM, intramuscularly; IV, intravenously; MIC, minimum inhibitory concentration; PO, orally.

[a] Pretreatment and posttreatment isolates from 2 of these cases had discordant antibiograms, suggesting that these 2 cases were reinfections, not treatment failures.

[b] One urethral infection originally treated with cefixime 400 mg and doxycycline also failed retreatment with cefixime 400 mg PO × 1.

[c] One rectal infection originally treated with cefixime 400 mg PO × 1 also failed retreatment with cefixime 800 mg Po × 1.

[d] This rectal infection, originally treated with cefixime 800 mg, also failed retreatment with cefixime 400 mg PO × 1 plus doxycycline 100 mg PO twice daily × 7 days.

Table 4.

Azithromycin Minimum Inhibitory Concentrations in the Gonococcal Isolate Surveillance Project, United States, 1992–2013

Time Period	MIC_{50}, µg/mL	MIC_{90}, µg/mL	Maximum MIC, µg/mL	% with MIC ≥2 µg/mL
1992–1995	0.125	0.25	2.0	0.01
1996–2000	0.125	0.25	8.0	0.1
2001–2005	0.125	0.25	16.0	0.3
2006–2010	0.25	0.5	16.0	0.3
2011–2013	0.25	0.5	256.0	0.4

In 2005, the Gonococcal Isolate Surveillance Project began using a new media formulation for azithromycin susceptibility testing, which resulted in a one-dilution increase in azithromycin MICs.

Source: Gonococcal Isolate Surveillance Project, unpublished data.

Abbreviations: MIC_{50}, minimum concentration needed to inhibit 50% of isolates; MIC_{90}, minimum concentration needed to inhibit 90% of isolates.

Table 5.

Cefixime Minimum Inhibitory Concentrations in the Gonococcal Isolate Surveillance Project, United States, 1992–2013

Time Period	MIC_{50}, µg/mL	MIC_{90}, µg/mL	Maximum MIC, µg/mL	% With MIC ≥0.125 µg/mL	% With MIC ≥0.25 µg/mL	% With MIC ≥0.5 µg/mL
1992–1995	0.015	0.06	2.0	3.3	0.6	0.1
1996–2000	0.015	0.06	1.0	2.2	0.3	<0.1
2001–2005	0.008	0.03	0.5	0.7	0.1	<0.1
2006, 2009–2010[a]	0.015	0.03	0.5	1.8	0.7	0.1
2011–2013	0.015	0.03	1.0	2.7	0.9	<0.1

Source: Gonococcal Isolate Surveillance Project, unpublished data.

Abbreviations: MIC_{50}, minimum concentration needed to inhibit 50% of isolates; MIC_{90}, minimum concentration needed to inhibit 90% of isolates.

[a]Cefixime susceptibility testing was not conducted during 2007–2008.

Table 6.

Clinical Effectiveness Data for the Treatment of Uncomplicated Gonococcal Infections of the Pharynx

Antimicrobial Regimen, Reference	Geographic Location, Year of Study	Anatomic Site of Infection	Study Design	Percentage (no./No.) Cured
New (published in 2008 or later) studies evaluating single drug regimens				
Azithromycin				
1–2 g PO [65]	United States, 1999–2011	Pharynx	Retrospective analysis	86.9% (13/15)
1–2 g PO [15]	Multiple	Pharynx	Systematic review and meta-analysis of clinical studies	97.9% (46/47)
Cefixime				
400 mg PO [65]	United States, 1999–2011	Pharynx	Retrospective analysis	79.2% (19/24)
400 mg PO [66]	United Kingdom, 2001–2008	Pharynx	Retrospective analysis	100% (27/27)
400 mg PO [67]	United Kingdom, 2004–2007	Pharynx	Retrospective analysis	87.6% (14/16)
400 mg PO or ofloxacin 400 mg PO [29]	Canada, 1995–2007	Pharynx	Retrospective analysis	91% (111/122)
Cefpodoxime				
400 mg PO	United States, 1999–2011	Pharynx	Retrospective analysis	63.6% (21/33)
Ceftriaxone				
125–250 mg IM [65]	United States, 1999–2011	Pharynx	Retrospective analysis	90.9% (40/44)
250 mg IM [67]	United Kingdom, 2004–2007	Pharynx	Retrospective analysis	88.2% (15/17)
1 g IV [17]	Japan, 2004–2006	Pharynx	Clinical trial	100% (25/25)
New (published in 2008 or later) studies evaluating combination drug regimens				
Cefixime + azithromycin				
Cefixime 400 mg PO + azithromycin 1 g PO [65]	United States, 1999–2011	Pharynx	Retrospective analysis	94.0% (47/50)
Cefixime 400 mg PO + azithromycin 1 g PO [67]	United Kingdom, 2004–2007	Pharynx	Retrospective analysis	100% (24/24)
Cefixime 400 mg PO ± azithromycin 1 g PO [68]	United Kingdom, 2003–2005	Pharynx	Retrospective analysis	97.8% (44/45)
Cefixime + doxycycline				
Cefixime 400 mg PO + doxycycline 100 mg PO twice daily × 7 d [65]	United States, 1999–2011	Pharynx	Retrospective analysis	71.0% (22/31)
Cefixime 400 mg PO + doxycycline 100 mg PO twice daily × 7 d [67]	United Kingdom, 2004–2007	Pharynx	Retrospective analysis	73.3% (11/15)
Cefpodoxime + azithromycin				
Cefpodoxime 400 mg PO + azithromycin 1 g PO [65]	United States, 1999–2011	Pharynx	Retrospective analysis	92.3% (60/65)
Cefpodoxime + doxycycline				

Antimicrobial Regimen, Reference	Geographic Location, Year of Study	Anatomic Site of Infection	Study Design	Percentage (no./No.) Cured
Cefpodoxime 400 mg PO + doxycycline 100 mg PO twice daily × 7d [65]	United States, 1999–2011	Pharynx	Retrospective analysis	54.5% (6/11)
Ceftriaxone + azithromycin				
Ceftriaxone 125–250 mg IM + azithromycin 1 g PO [65]	United States, 1999–2011	Pharynx	Retrospective analysis	88.3% (53/60)
Ceftriaxone 250 mg IM + azithromycin 1 g PO [67]	United Kingdom, 2004–2007	Pharynx	Retrospective analysis	100% (5/5)
Ceftriaxone + doxycycline				
Ceftriaxone 125–250 mg IM + doxycycline 100 mg PO twice daily × 7 d [65]	United States, 1999–2011	Pharynx	Retrospective analysis	100% (2/2)
Ceftriaxone 125–250 mg IM + doxycycline 100mg PO twice daily × 7 d [67]	United Kingdom, 2004–2007	Pharynx	Retrospective analysis	90.9% (10/11)
Gemifloxacin + azithromycin				
Gemifloxacin 320 mg PO + azithromycin 2 g PO [8]	United States, 2010–2012	Pharynx	Randomized clinical trial	100% (15/15)
Gentamicin + azithromycin				
Gentamicin 240 mg IM + azithromycin 2 g PO [8]	United States, 2010–2012	Pharynx	Randomized clinical trial	100% (10/10)
Older (published prior to 2008) summed clinical trials data on selected antimicrobials				
Azithromycin				
1 g PO [13]	Multiple	Pharynx	Systematic review and meta-analysis of clinical trials	100% (3/3); 95% CI, 29.2%–100%
2g PO [13,21]	Multiple	Pharynx	Systematic review and meta-analysis of clinical trials	100% (19/19); 95% CI, 82.3%–100%
Cefixime				
400 mg PO [21]	Multiple	Pharynx	Systematic review and meta-analysis of clinical trials	92.3%; 95% CI, 74.9%–99.1%
800 mg PO [13, 21]	Multiple	Pharynx	Systematic review and meta-analysis of clinical trials	80.0% (12/15); 95% CI, 51.9%–95.7%
Ceftriaxone				
125mglM [21]	Multiple	Pharynx	Systematic review and meta-analysis of clinical trials	94.1%; 95% CI, 85.6%–98.4%
250 mg IM [21]	Multiple	Pharynx	Systematic review and meta-analysis of clinical trials	99.0%; 95% CI, 94.4%–100%

Abbreviations: CI, confidence interval; IM, intramuscularly; IV, intravenously; MIC, minimum inhibitory concentration; PO, orally.