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Effectiveness of Cefixime for the Treatment of *Neisseria gonorrhoeae* Infection at 3 Anatomic Sites: A Systematic Review and Meta-Analysis

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Background: To treat *Neisseria gonorrhoeae* infection, the Centers for Disease Control and Prevention recommends a single oral dose of cefixime as an alternative to injectable ceftriaxone.

Methods: We conducted a systematic review and meta-analysis to describe the effectiveness of cefixime in treating *N. gonorrhoeae* infection at 3 different anatomic sites.

We searched PubMed and Embase database to abstract treatment success rates and cefixime dosage/frequency for studies that reported the anatomical site of infection. We included reports published between January 1, 1980, and December 7, 2021. Twenty studies published between 1989 and 2015 were included in our meta-analysis. We calculated pooled treatment success percentages and 95% confidence intervals (CIs) using random-effects models.

Results: Of patients who received a 400-mg single dose of cefixime, 824 of 846 (97%; 95% CI, 96%–98%) patients with urogenital infection, 107 of 112 (97%; 95% CI, 84%–100%) patients with rectal infection, and 202 of 242 (89%; 95% CI, 76%–96%) patients with pharyngeal infection were cured. Of patients who received an 800-mg single dose of cefixime, 295 of 301 (98%; 95% CI, 96%–99%) patients with urogenital infection and 21 of 26 (81%; 95% CI, 61%–92%) patients with pharyngeal infection were cured.

Conclusions: Our meta-analysis found that cefixime is highly effective at treating urogenital infections and less effective at treating pharyngeal infections. We recommend more investigation into the effectiveness of cefixime in treating rectal infections and studying multidose therapy for the cefixime treatment of pharyngeal infection.

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Neisseria gonorrhoeae infection is a public health concern worldwide, due in large part to the fact that *N. gonorrhoeae* has demonstrated unprecedented capacity to develop antibiotic resistance.[1] There is evidence of *N. gonorrhoeae* antimicrobial resistance to all recommended antimicrobial agents.[2,3] The Centers for Disease Control and Prevention (CDC) identified antimicrobial-resistant *N. gonorrhoeae* as 1 of the top 3 ongoing public health threats.[4] For those reasons, identifying effective therapies is critical for clinicians, public health professionals, and patients.

Current recommendations for the treatment of gonorrhea rely on ceftriaxone as first-line therapy. In their 2020 European guidelines on the treatment of gonorrhea, the International Union against Sexually Transmitted Infections put forward 2 recommendations. The first International Union against Sexually Transmitted Infections recommendation was dual therapy of ceftriaxone 1 g intramuscularly as a single dose with azithromycin 2 g as a single oral dose. Their second recommendation was monotherapy of ceftriaxone 1 g intramuscularly alone.[5] The British Association for Sexual Health and HIV, in their 2018 guidelines on the treatment of infection with *N. gonorrhoeae*, also recommended ceftriaxone 1 g intramuscularly.[6] The CDC's 2020 update on treatment guidelines for gonococcal infection recommended a single intramuscular dose of ceftriaxone 500 mg as first-line therapy to treat gonorrhea.[7]

In addition, CDC recommends a single oral dose of cefixime 800 mg as an alternative if ceftriaxone is not available.[7] The CDC did not recommend cefixime as first-line therapy because it fails to provide the same bactericidal effect as ceftriaxone, because of reduced susceptibility in surveillance data, and because it is unreliable in the treatment of pharyngeal gonorrhea.[7] However, concerns have been raised about the availability of ceftriaxone. The ease of one-time oral administration of cefixime may justify the continued use of cefixime in certain settings.[8,9]

Recent data from the CDC's Gonococcal Isolate Surveillance Project have raised questions about the appropriate dosage of cefixime in the treatment of gonorrhea. Although cefixime minimal inhibitory concentrations rose steadily over the past 30 years, this trend has recently reversed in the United States, Canada, and England.[10,11] In addition, the effectiveness of cefixime at various anatomical sites of infection is poorly understood[12,13] We performed a systematic review and meta-analysis to compare the effectiveness of 400- and 800-mg single-dose cefixime at treating urogenital, rectal, and pharyngeal gonococcal infections.

MATERIALS AND METHODS

Search Strategy and Selection Criteria

The systematic review was conducted in accordance with PRISMA guidelines.[14] We began by searching PubMed

(https://pubmed.ncbi.nlm.nih.gov/) using the following search query: ((("Gonorrhea") AND ("Cefixime")) AND ("1980/01/01"[Date - Publication]: "2021/12/31"[Date - Publication])) AND (English[Language]) AND ((randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab] OR open study [tiab]) NOT (animals [mh] NOT humans [mh])). The query restricts our search to articles published between the dates of January 1, 1980, and December 31, 2021.

We performed the same search on Embase using the equivalent search query translated into Embase's syntax. The exact search query used in our Embase search is the following: ("gonorrhea' AND "cefixime") AND [1980–2021]/py AND english:la AND (("randomized controlled trial":it OR "controlled clinical trial":it OR "randomized":ab,ti OR "placebo":ab,ti OR "drug therapy":lnk OR "randomly":ab,ti OR "trial":ab,ti OR "groups":ab,ti OR "open study":ab,ti) NOT ("animals"/exp NOT "humans"/exp)).

We excluded studies that were not in English or studies that were single case reports or case series. We did not encounter any studies investigating multidose therapy with cefixime. We included studies that specified the dose of cefixime administered, the schedule of cefixime administration (e.g., single dose), and the anatomical site of infection by *N. gonorrhoeae*. We also included studies in which the test of cure was performed by culture or by nucleic acid amplification test. Authors reviewed each article returned by the search query. Determinations on the relevance of each article to our study was determined by the first author and verified by the second. Each study was individually assessed for bias.[15] We used Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) to manage the appropriate data from the included articles in performing a meta-analysis on the effectiveness of cefixime in treating gonorrhea at different anatomical sites. Of the articles that met our inclusion criteria and were determined to be relevant to our study, we abstracted the cefixime dose, characteristics of study participants, and the number and percent of treatment successes and failures reported in the articles.

Data Analysis

We compared the effectiveness of cefixime in eliminating *N. gonorrhoeae* infection at the 3 anatomical sites (urogenital, pharyngeal, and rectal). We performed the analysis separately by dosage (single cefixime dose of 400 or 800 mg). The 95% confidence intervals (CIs) of individual studies were calculated and visualized in forest plots. A logistic normal random-effects model was used to calculate 95% CI and pooled estimates. We calculated and present study-specific proportions with 95% CIs by anatomic site and the pooled treatment success estimates by anatomic site with 95% Wald CIs. Heterogeneity was quantified using the I^2 measure where there were greater than 2 degrees of freedom.[16] Those analyses were performed using Stata 16 software (College Station, TX).

We conducted an analysis of publication bias using a doi plot and the Luis Furuya-Kanamori (LFK) index using a logit transformation of the cure proportion from each study.[17] In addition, we conducted a sensitivity analysis where we excluded the results of each study one at a time to assess the change in the estimates of pooled treatment success.

RESULTS

The search performed on PubMed returned 16 studies. The search on Embase returned an additional 4 studies (Fig. 1). Twenty total studies were included in our meta-analysis (Table 1). We summarized patient characteristics and geographic locations of the included studies (Table 2). Based on the GRADE scale of study quality, 8 studies had a "high" quality of evidence, 10 studies had a "moderate" quality of evidence, and 2 articles had a "low" quality of evidence[22] (Table 2). We only encountered studies that reported dosages of 200, 400, or 800 mg. One study found outcomes with a cefixime dosage of 200 mg; we report this study alone but did not include it in our meta-analysis.[18] In that study, 93 of 98 (94.9%) patients presenting with uncomplicated urogenital gonococcal infection were cured, 4 of 4 (100.0%) patients presenting with uncomplicated rectal infection were cured, and no pharyngeal infections were included.

We found 13 studies that reported outcomes in urogenital infections, 7 studies that reported outcomes in rectal infections, and 11 studies that reported outcomes in pharyngeal infections treated with a 400-mg single dose of cefixime. Of patients who received 400 mg of cefixime, 824 of 846 (97%; 95% CI, 96%–98%) patients with urogenital infection, 107 of 112 (97.0%; 95% CI,

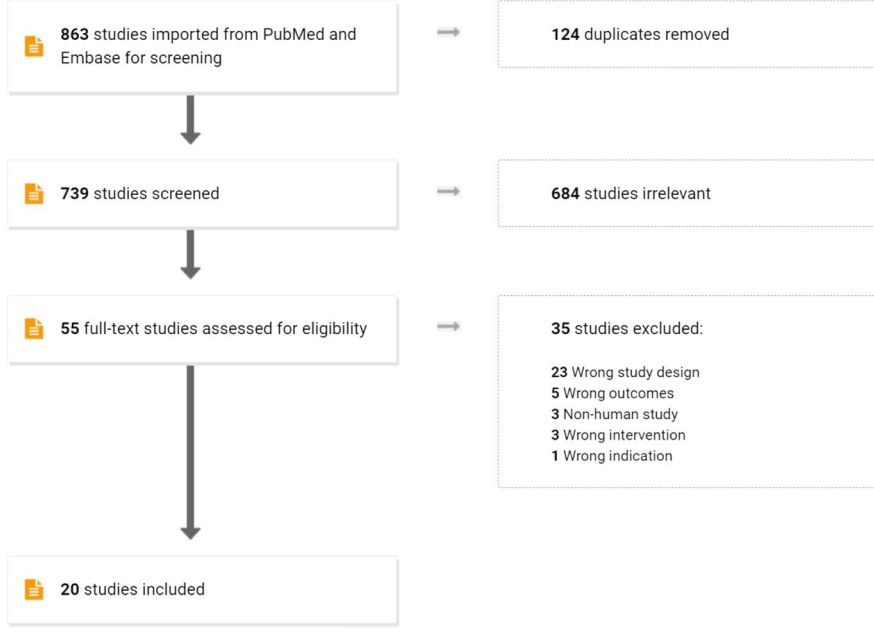

Figure 1. Screening process for the systematic review on PubMed and Embase.

TABLE 1. Studies of Cefixime Treatment for *Neisseria Gonorrhoeae* Infection, 1990 to 2015

			Urogenital				Rectal				Pharyngeal			
Authors	**Publication Year**	**Cefixime Dose, mg**	**Successes**	**Failures**	**Total**	**% Success**	**Successes**	**Failures**	**Total**	**% Success**	**Successes**	**Failures**	**Total**	**% Success**
Verdon et al.[18]	1993	200	93	5	98	94.90	4	0	4	100.00				
Aplasca De Los Reyes et al.[31s]	2001	400	25	1	26	96.15								
Asbach[32s]	1991	400	43	0	43	100.00								
Barbee et al.[33s]	2013	400									19	5	24	79.17
Gratrix et al.[19]	2013	400									47	18	65	72.31
Handsfield et al.[20]	1991	400	87	4	91	95.60	10	10	10	100.00	8	0	8	100.00
Hjelmevoll et al.[34s]	2012	400	25	0	25	100.00	1	0	1	100.00	1	0	1	100.00
Hook III et al.[35s]	1997	400	145	5	150	96.67	3	0	3	100.00	10	2	12	83.33
Kuhlwein et al.[36s]	1989	400	30	0	30	100.00								
McMillan et al.[37s]	2007	400	32	0	32	100.00	12	0	12	100.00	53	0	53	100.00
Miller Jr.[38s]	1997	400	79	4	83	95.18								
Moran et al.[39s]	1995	400									8	0	8	100.00
Mroczkowski et al.[40s]	1997	400	124	1	125	99.20	37	1	38	97.37	11	5	16	68.75
Plourde et al.[41s]	1992	400	118	3	121	97.52								
Portilla et al.[42s]	1992	400	65	1	66	98.48								
Ramus et al.[43s]	2001	400	44	2	46	95.65	16	0	16	100.00	6	0	6	100.00
Sathia et al.[44s]	2007	400									14	2	16	87.50
Singh et al.[21]	2015	400	7	1	8	87.50	28	4	32	87.50	25	8	33	75.76
Dunnett et al.[45s]	1992	800	71	2	73	97.26								
Handsfield et al.[20]	1991	800	87	1	88	98.86	6	0	6	100.00	6	1	7	85.71
Megran et al.[46s]	1990	800	96	1	97	98.97								
Moran et al.[39s]	1995	800									12	3	15	80.00
Portilla et al.[42s]	1992	800	40	2	42	95.24								
Singh et al.[21]	2015	800	1	0	1	100.00	6	0	6	100.00	3	1	4	75.00

TABLE 2. Characteristics of Participants, Geographic Locations, and GRADE Quality Score of Studies Included in the Meta-Analysis of Cefixime for the Treatment of *Neisseria Gonorrhoeae* Infection, 1990 to 2015

Study	Participant Sex	Participant Sexual Orientation	Study Location	GRADE Score
Aplasca De Los Reyes et al.[31s]	Female only	Not reported	Manila, Philippines Cebu, Philippines	High
Asbach[32s]	Female only	Not reported	Remscheid, Germany	High
Barbee et al.[33s]	Male and female	Not reported	Seattle, WA	Moderate
Dunnett et al.[45s]	Male and female	Not reported	Rockford, IL	Low
Gratrix et al.[19]	Male and female	Heterosexual MSM	Alberta, Canada	Moderate
Handsfield et al.[20]	Male and female	Straight Bisexual women	Seattle, WA Brooklyn, NT Baltimore, MD Denver, CO	High
Hjelmevoll et al.[34s]	Male and female	Heterosexual MSM	Oslo, Norway	Moderate
Hook III et al.[35s]	Male and female	Not reported	10 locations in the United States (cities and states not reported)	High
Kuhlwein et al.[36s]	Male only	Not reported	Germany (city not reported)	Low
McMillan et al.[37s]	Male and female	Heterosexual MSM	Edinburgh, Scotland, United Kingdom	Moderate
Megran et al.[46s]	Male only	Heterosexual bisexual MSM	Canada (city not reported)	High
Miller Jr.[38s]	Female only	Not reported	United States (city not reported)	Moderate
Moran et al.[39s]	Male and female	Not reported	Multiple locations globally	Moderate
Mroczkowski et al.[40s]	Female only	Not reported	Baltimore, MD Birmingham, AL Boston, MA Brooklyn, NY Denver, CO Indianapolis, IN New Orleans, LA San Francisco, CA Seattle, WA	High
Plourde et al.[41s]	Male and female	Heterosexual	Nairobi, Kenya	Moderate
Portilla et al.[42s]	Male and female	Not reported	New Orleans, LA	High
Ramus et al.[43s]	Female only	Not reported	Dallas, TX	High
Sathia et al.[44s]	Not reported	Not reported	London, United Kingdom	Moderate
Singh et al.[21]	Male and female	Heterosexual MSM	Calgary, Alberta, Canada Edmonton, Alberta, Canada Vancouver, British Columbia, Canada Ottawa, Ontario, Canada	Moderate
Verdon et al.[18]	Male and female	Heterosexual Homosexual	Denver, CO Seattle, WA	Moderate

MSM indicates men who have sex with men.

84%–100%) patients with rectal infection, and 202 of 242 (89%; 95% CI, 76%–96%) patients with pharyngeal infection were cured. Figure 2 shows the pooled treatment success proportions calculated from the meta-analysis for studies that used a single 400-mg dose.

We found 5 studies that reported outcomes of urogenital infections, 2 studies that reported outcomes of rectal infections, and 3 studies that reported outcomes of pharyngeal infections treated with an 800-mg single dose of cefixime. Of patients who received 800 mg of cefixime, 295 of 301 (98%; 95% CI, 96%–99%) patients with urogenital infection and 21 of 26 (81%; 95% CI, 61%–92%) patients with pharyngeal infection were cured. Combining the 2 studies that included rectal infections treated with an 800-mg single dose of cefixime, 12 of 12 patients were cured.[20,21] Figure 3 shows the pooled treatment success proportions calculated from the meta-analysis for studies that used a single 800-mg dose. Because there were fewer than 3 studies reporting outcomes of patients with rectal infections treated with 800 mg, heterogeneity could not be assessed with the I^2 statistic. Significant intragroup heterogeneity was only observed for the pharyngeal group (I^2 statistic = 75.2%, $P < 0.001$).

In our analysis of potential publication bias, we found that, for both the 400- and 800-mg dose studies, results showed asymmetry indicating evidence of potential publication bias (LFK index for 400-mg dose studies = −2.04; LFK index for 800 mg does studies = −6.62). The sensitivity analyses that excluded one study at a time found that the pooled treatment success proportion estimates did not change more than 2% except in the case of the pharyngeal results in which we excluded each the McMillan and Gratrix studies. With those exclusions, the 400-mg dose treatment success proportion for pharyngeal infections would be 85% (77%, 92%) and 94% (81%, 100%), without each study respectively.

DISCUSSION

We performed a systematic review and meta-analysis to compare the effectiveness of single-dose oral cefixime in the treatment of urogenital, rectal, and pharyngeal gonococcal infections.

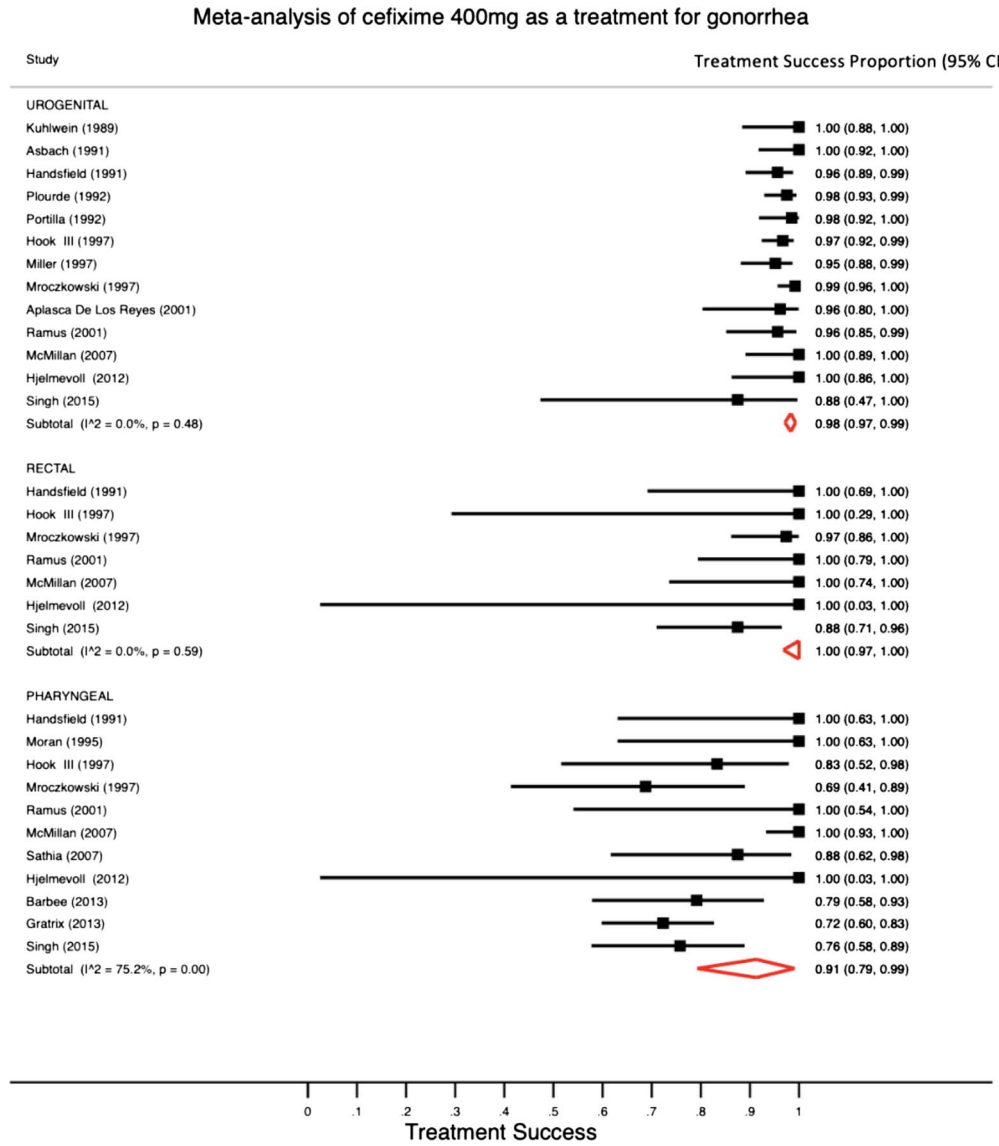

Figure 2. A meta-analysis with pooled estimates and 95% CIs for the single-dose cefixime 400 mg for the treatment of *N. gonorrhoeae* infection using a random-effects model.

Across both dosages of cefixime 400 and 800 mg, cefixime was more effective at treating urogenital infections and less effective at treating pharyngeal infections. More investigation into the effectiveness of cefixime single dose 800 mg in treating rectal infections is warranted.

The difficulty of treating pharyngeal gonorrhea is an ongoing challenge.[23] It has been noted that antibiotics have difficulty penetrating pharyngeal mucosa. The particular pharmacokinetic and pharmacodynamic mechanisms are poorly understood.[10,24] A multidose regimen of cefixime could theoretically overcome the issue of limited pharyngeal mucosa penetration, but this theory requires further investigation.

Resistance-guided therapy has demonstrated promise in treating gonorrhea.[25] Presently, *N. gonorrhoeae* currently demonstrates widespread ciprofloxacin resistance due to a single point mutation at the serine 91 codon of the *GyrA* gene. However, not all strains of *N. gonorrhoeae* exhibit this mutation. Allan-Blitz et al.[26] described testing for the presence of the *GyrA* mutation *N. gonorrhoeae* to determine whether or not that particular mutation is present to guide therapy. Further studies have demonstrated a high effectiveness of ciprofloxacin in treating gonorrhea when resistance-guided therapy is used.[27] Currently, there is no widely available genetic resistance test for cefixime, so resistance-guided therapy is only currently feasible in guiding the use of ciprofloxacin.

We found no other systematic reviews that investigated the effectiveness of cefixime for treatment of gonorrhea by anatomical site. In 2018, Tanvir et al.[28] published a systematic review that aimed to characterize the overall effectiveness of a single oral dose of cefixime 400 mg compared with other drugs that are commonly used to treat gonococcal infections. All 8 studies that were included in their final meta-analysis were uncovered by our search query and were included in our meta-analysis. Through their meta-analysis, Tanvir et al. reported an overall success rate greater than 98% for a single oral dose of cefixime 400 mg but did not stratify by anatomic site of infection.

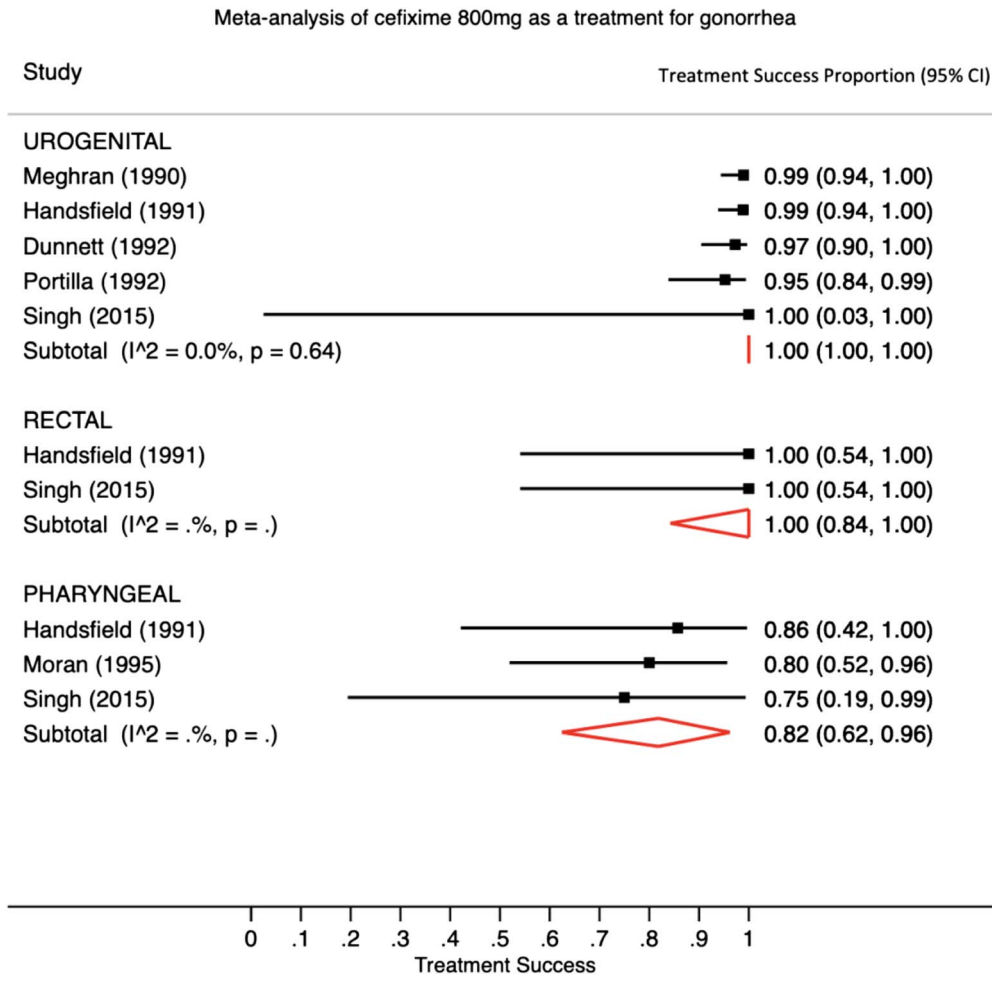

Figure 3. A meta-analysis with pooled estimates and 95% CIs for the single-dose cefixime 800 mg for the treatment of *N. gonorrhoeae* infection using a random-effects model. Footnote: There is significant heterogeneity for studies demonstrating treatment success for pharyngeal gonorrhea infections. The I^2 statistic could not be calculated when there were 3 or fewer studies.

In 2013, Gratrix et al.[19] published a retrospective review of pharyngeal gonorrhea treatment failures from clinics located in Alberta, Canada. Their study concluded that cefixime monotherapy is unreliable for the treatment of pharyngeal gonorrhea. Our study lends support to that conclusion, as we found that cefixime is less effective at treating pharyngeal gonococcal infections at both 400- and 800-mg single doses compared with the other 2 anatomical sites we investigated. Although Gratrix et al. found a much lower treatment failure rate when cefixime was combined with azithromycin, the move away from combination therapy due to increasing antimicrobial resistance of *N. gonorrhoeae* to azithromycin warrants further investigation into longer duration or higher-dose therapy.

Because of the rapid development of antibiotic resistance in *N. gonorrhoeae*, investigation into alternative therapies for treatment is necessary.[1] Our findings suggest that, for urogenital gonococcal infections, cefixime is reliable at treating infection by *N. gonorrhoeae*. Our findings corroborate the CDC's recommendation of cefixime single dose 800 mg for use in expedited partner therapy in the case of uncomplicated urogenital infection.[7] Low-resource settings and other settings in which oral treatment is preferable to treatment by injection make cefixime an attractive choice for providers when considering treatment options for gonococcal infection, especially in settings in which data suggest that local resistance is low.[29]

There were limitations to our study. First, our study was limited to reports available in English, which left out study reports investigating treatment of gonorrhea with cefixime in other languages. In addition, the analysis performed in our study may have been affected by positive publication bias, whereby studies demonstrating increased failure of cefixime may not have been reported. We did not control for study design. We included all studies that reported the effectiveness of cefixime treatment by anatomical site and did not exclude nonrandomized studies. Furthermore, recent literature has indicated the emergence of increasing cefixime resistance in *N. gonorrhoeae* in Southeast Asia.[10] However, the results from our meta-analyses may not reflect that emerging trend because our search queries did not return any studies reporting on cefixime treatment outcomes by anatomical site from that region. Because of the broad range of publication years included by our search queries, we included several studies that used test of cure by culture. The lower sensitivity of test of cure by culture compared with test of cure by nucleic acid amplification test may have introduced heterogeneity to our study's results.[30]

Our systematic review and meta-analysis comparing the effectiveness of cefixime at treating urogenital, rectal,

and pharyngeal gonococcal infections found that, at both single 400- and single 800-mg doses, cefixime is more effective at treating urogenital infections and less effective at treating pharyngeal infections. We recommend more investigation into the effectiveness of cefixime single dose 800 mg in treating rectal infections and the use of multidose therapy for cefixime treatment of pharyngeal infection.

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For further references, please see "Supplemental References," http://links.lww.com/OLQ/A892.