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Review Article

Systematic review and meta-analysis on efficacy of cefixime for treating gonococcal infections

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ABSTRACT

Background: *Neisseria gonorrhea* is known to have developed a high level of resistance against different classes of antimicrobials. Patients with coagulation disorders where intramuscular injections are contraindicated, oral cefixime in combination therapy can be utilized as an alternative regimen. Cefixime in combination with another macrolide might be considered as an alternative treatment option. The aim of this systematic review is to assess the efficacy of 400 mg cefixime against a range of comparator drugs.

Methodology: Extensive literature search for randomized controlled trials was performed using Medline, Cochrane Registry of Controlled Trials, Embase, and Clinical trials registers. The trials assessed the efficacy of cefixime against a range of comparator drugs. Primary outcome of the study was the clinical resolution of signs and symptoms and negative culture at the end of follow-up period.

Results: After screening for a total of 1184, only 8 studies were eligible for a meta-analysis. Risk ratio random effects model was used with a 95% confidence interval (CI). The pooled efficacy of Cefixime was at 97% at 95 CI 1.01 (0.98, 1.05). No statistically significant difference was found between oral cefixime and comparator drugs.

Conclusion: A total of 11 studies were included following a review of 1184 publications. 8 randomized controlled trials for 400 mg oral cefixime were included in meta-analysis. Despite a high grade of evidence, a high risk of bias was found among studies. Hence, more high quality randomized controlled trials on cefixime needs to be performed in future to guide the treatment of gonococcal infections.

Keywords: Cefixime, efficacy, meta-analysis, *Neisseria gonorrhea,* sexually transmitted disease, sexually transmitted infections, systematic review

Introduction

Gonorrhea is reported to be the second most commonly reported communicable disease.[1] In 2008, a survey conducted by the World Health Organization (WHO) estimated that there were around 106 million new cases of gonorrhea worldwide. Targeted microbiologic diagnosis of this infection with *Neisseria gonorrhea* (N.G.) should be conducted in all individuals at risk or susceptible to acquire N.G. A specific and prompt diagnosis could possibly reduce the percentage of complications, transmissions, or reinfections. Due to the specificity and sensitivity, a Gram Strain of urethral secretions that show polymorphonuclear leukocytes with intracellular Gram-negative diplococci can be considered as diagnostic for infection with N.G in symptomatic individuals.[2]

The treatment of N.G is further complicated due to the tendency of N.G to develop resistance to antimicrobials.[3] The evolution of resistance to antimicrobials agents in N.G. isolates is a global burden in the treatment toward gonococcal infections. The ability of this specific disease to resist significant levels of penicillins, tetracycline, and fluoroquinolones and oral cephalosporins[4–7] have recently escalated in far East Asia.[8] In the 1990s, it was internationally recommended to use the third generation cephalosporins. However, investigations conducted in the past have reported on the treatment failures with cefixime. Nevertheless, it is still recommended as the drug of choice for N.G infections in certain countries.[9] Hence, a regimen of parenteral cephalosporin such as ceftriaxone is generally prescribed as the first line of treatment for uncomplicated gonococcal infections. Cefixime in combination with another macrolide, such as azithromycin might be considered as an alternative oral treatment option.[2] The recommendations made by the Clinical and Laboratory Standards Institute the minimum inhibitory concentration breakpoint for oral cephalosporins cefixime and cefpodoxime susceptibility were <0.25 mg/L and 0.5 mg/L.[10]

The objective of this systematic review is to assess the efficacy of a single oral dose of cefixime against a range of comparator drugs used to treat uncomplicated gonococcal infections, such as ceftriaxone, fluoroquinolones, and amoxicillin. The authors also want to assess whether the efficacy of cefixime for treating uncomplicated gonococcal infections is superior to comparators drugs or not?.

Materials and Methods

Overview of methodology

An extensive review of the literature was done on patients with uncomplicated gonorrhea treated with oral cefixime.

Search strategy

Literature search for randomized controlled trials was performed using Medline, Cochrane registry of controlled trials, Embase, and Clinical trials registers. The studies filtered had no restrictions on dates when using Medline. The studies included in this review ranged from the timeline of 1946 to December 2017, randomized controlled trials and observational comparative studies were included in this review.

Keywords included "*Neisseria gonorrhea,*" "Cefixime," "Cephalosporins," "Ceftriaxone," "Gonococcal urethritis," "Neisseria," and "Gonococcal infections." In addition, studies were also retrieved from databases such as "ScienceDirect," "CINAHL," and Clinical trial registries in North America and the United Kingdom and also by hand searching research articles for further references.

Other databases

Clinical trial registers of China, Europe, Russia, India, Japan, WHO, and Brazil were also searched extensively.

Participants, intervention, and comparators

Inclusion criteria

The following criteria were included in this study:

1. Healthy male and female patients above 15 years of age.
2. Patients with a history of exposure to infected individuals.
3. Patients who were diagnosed with a gonorrhea infection microbiologically by culture and microscopy or nucleic acid amplification test (NAAT).
4. AND
5. Patients who were diagnosed with gonococcal infection on clinical grounds
6. Patients who went through a proper procedure of informed consent, before they enrolled in the randomized the controlled trial.
7. Test of cure was performed after follow-up period, either by the culture of NAAT.

Exclusion criteria

1. Patients with non-gonococcal urethritis were excluded from the study.
2. Patients not diagnosed microbiologically were also excluded from this review.
3. Patients with an impaired immune system with conditions such as HIV, Diabetes mellitus, or any other autoimmune disease such as SLE.
4. Patients with a history of allergy to penicillin or cephalosporin.
5. Patients with a history of renal failure.

Types of interventions

Studies where cefixime was administered to the patients in the following manner

1. 800 mg × Once daily orally for 1 day.
2. 400 mg × Twice daily orally for 1 day.
3. 200 mg × Once daily orally for 1 day.
4. 400 mg × Once daily orally for 1 day.

Primary outcome measures

Primary outcome measures were defined as:

1. Microbiological cure (negative culture/microscopy) at the end of the treatment and follow-up.
2. Clinical resolution of signs and symptoms such as abdominal pain, genital pain, discharge from urethra and dysuria at the end of the follow-up period.

Secondary outcome measure

Secondary outcome measures were defined as:

1. Adverse reaction related to drug intakes such as diarrhea, loose stools, abdominal pain, headaches, nausea, rashes, or pseudomembranous colitis.
2. Patients requiring further symptomatic or antimicrobial therapy.

Data collection and analysis

Two authors Syed Bilal Tanvir and Syed Saad bin Qasim independently reviewed the studies for eligibility. Study selection was based on abstracts and titles of research articles. Any conflict regarding inclusion or exclusion was mainly resolved by consensus.

Data sources, studies sections, and data extraction

A customized form was developed and tested for data extraction for the included studies. The form was derived from the template provided by the Cochrane data extraction tool. The form was customized to extract the following data from the research articles Author name.

- Year the study was published
- Study design
- Dosage and route of cefixime

- Dosage and route of comparator drug
- Types of participants
- Primary outcome measures such as cure rate
- Adverse events
- Length of treatment
- Follow-up duration
- Method of follow-up
- Method of diagnosis.

The data extracted from the studies were rechecked by the other authors for mistakes.

Data analysis

Risk ratio (RR) random effects model was used with a 95% confidence interval (CI). Cochrane Revman 5.0 software was used for this purpose. Studies were grouped according to the class of the drugs used to treat uncomplicated gonococcal infections. The pooled efficacy of cefixime was calculated against a range of comparator drugs at 95 CI 1.01). Studies were assessed for the statistically significant difference between oral cefixime and comparator drugs. Heterogeneity was also assessed among different studies.

Quality assessment of randomized and non-randomized observational studies

A modified downs WW and black method checklist were used for this purpose. The checklist has 27 questions for assessing the quality of the studies and for the assessment of the risk of bias. Confounding, Selection bias, External validity, and reporting bias were included. The last question in the checklist was adapted from another study and assessed the power of the study.

Results

The results concluded that there was a lack of high quality of evidence on the use of oral cefixime for the treatment of both complicated and uncomplicated gonorrhea. A comprehensive literature search was done despite that only 8 RCTs were identified, where patients were treated for both complicated and uncomplicated gonorrhea treated with oral cefixime.

Summary of Studies retrieved for the review is included in Figure 1.

Study selection and characteristics of the included studies are mentioned in Table 1

After screening for a total of 1184 studies, using different databases, 230 relevant abstracts were screened for inclusion, in the systematic review and meta-analysis. A total of 255 studies from PubMed, 28 studies from Cochrane Central Register of Controlled Trials, and 851 results were obtained for EMBASE.

Out of the relevant 255 abstracts that were screened for eligibility, only 11 studies were included in the narrative review while only 8 studies were eligible for a meta-analysis.

Out of the 230 abstracts screened for this review, 219 abstracts were excluded from the review because of the following reasons.

- Studies where the diagnosis of uncomplicated and complicated gonorrhea, were not made microbiologically by performing, pharyngeal, rectal or urethral swab, or NAAT.
- Studies involving patients with hematological malignancies and immunocompromised conditions such as diabetes, HIV, and other systemic diseases.
- Studies where cefixime was not being assessed for its efficacy/effectiveness but after pharmacokinetic or pharmacodynamics activity.
- Study where the primary outcome of the study was adverse effects of cefixime or comparator drug.
- A total of 11 studies were included in this review for final narrative and qualitative review. Out of the 11 studies, 2 studies were excluded. Finally, only 8 studies were included in the meta-analysis as they were randomized controlled trials [Figure 1].

Study selection and characteristics of the included studies

Of the 8 studies included in the review of meta-analysis, 3 studies compared the effectiveness of cefixime versus fluoroquinolone (ciprofloxacin and grepafloxacin)[11-13] while 5 studies compared the efficacy of cefixime versus ceftriaxone.[13-17]

While 2 studies were noncomparative in study design, assessing the efficacy of cefixime in a patient with complicated gonorrhea;[13,18] finally, one study compared the effectiveness of cefixime versus amoxicillin and probenecid.[19]

Data analysis of individual studies [Figure 2]

In trials comparing the cure rate of cefixime versus fluoroquinolone.

- Cure rates (3 studies). The cure rate was 92% (325/352 patients in 800 mg cefixime group) compared with 97.6% (293/300 patients in ceftriaxone group). RR (random effects model) 95 CI (0.06, 6.25) $P = 0.68$. Hence, no statistical significant difference was found between ceftriaxone and cefixime group. There was also a high heterogeneity in this analysis $P = 0.03$ I^2 72%.

In trials comparing the cure rate of cefixime versus ceftriaxone

- Cure rate (4 studies). The cure rate was 99% (312/316 in 800mg cefixime group) compared with 97.5% (394/404 in fluoroquinolone group) RR (Random effects model) 95 CI 1.77 (1.00–1.04) $P = 0.39$. Hence, no statistical significant differences were found in this study analysis.

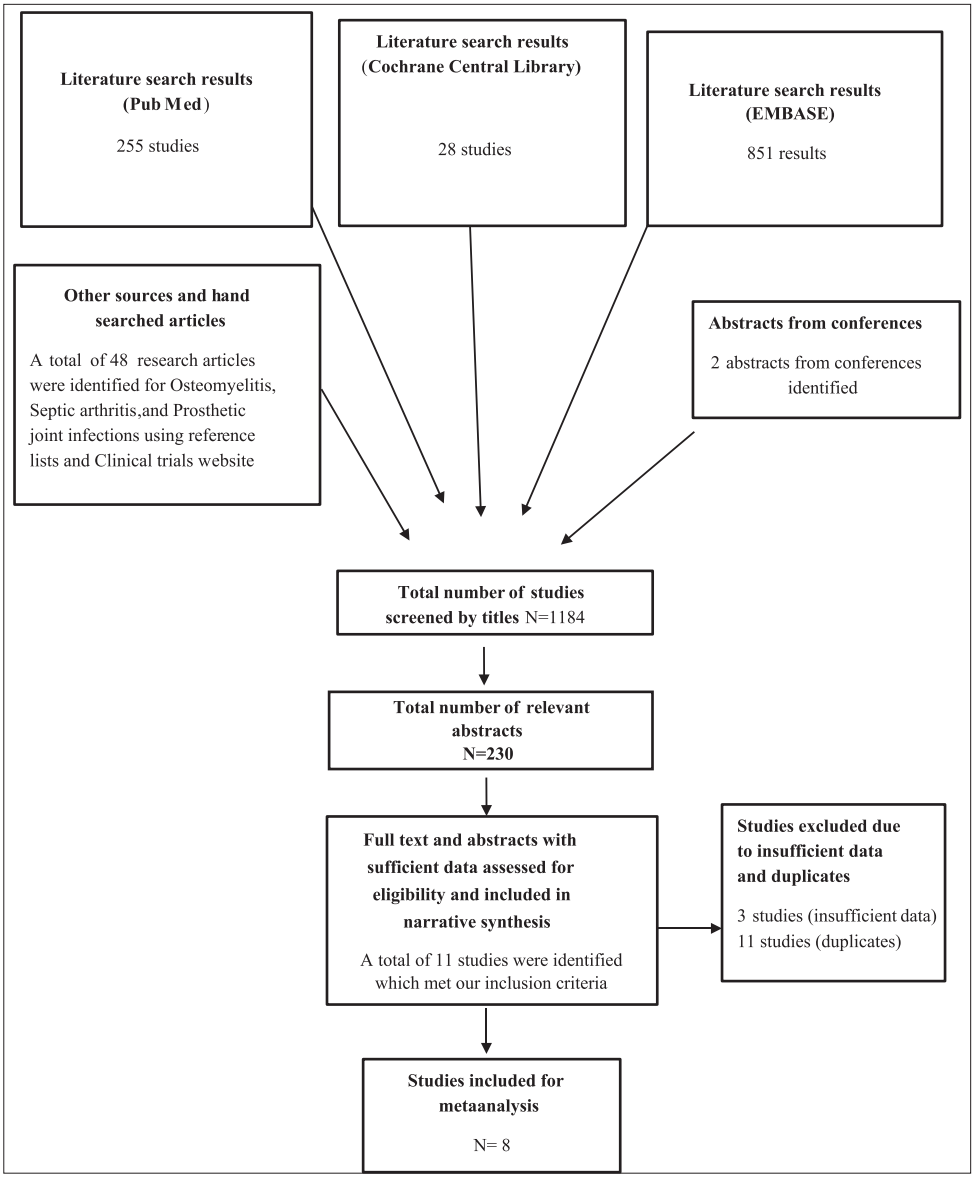

Figure 1: Flow diagram for studies retrieved for the review

There was a high heterogeneity in this analysis $P = 0.12$ $I^2 = 0\%$.

Trial comparing the cure rate of cefixime versus ceftriaxone:

- Cure rate (1 study). The cure rate was 98% (90/97 patients in cefixime 800 mg orally) compared with 95.6% (amoxicillin and probenecid group). RR (Random effects model) 95% CI (1.01, 1.10) $P = 0.48$. Hence, the comparison was statistically significant. Hence, the statistically significant difference was found between the efficacy of cefixime and amoxicillin and probenecid. Test for heterogeneity was not applicable in this group.

Adverse events

Meta-analysis of adverse events was not performed in this systematic review. The major reason was improper reporting methods for adverse events or absence of data for adverse events.

Patient characteristics

1577 patients were included in this systematic review, of which 1151 patients were included in meta-analysis. The male to female ratio was 1/1.40.

Risk of bias

A modified downs and black method checklist were used to determine the risk of bias. Primarily four parameters were assessed to determine the risk of bias among studies. Confounding, Selection bias, External validity, and reporting bias were included. The last question in the checklist was adapted from another study and assessed the power of the

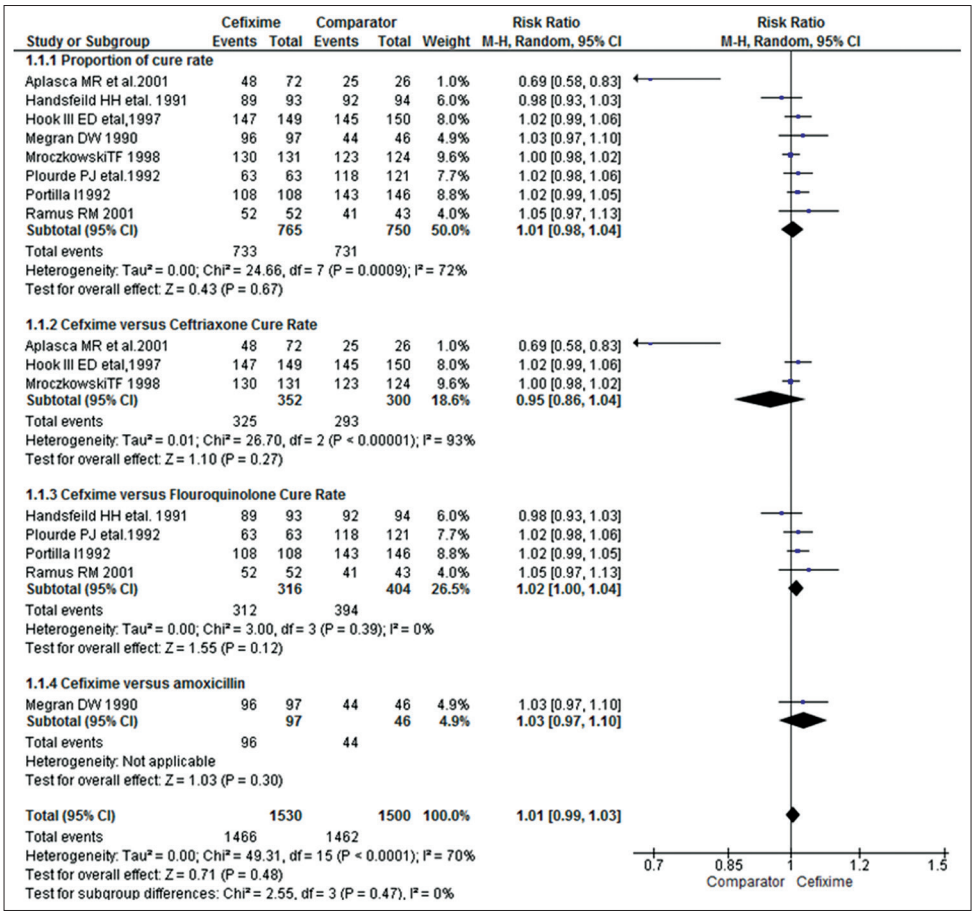

Figure 2: Meta-analysis of the included studies

study. Risk of bias is expressed in the form of percentages in Table 2. Questions number 1–10 is related to reporting; number 11–13 related to external validity; 14–20 related to internal validity bias and 21–26 selection; and 27 related to the power of the study.

Discussion

Summary of main findings

This systematic review found out that there is insufficient evidence data to prove or disprove the benefits of cefixime for the treatment of gonorrhea on adult patients. A total of 8 studies of single-dose oral cefixime were identified and included in the meta-analysis. The success rate of the treatment ranged from 92% to 99 %. This systematic review compared the success rate of the treatment at the end of the follow-up period between cefixime and comparator antibiotics. Previously a systematic review and meta-analysis have been conducted to determine the efficacy of intramuscular (IM) ceftriaxone. This systematic review found out ceftriaxone to have better efficacy than cefixime which had a pooled percentage cure rate of 78.1%. All of these studies mentioned in this systematic have met out inclusion criteria.[11,13-17,19] Furthermore, the efficacy of cefixime was also compared with fluoroquinolones such as grepafloxacin and ciprofloxacin and found a pooled cure rate of 97.5% 95% CI 1.02 (1.00, 1.04)[12] while the pool cure rate of cefixime was found to be 99% 95% CI 1.02 (1.00, 1.04).[13,15-17] This systematic review also found out the cure rate of cefixime to be at 98% 95 CI 1.01(0.97, 1.10) when compared with amoxicillin and probenecid, having a cure rate of 95% 95% CI(0.97, 1.10).[19]

According to the WHO guidelines and BASHH treatment guidelines, fluoroquinolones are no longer recommended as the mainstay for treating gonococcal infections due to high amounts of resistance.[2] A single dose of 400 mg cefixime orally taken once coupled with 2 g of azithromycin is recommended as an alternative treatment option for uncomplicated gonorrhea.[7] However, in patients where IM injection are contraindicated in conditions such as hemophilia, or patients under therapy with anticoagulants, it might prove as a useful alternative to IM ceftriaxone. Furthermore, in resource poor settings where IM ceftriaxone is not available, it might prove as a useful substitute. Although a steady increase in the prevalence of high cefixime MIC suggests that in future the effectiveness of these drugs might slowly decline. Despite this fact, another oral cephalosporin such as cefuroxime and cefpodoxime cannot be recommended as an adequate substitute to cefixime

Table 1: Study selection and characteristics of the included studies

Author and year	Study design	Dosage and route of cefixime	Dosage and route of comparator drug	Participants	Outcome measure (primary)	Adverse events	Length of treatment	Follow-up duration	Method of diagnosis	Additional information
Aplasca *et al.*[11]	RCT	400 mg Orally single dose	500 mg ciprofloxacin orally single dose	Female sex workers	92.2% cure rate 17.8% Positive culture	Not mentioned	1 day	4–7 days after treatment	culture	none
Mroczkowski III *et al.*,[12]	RCT	400 mg orally single dose	500 mg grepafloxacin orally single dose	Males with uncomplicated gonococcal urethritis	97% cure rate 3% positive culture	3% headache 2% nausea	1 day	5–10 days after treatment	culture	none
Deguchi *et al.*[20]	RCT	200 mg cefixime oral x BD	Cefixime 400 mg oral OD	Men with gonococcal urethritis	88.2% cure rate 11.8% Positive culture	No adverse events reported	Two 200mg cefixime dosage 6 hourly for 1 day	3 to 7 days after treatment	Culture (modified Thayer martin media)	none
Holdcroft[14]	RCT	400mg or 800 mg cefixime orally as single dose	Ceftriaxone 250 mg IM single dose	Men and women with uncomplicated gonorrhea	96% cure rate (Cefixime 400 mg) 98% cure rate (Cefixime 800mg)	Gastrointestinal side effects in patients who took 800mg Cefixime	1 day	Not mentioned	Urethral, pharyngeal and rectal culture	none
Megran[19]	RCT	800 mg orally Single dose	Amoxicillin 3g plus probenecid 1g	Men with uncomplicated gonorrhea	97.1% cure rate overall	Nausea, gastric distress, dizziness, headache, and rash	1 day	6 to 9 days after treatment	Urethral, pharyngeal and rectal culture	Patients had *C. trachomitis* and *ureaplasma* infection
Handsfeild[13]	RCT	400mg or 800 mg cefixime orally as single dose	Ceftriaxone 250 mg IM single dose	Men and women with exposure tested culture positive	96% cure rate (cefixime 400mg) 98% cure rate (cefixime 800mg)	Diarrhea, flatulence, and GI reactions	1 day	3 to 10 days after treatment	Urethral, pharyngeal and rectal culture	none
Mroczkowski[12]	RCT	400 mg orally single dose	Grepafloxacin 400 mg orally single dose	Women above 16 years of age with sexual exposure	99% cure rate	Headache, chest pain and vaginal discharge	1 day	5 to 10 days after treatment	Cervix pharyngeal and rectal culture	none
Plourde[15]	RCT	400 mg orally single dose	Ceftriaxone 250 mg IM single dose	Culture positive men and women 15-65 years of age	98% cure rate	Candidal vaginitis and fever	1 day	4 to 7 days after treatment	Cervix pharyngeal and rectal culture	Treatment failure in 3 patients
Portilla[16]	RCT	400 mg or 800 mg orally as single dose	Ceftriaxone 250 mg IM single dose	Adult males and females with uncomplicated gonorrhea	97% cure rate	Diarrhea and loose stools which were self-limiting	1 day	After 4 to 9 days of treatment	Cervix pharyngeal and rectal culture	29 patients loss to follow-up, 1 self-medicated, 1 returned late

(Contd...)

Table 1: (*Continued*)

Author and year	Study design	Dosage and route of cefixime	Dosage and route of comparator drug	Participants	Outcome measure (primary)	Adverse events	Length of treatment	Follow-up duration	Method of diagnosis	Additional information
Ramus[17]	RCT	400 mg orally single dose	Ceftriaxone 125 mg IM single dose	Pregnant females who were culture positive	96.8% cure rate (anogenital) 100% cure rate (pharynx)	No adverse effects were reported	1 day	Within 1 week	Cervix pharyngeal and rectal culture	Concomitant infection of chlamydia in 53% of patients treated with azithromycin
Verdon[18]	Open noncomparative study	200 mg orally single dose	Not applicable	Males and females above 16 and 18 years who were clinically diagnosed	95% cure rate	Transient nausea, rash and mild diarrhea	1 day	Within 4 to 7 days	Cervix, endocervical pharyngeal and rectal culture	24 failed to return to follow-up

Table 2: Risk of bias and quality assessment of the included studies

	Criteria for Critical Appraisal	Aplasca MR *et al.* 2001	Hook III ED *etal*, 1997	Deguchi T *etal.* 2003	Holdcroft C 1992	Megran DW 1990	Handsfeild HH *etal.* 1991	Mroczkowski TF 1998	Plourde PJ *etal.* 1992	Portilla I 1992	Ramus RM 2001	Verdon MS *et al.* 1993	Total Score	Total Score percentage (%)
1	Is the Hypothesis/aim objective of the study clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11	100
2	Are the main outcomes to be measured clearly described in the Introduction or Methods section?	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	9	81.818
3	Are the characteristics of the patients included in the study clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11	100
4	Are the interventions of interest clearly defined?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11	100

(Contd...)

Table 2: Risk of bias and quality assessment of the included studies

5	Are the distribution of principal confounders in each group of subjects to be compared clearly described?	N	N	N	N	Y	P	P	P	N	P	N	1	9.0909
6	Are the main findings of the study clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	9	81.818
7	Does the study provide estimates of the random variability in the data for the main outcome?	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	9	81.818
8	Have all the adverse events that may be a consequence of intervention been reported ?	N	N	Y	N	N	-	Y	N	Y	N	N	3	27.273
9	Have the characteristics of patient loss to follow-up been described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11	100
10	Have the actual probability values been reported for the main outcomes except where probability value is less than 0.001?	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	9	81.818
11	Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	10	90.909
12	Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	Y	U	N	Y	Y	Y	Y	Y	Y	Y	Y	9	81.818

(Contd...)

Table 2: Risk of bias and quality assessment of the included studies

13	Were the staff, places and facilities where the patients were treated, representative of the treatment the majority of the patients receive?	U	U	Y	U	U	U	U	Y	Y	Y	U		0
14	Was an attempt made to blind study subjects to the intervention they have received?	N	N	N	N	N	N	N	N	N	N	N	0	0
15	Was an attempt made to blind those measuring the main outcomes of the intervention?	N	N	N	N	N	N	N	N	N	N	N	0	0
16	If any of the results of the study were based om “data dredging”, was this made clear?	N	Y	N	U	U	U	U	U	U	U	U	1	9.0909
17	In trials and cohort studies, do the analyses adjust for different lengths of follow up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	U	Y	Y	U	Y	Y	Y	N	Y	Y	Y	8	72.727
18	Were the statistical tests used to assess the main outcomes appropriate?	Y	Y	Y	U	U	Y	Y	Y	Y	Y	Y	9	81.818
19	Was compliance with the intervention reliable?	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	90.909
20	Were the main outcome measures used accurate (valid and reliable)?	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	10	90.909

(Contd...)

Table 2: Risk of bias and quality assessment of the included studies

21	Were the cases and controls or patients in different intervention group recruited from the same population?	-	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	9	81.818
22	Were the cases and controls or patients in trials recruited over the course of same time period?	Y	Y	Y	U	N	Y	Y	Y	Y	Y	Y	9	81.818
23	Were the study subjects randomised to intervention groups?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11	100
24	Were the randomised intervention assignments concealed from both patient and healthcare staff until recruitment was complete and irrevocable?	N	N	N	U	U	U	N	N	N	N	N	0	0
25	Was there adequate adjustment for confounding in the analysis from which the main findings were drawn?	N	N	N	U	N	Y	N	U	U	N	U	1	9.0909
26	Were losses of patients to follow-up taken into account?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11	100
27	Was the sample size calculation provided or was the size greater than 50?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11	100
	Total score	15	19	20	12	16	20	20	19	21	18	19		
	Total score in Percentages (%)	55.556	70.37	74.074	44.444	59.259	74.074	74.074	70.37	77.778	66.667	70.37		

NB: Score system is based on percentages calculated from the total Y, Yes=1; N, No=0; U, Unable to determine=0; NA not applicable,thereforescores not included. Questions number 1 to 10 are related to Reporting; number 11 to 13 related to External Validity; 14 to 20 Internal Validity bias & 21 to 26 selection; 27 related to power of the study

and ceftriaxone as they possess low efficacy and inadequate pharmacodynamics.[10]

Limitations

Most of the studies included in this systematic review are more than a decade old. Hence, these studies cannot be conclusively relied on by the academics and clinicians for the treatment of patients. Another major limitation of the study is that the adverse effects of different drugs were either not reported or appropriate methods were not used to separately report them. There was a very high level of heterogeneity among studies as well.

Conclusion

Data collected in this systematic review suggest that cefixime might prove to be a useful option for the treatment of gonorrhea infection with a success rate of over 98%. This systematic review and meta-analysis suggest cefixime to be clinically more effective when compared with a fluoroquinolone. However, the efficacy of ceftriaxone is still superior when compared with cefixime, which is in line with the current guidelines of WHO and BASHH. Hence, more high quality randomized controlled trials for cefixime in combination with another macrolide needs to be conducted in future to guide the clinicians in treating uncomplicated gonococcal infections in patients where IM injections are contraindicated.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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