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

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WEBSITE: ijhs.org.sa
ISSN: 1658-3639
PUBLISHER: Qassim University

ABSTRACT

Background: Neisseria gonorrhoea 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 gonorrhoea, 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 gonorrhoea (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 cephalosporins⁴–⁷ 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.¹⁰ The recommendations made by the Clinical and Laboratory Standards Institute the minimum inhibitory concentration breakpoints for oral cephalosporins cefixime and cefpodoxime susceptibility were <0.25 mg/L and 0.5 mg/L.¹¹
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 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
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;[15,16] 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 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.
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
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).[2] 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>
<thead>
<tr>
<th>Author and year</th>
<th>Study design</th>
<th>Dosage and route of cefixime</th>
<th>Dosage and route of comparator drug</th>
<th>Participants</th>
<th>Outcome measure (primary)</th>
<th>Adverse events</th>
<th>Length of treatment</th>
<th>Follow-up duration</th>
<th>Method of diagnosis</th>
<th>Additional information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aplasca et al[11]</td>
<td>RCT</td>
<td>400 mg Orally single dose</td>
<td>500 mg ciprofloxacin orally single dose</td>
<td>Female sex workers</td>
<td>92.2% cure rate 17.8% Positive culture</td>
<td>Not mentioned</td>
<td>1 day</td>
<td>4–7 days after treatment</td>
<td>culture</td>
<td>none</td>
</tr>
<tr>
<td>Mroczkowski III et al.[12]</td>
<td>RCT</td>
<td>400 mg orally single dose</td>
<td>500 mg grepafloxacin orally single dose</td>
<td>Males with uncomplicated gonococcal urethritis</td>
<td>97% cure rate 3% positive culture</td>
<td>3% headache 2% nausea</td>
<td>1 day</td>
<td>5–10 days after treatment</td>
<td>culture</td>
<td>none</td>
</tr>
<tr>
<td>Deguchi et al.[20]</td>
<td>RCT</td>
<td>200 mg cefixime oral x BD</td>
<td>Cefixime 400 mg oral OD</td>
<td>Men with gonococcal urethritis</td>
<td>88.2% cure rate 11.8% Positive culture</td>
<td>No adverse events reported</td>
<td>Two 200mg cefixime dosage 6 hourly for 1 day</td>
<td></td>
<td>Culture (modified Thayer martin media)</td>
<td>none</td>
</tr>
<tr>
<td>Holdcroft[14]</td>
<td>RCT</td>
<td>400mg or 800 mg cefixime orally as single dose</td>
<td>Ceftriaxone 250 mg IM single dose</td>
<td>Men and women with uncomplicated gonorrhea</td>
<td>96% cure rate (Cefixime 400 mg) 98% cure rate (Cefixime 800mg)</td>
<td>Gastrointestinal side effects in patients who took 800mg Cefixime</td>
<td>1 day</td>
<td>Not mentioned</td>
<td>Urethral, pharyngeal and rectal culture</td>
<td>none</td>
</tr>
<tr>
<td>Megran[19]</td>
<td>RCT</td>
<td>800 mg orally Single dose</td>
<td>Amoxicillin 3g plus probenecid 1g</td>
<td>Men with uncomplicated gonorrhea</td>
<td>97.1% cure rate overall</td>
<td>Nausea, gastric distress, dizziness, headache, and rash</td>
<td>1 day</td>
<td>6 to 9 days after treatment</td>
<td>Urethral, pharyngeal and rectal culture</td>
<td>Patients had C. trachomatis and ureaplasma infection</td>
</tr>
<tr>
<td>Handsfield[13]</td>
<td>RCT</td>
<td>400mg or 800 mg cefixime orally as single dose</td>
<td>Ceftriaxone 250 mg IM single dose</td>
<td>Men and women with exposure tested culture positive</td>
<td>96% cure rate (ceftriaxone 400mg) 98% cure rate (ceftriaxone 800mg)</td>
<td>Diarrhea, flatulence, and GI reactions</td>
<td>1 day</td>
<td>3 to 10 days after treatment</td>
<td>Urethral, pharyngeal and rectal culture</td>
<td>none</td>
</tr>
<tr>
<td>Mroczkowski[12]</td>
<td>RCT</td>
<td>400 mg orally single dose</td>
<td>Grepafloxacin 400 mg orally single dose</td>
<td>Women above 16 years of age with sexual exposure</td>
<td>99% cure rate</td>
<td>Headache, chest pain and vaginal discharge</td>
<td>1 day</td>
<td>5 to 10 days after treatment</td>
<td>Cervix pharyngeal and rectal culture</td>
<td>none</td>
</tr>
<tr>
<td>Ploure[15]</td>
<td>RCT</td>
<td>400 mg orally single dose</td>
<td>Ceftriaxone 250 mg IM single dose</td>
<td>Culture positive men and women 15-65 years of age</td>
<td>98% cure rate</td>
<td>Candidal vaginitis and fever</td>
<td>1 day</td>
<td>4 to 7 days after treatment</td>
<td>Cervix pharyngeal and rectal culture</td>
<td>Treatment failure in 3 patients</td>
</tr>
<tr>
<td>Portilla[16]</td>
<td>RCT</td>
<td>400 mg or 800 mg orally as single dose</td>
<td>Ceftriaxone 250 mg IM single dose</td>
<td>Adult males and females with uncomplicated gonorrhea</td>
<td>97% cure rate</td>
<td>Diarrhea and loose stools which were self-limiting</td>
<td>1 day</td>
<td>After 4 to 9 days of treatment</td>
<td>Cervix pharyngeal and rectal culture</td>
<td>29 patients loss to follow-up, 1 self-medicated, 1 returned late</td>
</tr>
</tbody>
</table>

(Contd...)
Table 1: (Continued)

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

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

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>1 Is the Hypothesis/aim objective of the study clearly described?</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>11</td>
<td>100</td>
</tr>
<tr>
<td>2 Are the main outcomes to be measured clearly described in the Introduction or Methods section?</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>9</td>
<td>81.818</td>
</tr>
<tr>
<td>3 Are the characteristics of the patients included in the study clearly described?</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>11</td>
<td>100</td>
</tr>
<tr>
<td>4 Are the interventions of interest clearly defined?</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>11</td>
<td>100</td>
</tr>
</tbody>
</table>

(Contd...)
Table 2: Risk of bias and quality assessment of the included studies

|   | Are the distribution of principal confounders in each group of subjects to be compared clearly described? | Y | Y | Y | N | N | Y | P | P | P | N | P | N | 1 | 9.0909 |
|---|-----------------------------------------------------------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|   | Are the main findings of the study clearly described?           | Y | Y | Y | N | N | Y | Y | Y | Y | Y | Y | 9 | 81.818 |
|   | 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 |
|   | 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 |
|   | Have the characteristics of patient loss to follow-up been described? | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | 11 | 100  |
|   | 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 |
|   | 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 |
|   | 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>
<thead>
<tr>
<th>Table 2: Risk of bias and quality assessment of the included studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>13. Were the staff, places and facilities where the patients</td>
</tr>
<tr>
<td>were treated, representative of the treatment the majority</td>
</tr>
<tr>
<td>of the patients received?</td>
</tr>
<tr>
<td>14. Was an attempt made to blind study subjects to the</td>
</tr>
<tr>
<td>intervention they have received?</td>
</tr>
<tr>
<td>15. Was an attempt made to blind those measuring the main</td>
</tr>
<tr>
<td>outcomes of the intervention?</td>
</tr>
<tr>
<td>16. If any of the results of the study were based on “data</td>
</tr>
<tr>
<td>dredging”, was this made clear?</td>
</tr>
<tr>
<td>17. In trials and cohort studies, do the analyses adjust for</td>
</tr>
<tr>
<td>different lengths of follow-up of patients, or in case-control</td>
</tr>
<tr>
<td>studies, is the time period between the intervention and</td>
</tr>
<tr>
<td>outcome the same for cases and controls?</td>
</tr>
<tr>
<td>18. Were the statistical tests used to assess the main</td>
</tr>
<tr>
<td>outcomes appropriate?</td>
</tr>
<tr>
<td>19. Was compliance with the intervention reliable?</td>
</tr>
<tr>
<td>20. Were the main outcome measures used accurate (valid</td>
</tr>
<tr>
<td>and reliable)?</td>
</tr>
</tbody>
</table>
Table 2: Risk of bias and quality assessment of the included studies

<table>
<thead>
<tr>
<th></th>
<th>21</th>
<th>Were the cases and controls or patients in different intervention group recruited from the same population?</th>
<th>-</th>
<th>Y</th>
<th>Y</th>
<th>Y</th>
<th>Y</th>
<th>Y</th>
<th>Y</th>
<th>Y</th>
<th>Y</th>
<th>Y</th>
<th>Y</th>
<th>N</th>
<th>Y</th>
<th>9</th>
<th>81.818</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>22</td>
<td>Were the cases and controls or patients in trials recruited over the course of same time period?</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>U</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>9</td>
<td>81.818</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>Were the study subjects randomised to intervention groups?</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>11</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>Were the randomised intervention assignments concealed from both patient and healthcare staff until recruitment was complete and irrevocable?</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>Was there adequate adjustment for confounding in the analysis from which the main findings were drawn?</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>U</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>U</td>
<td>U</td>
<td>N</td>
<td>U</td>
<td>1</td>
<td>9.0909</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>Were losses of patients to follow-up taken into account?</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>11</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>Was the sample size calculation provided or was the size greater than 50?</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>11</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

Total score: 15
Total score in Percentages (%): 55.556

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, therefore scores 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.\textsuperscript{[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 gonorrhoea 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.

**Funding**

No external funding was provided for this review.

**References**