Treatment of uncomplicated UTI in males: a systematic review of the literature

Karen Farrell, Meera Tandan, Virginia Hernandez Santiago, Ildiko Gagyor, Anja Maria Braend, Marius Skow, Ingvild Vik, Filip Jansaaker, Gail Hayward, Akke Vellinga

DOI: https://doi.org/10.3399/bjgpopen20X101140

To access the most recent version of this article, please click the DOI URL in the line above.

Received 13 July 2020
Revised 02 September 2020
Accepted 07 September 2020

© 2020 The Author(s). This is an Open Access article distributed under the terms of the Creative Commons Attribution 4.0 License (http://creativecommons.org/licenses/by/4.0/). Published by BJGP Open. For editorial process and policies, see: https://bjgpopen.org/authors/bjgp-open-editorial-process-and-policies

When citing this article please include the DOI provided above.
Treatment of uncomplicated UTI in males: a systematic review of the literature.

Karen Farrell
MA
Discipline of General Practice
HRB Primary Care Clinical Trials Network Ireland
School of Medicine
National University of Ireland, Galway
1 Distillery Road
Galway, Ireland
+353 91 495194
Farrell.k93@gmail.com

Meera Tandan
PhD
Cecil G. Sheps Center for Health Service Research
University of North Carolina-Chapel Hill
United States
+19195259731
tandanmeera@gmail.com

Virginia Hernandez Santiago
PhD
Division of Population and Behavioural Sciences
School of Medicine
University of St Andrews
North Haugh
St Andrews KY16 9TF
United Kingdom
07847492374
vhs2@st-andrews.ac.uk
ORCID: 0000-0002-8544-1483

Ildikó Gágyor
MD
Department of General Practice
Universitätsklinikum Wurzburg
Josef-Schneider-Str. 2/D7
97080 Wurzburg
(0049)931-201-47802
Gagyor_I@ukw.de
ORCID 0000-0002-7974-7603

Anja Maria Brænd
MD PhD
Department of General Practice
Institute of Health and Society
University of Oslo
Norway.
+47 922 93 238.
ambraend@medisin.uio.no.
ORCID: 0000-0003-0940-7555

Marius Skow
MD
The Antibiotic Centre for Primary Care,
Department of General Practice
Institute of Health and Society,
University of Oslo
Oslo, Norway
m.a.h.skow@medisin.uio.no
ORCID: 0000-0002-0489-1985

Ingvild Vik
PhD
The Antibiotic Centre for Primary Care
Department of General Practice
Institute of Health and Society
University of Oslo
Norway
ingvild.vik@medisin.uio.no
ORCID: 0000-0002-8947-2914

Filip Jansåker
MD
1) Center for Primary Health Care Research, Lund University, Malmö, Sweden,
2) Department of Clinical Microbiology, Rigshospitalet, Copenhagen, Denmark
erik.filip.jansaaker@regionh.dk
ORCID: 0000-0003-0670-9996

Gail Hayward
MRCGP D.Phil
Nuffield Dept Primary Care Health Sciences
University of Oxford
UK
gail.hayward@phc.ox.ac.uk
Akke Vellinga
MSc, MEpidemiology, PhD Medicine
School of Medicine
National University of Ireland, Galway
1 Distillery Road
Galway, Ireland
+ 353 91 495194
akke.vellinga@nuigalway.ie

ORCID: 0000-0002-6583-4300
Treatment of uncomplicated UTI in males: a systematic review of the literature.

Abstract

Background:

Urinary tract infections (UTI) affect around 20% of the male population in their lifetime. The incidence of UTI in men in the community is 0.9 to 2.4 cases per 1,000 under the age of 55 years and 7.7 per 1,000 over 85 years.

Aim:

To evaluate the outcomes of randomised controlled trials (RCTs) comparing the effectiveness of different antimicrobial treatments and durations for uncomplicated UTIs in adult males in outpatient settings.

Method:

RCTs of adult male patients with an uncomplicated UTI treated with oral antimicrobials in any outpatient setting. The outcomes were symptom resolution within two weeks of starting treatment, duration until symptom resolution, clinical cure, bacteriological cure and frequency of adverse events.

Results:

From the 1041 abstract screened, 3 provided sufficient information on outcomes.

One study compared trimethoprim-sulfamethoxazole for 14 days with 42 days in 2*21 males. Fluoroquinolones were compared in the two other RCTs: lomefloxacin (10 males) with norfloxacin (11 males), and ciprofloxacin for 7 and 14 days (2*19 males).
Combining the results from the three RCTs shows that for 75% males with a UTI (76/101) bacteriological cure was reported at the end of the study. Of the 59 patients receiving a fluoroquinolone, 57 (97%) reported bacteriological and clinical cure within 2 weeks after treatment.

**Conclusion:**

The evidence available is insufficient to make any recommendations in relation to type and duration of antimicrobial treatment for male UTIs. Sufficiently powered RCTs are needed to identify best treatment type and duration for male UTIs in primary care.
Keywords

Males

Urinary Tract Infections

Antibiotic treatment

Primary Care

Randomised clinical trial

Review
How this fits in
As the prevalence of urinary tract infection is much higher in females, most of the research has focused on this group. Only three RCT including a total of 101 males compared different antibiotic treatments for UTI. The clear lack of RCTs and evidence of best practice, shows the urgent need for sufficiently powered RCTs to identify best treatment and duration for male UTIs.
Introduction
Urinary tract infections (UTI) affect around 20% of the male population in their lifetime (1). Incidence of UTI in the community is 0.9 to 2.4 cases per 1,000 men below the age of 55 years, and up to 7.7 per 1,000 in men aged 85 years and older (2). UTIs are a common cause of bacteraemia and recurrent infections in this population (3, 4). UTIs are the second most common cause for antibiotic use in primary care (5).

Treatment guidelines for male UTIs vary. In the UK, the National Institute of Health and Care Excellence (NICE), Ireland (Strategy for the control of Antimicrobial Resistance in Ireland, SARI) and Scotland (Intercollegiate Guideline Network (SIGN)) guidelines recommend trimethoprim or nitrofurantoin as a first-line treatment options for 7 days for male UTIs, or pivmecillinam or ciprofloxacin in case of chronic kidney disease (defined by national cut off points). The use of second-line antibiotics is assessed based on culture results while also considering any alternative diagnosis (6-8). This is similar to Denmark, Sweden, Norway and Germany, where trimethoprim and nitrofurantoin are also first-line treatment, in addition to pivmecillinam (9-12).

Diagnosing and treating a male UTI is challenging, partly due to infrequent presentation and limited evidence available for this acute condition (13), and GPs often treat these as complicated UTIs ‘to be sure’ (14), which usually involves the use of second-line antimicrobial agents, or longer courses. Up to now, most literature has been focused on research and optimal prescribing for UTIs in females, where treatment guidelines and duration are more clear-cut (15-18). Even though there is a low incidence of UTIs in men under 55, incidence in older men is similar to female UTIs, particularly in patients with prostate problems, those with indwelling catheters, and those who are hospitalised or in long-term care facilities (19, 20).

Prescribing guidelines have inconsistent advice on type and duration of antibiotic courses for male UTIs (21). Unlike randomised controlled trials (RCTs) on female UTIs (22), few RCTs include men with
community acquired UTIs who are treated in primary care (23). Symptoms of a typical male UTI include: lower urinary tract irritative symptoms such as urgency, frequency, dysuria and nocturia (24). If not treated timely and appropriately, these symptoms may lead to pyelonephritis (kidney infection), which is characterised by fever, and costovertebral angle tenderness (25).

This review aims to identify RCTs evaluating the effectiveness and duration of different antimicrobial regimens for uncomplicated UTIs in adult males in an outpatient setting.
Methods

Study Design and Registration

This systematic review is registered in PROSPERO (international prospective register for systematic reviews), registration number CRD42019133560.

Data Source and Search Strategy

The Cochrane methodology was adopted to perform a systematic search of the literature (26). We conducted our search in MEDLINE, EMBASE, PUBMED and the Cochrane Register of Controlled Trials (CENTRAL), Cochrane Library and Wiley) and CINAHL EBSCO host from inception to 13th of March to 10th of April 2019 to identify potentially relevant randomised trials focusing on male UTIs. The search terms included were urinary tract infections, men, male, treatment, treatment dose, duration, regimens and therapies, antimicrobials, antibiotics, randomised controlled trial*, placebo trials, pragmatic trials, RCT. Further to simplify the search terms, we also searched for urinary tract, recurrence, uncomplicated, acute cystitis for urinary tract infections and specific list of antimicrobials including ciprofloxacin, norfloxacin, fluoroquinolones, nalidixic acid, ofloxacin, moxifloxacin, amoxicillin, amoxiclav, cephalexin, nitrofurantoin, fosfomycin, trimethoprim, trimethoprim/sulfamethoxazole, beta-lactam, pivampicillin, pivmecillinam. The reference lists of articles identified during the screening process were searched to identify any relevant papers for inclusion.

Screening and eligibility

All RCTs identified were uploaded to the bibliographic management software (EndNote X9 for Windows). Duplicate studies were removed. All potentially relevant papers identified during the screening process were uploaded to Covidence review software management (27). Title, abstract and full-text screening was completed by two researchers independently and articles that remained
unclear were discussed collectively until consensus was reached. Figure one shows the PRISMA Flow Diagram.

**Inclusion and Exclusion Criteria**

Studies included were trials in adult male patients treated with antimicrobials for urinary tract infection that reported outcome data on orally administrated antimicrobials comparing different treatments (antimicrobial with antimicrobial or placebo/no treatment/symptomatic) in outpatient settings.

Exclusion criteria: conditions not consistent with uncomplicated UTI, setting other than primary care, prophylactic or pharmacokinetic studies.

**Data Extraction**

Two reviewers independently extracted data from selected full-text articles for inclusion. A standardised form was developed in Covidence, which included year of publication, study population, study period, study site (country), demographic characteristics and number of participants, type, dose and duration of antimicrobial treatments being compared, number of days until resolution of symptoms, recurrence of symptoms, emergence of resistance, name and types of adverse events that occurred.

**Study Outcomes**

Outcome data extracted from the eligible RCTs included:

- Relief of symptoms within two weeks of starting treatment (defined as ‘cure’)
- Duration until relief of symptoms
- Relief of symptoms at end of the study (according to study duration time periods: 2 weeks, 30 days, 6 weeks).
- Bacteriological cure
- Recurrence of symptoms (according to study duration time periods: 6 weeks, 5-9 days and 30 days after end of treatment)
- Frequency and type of adverse events
- Antimicrobial resistance (but this was never reported)

**Risk of bias assessment**

Quality was assessed by two reviewers independently for each paper using the Cochrane Risk of Bias Tool for Randomised controlled Trials proposed by Higgins *et al* (28). Disagreement about particular studies were resolved by discussion to develop consensus; a third reviewer was available when necessary.
Results

A total of 1,051 titles and abstracts, and 80 full-text papers were reviewed and three RCTs met the inclusion criteria. Figure 1 below represents the PRISMA flow diagram for study inclusion, with full characteristics of included RCTs in Table 1.

A RCT by van Nieuwkoop et al. (2017) compared 7 with 14 days of oral ciprofloxacin (500mg, twice daily) in 357 women and men aged ≥18 years with a diagnosis of febrile UTI in 35 primary care centres and 7 emergency departments (29). Outcomes included clinical and bacteriological cure and recurrence on day 30 (1-2 weeks after the end of therapy). For this review the authors extracted and shared data from 38 men who were treated in primary care.

Gleckman et al. (1979) conducted an RCT in 42 men with recurrent UTI presenting at the outpatient clinic of the Boston Veterans Administration Center. Patients were randomised to 2 weeks or 6 weeks of trimethoprim-sulfamethoxazole (160/800, twice daily) (30). Outcomes reported were bacteriological cure, relapse (therapeutic failure) and recurrence (new infection) up at any time during the follow up. Follow up was 6 weeks, with 2 weekly cultures after the end of treatment.

The third paper was by Iravani (1962) who enrolled 727 adults with uncomplicated UTI into 7-10 days lomefloxacin (once daily) or norfloxacin (twice daily) in 27 centres throughout the United States (31). Outcomes were clinical and bacteriological cure reported 5-9 days after the end of therapy. Results were reported separately for 38 men enrolled in the study for whom outcome data 6 weeks after the end of treatment was available for 21.

The age of participants was not reported consistently across RCTs. Gleckman (30) reported an overall median age of 60. Males in the van Nieuwkoop (29) study had a median age of 71 and 60 (overall median 64) in each group (7 versus 14 days) and Iravani (31) reported a median age of 53 and 45 in each arm of the RCT.
Comorbidities reported were mainly diabetes, which was reported present in ten patients by Gleckman (30) and nine with diabetes in the van Nieuwkoop study (29) while Iravani (31) did not report on any comorbidities present.

All outcome data are presented in table 1, however the only outcome with sufficient data to allow comparison between RCTs was bacterial cure at the end of therapy.

Table 2 shows an overview of the outcomes of the RCTs. The van Nieuwkoop (2017) study showed 100% bacteriological cure for both durations of ciprofloxacin (7 days versus 14 days) and 90% (17 out of 19) and 100% (19 out of 19) clinical cure for each respectively.

Iravani (1992) compared lomefloxacin and norfloxacin and reported 100% (10 out of 10) and 91% (10 out of 11) bacteriological cure and 100% clinical cure for both groups one week post-therapy.

Gleckman (1979) compared trimethoprim-sulfamethoxazole for 14 days with 42 days with 21 patients in each group, and found all patients had an immediate bacteriological response. In the 14 days group, 6 (29%) reached bacteriological cure, 13 (62%) had recurrence, while in the six week group 13 (62%) and 6 (29%) were reported for each outcome.

Combining the results from the three RCTs shows that 76 male patients with UTI (out of 101 patients, 75%) reported bacteriological cure at the end of the study. Of the 59 patients receiving a fluoroquinolone, 57 (97%) reported bacteriological and clinical cure within 2 weeks after the end of treatment.

**Adverse events**

All three RCTs reported adverse events (AEs) from antimicrobial treatment, with both Gleckman (30) and Van Nieuwkoop (29) reporting separately for male participants. Adverse events were not reported separately for males and females in the Iravani (31) study. In Gleckman, two male patients in the 14-day course of trimethoprim group reported 5 adverse events (chills, sweats and flushing (1), transient rash and pruritus (1)), while 4 adverse events (diffuse urticarial (1), nausea & vomiting (1), rash (1), pruritus (1)) were reported in the 42-day group.
(1), elevated serums creatinine (2) were reported for 4 patients in the group receiving 42 days trimethoprim group. In the Van Nieuwkoop (29) study, two patients who were treated with ciprofloxacin for 7 days reported to have developed pyelonephritis, and no adverse events were reported in the 14 days ciprofloxacin group.

Risk of bias assessment
Risk of bias was low overall for the Van Nieuwkoop (29) study, while a high risk of bias was determined for the Iravani (31) study in three domains: blinding of participants, incomplete outcome data and other sources of bias (unclear time frame, allocation, outcome assessment, only 5% male). In Gleckman (30) risk of bias was unclear for blinding and allocation concealment, while high risk of bias was documented for incomplete outcome data. Table 3 provides an overview of the risk of bias assessment of the included RCTs.


Discussion

Summary

This review identified three randomised controlled trials (RCTs) evaluating the effectiveness and duration of different antimicrobial regimens for uncomplicated UTIs in adult males. Only three papers met the eligibility criteria after full-text screening and were included in the review, two of which are over 20 years old (Gleckman from 1979 (30) and Iravani from 1992 (31)).

Iravani (31) and van Nieuwkoop (29) included both male and female patients, but male only data was obtained from van Nieuwkoop and could be extracted from Iravani’s paper. Both RCTs compared a fluoroquinolone (ciprofloxacin/lomefloxacin and norfloxacin) for a course of 7-14 days and observed at least 97% clinical and bacteriological cure within 2 weeks. However, the total samples size comparing fluoroquinolones is only 59 and not sufficient to draw any conclusions from this. The Gleckman article focused solely on male participants, and was the only study to use trimethoprim to treat male UTIs. Bacteriological cure was reached in 29% of the 2 weeks treatment group, while the six week group reported 62% at the end of the study. One of the differences with the other RCTs was that Gleckman included male patients with a recurrent UTI but it is difficult to ascertain how this may affect the outcomes or the reliability of the findings because of the small sample size. There is clearly a lack of RCTs to allow comparison of findings, especially in relation to trimethoprim. This is particularly concerning as trimethoprim is firstline recommendation according to the NICE (6), SIGN (7) and Danish guidelines (10). Considering the age of the paper and its limited sample size, it emphasizes the need for more up to date and verifiable evidence. Furthermore, no RCTs are available comparing
any of the other types and durations of firstline treatments, such as nitrofurantoin or pivmecillinam. The use of fluoroquinolones as done in the other two RCTs, which is only recommended as secondline or for complicated infections, suggests that many GPs consider male UTIs complicated which may result in suboptimal antibiotic choices or longer courses.

Strengths and limitations

There is a lack of randomised controlled trials (RCTs) comparing antimicrobial treatment options and duration for male UTIs, and most RCTs in this population cover complicated UTIs (32), asymptomatic bacteriuria, mixed and recurrent infections (13, 33), and infections in patients with spinal cord injury (34), generally in the hospital setting (19).

Apart from the lack of evidence to identify the best treatment for male patients presenting with UTI to primary care, our review also shows the absence of relevant patient outcomes. Duration of symptoms, a relevant outcome for patients, is not reported across groups and RCTs and no inference about duration until clinical or bacteriological cure could be made.

Due to low sample size, information on adverse events, even though reported, is not sufficient to make conclusions in relation to type or duration of treatment. However, the variability and extent of adverse events reported in patients treated with trimethoprim in Gleckman 1979 (30) is noteworthy but should not be overstated as it may just reflect good reporting rather than higher risk of adverse events. Pyelonephritis was a serious AE reported by 2/19 patients treated with 7 days ciprofloxacin (29) and would reflect good reporting as no conclusion can be based on this due to the low numbers.

Comparison with existing literature

In a recent systematic review and meta-analysis of RCTs comparing long-term antibiotics for prevention of recurrent urinary tract infection in older adults, no RCTs could be
identified that compared treatments in the male population (35). An observational study by Montelin et al. (36) assessed nitrofurantoin and pivmecillinam for lower UTIs in men, and included patients treated with trimethoprim for comparison. No difference in any clinical outcome was observed between the three antibiotics prescribed (36). Similarly, a recent Danish study comparing treatment durations of pivmecillinam in men, suggested that 5 days with pivmecillinam (400 mg, three times a day) is sufficient in male UTI (37). These studies were retrospective and should ideally be repeated as a prospective RCT. Interestingly, a register study of male prescribing from Norway, found that even though fluoroquinolones and cefalexin were associated with lower antibiotic switch rates than the recommended firstline UTI antibiotics (pivmecillinam, nitrofurantoin and trimethoprim), the occurrence of switching was so low (7%) that the current guidelines were considered to be safe (38).

Implications for research and practice
From this review, it is clear there is a need for larger and more comprehensive RCTs which will include improved diagnosis of male UTI, comparison of different types of treatment as well as their duration and detail of the antimicrobial resistance of the isolated uropathogens. Improved outcome measures, including patient relevant outcomes such as duration of symptoms, should include the recording of symptom scores which would also improve our understanding of treatment and diagnosis of male UTI. As male UTIs are less frequent, to be able to do such a trial, multiple countries and settings could be included to provide a sufficient sample size and improve the treatment of male UTI.

Conclusion
In conclusion, the evidence available is insufficient to make any recommendations in relation to type and duration of antimicrobial treatment for male UTI. Sufficiently powered
RCTs are needed to improve our knowledge of male UTI and identify best treatment regimen for this population in primary care.

Acknowledgement

We would like to thank Dr van Nieuwkoop from the Department of Internal Medicine, Haga Teaching Hospital and Department of Infectious Diseases, Leiden University Medical Center, The Netherlands for his generous support by providing the data from his study (29).

Funding

No funding was received for this review.

Transparency declarations

None to declare.
References


37. Boel JB, Jansåker F, Hertz FB, Hansen KH, Thønings S, Frimodt-Møller N, et al. Treatment duration of pivmecillinam in men, non-pregnant and pregnant women for community-acquired...

Figure 1. PRISMA Flow Diagram

Records identified through database search (n = 1140)

Additional records identified through other sources (n = 88)

Records after duplicates removed (n = 1,052)

Title/Abstract screen (n = 1,052)

Records excluded (wrong study design, no antibiotic, wrong indication) (n = 938)

Full-text articles screen (n = 114)

Records excluded (n = 34)

→ Non-RCT (26)
→ Full text not available (7)
→ Ongoing study (1)

Total full-text review (n = 80)

Articles excluded after data extraction stage (n = 77)

→ Not able to extract male only UTI data (44)
→ Wrong indication (13)
→ Intravenous administration of antibiotic (10)
→ Study in hospital (8)
→ Studies with complicated infections i.e prostatitis (2)

Studies included for analysis (n = 3)
Table 1: Descriptive characteristics of studies included

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total study duration (months)</td>
<td>3</td>
<td>Not available</td>
<td>3</td>
</tr>
<tr>
<td>Total sample</td>
<td>42</td>
<td>727</td>
<td>200</td>
</tr>
<tr>
<td>Male Participants</td>
<td>42</td>
<td>38 (outcome available for 21)</td>
<td>38</td>
</tr>
<tr>
<td>Age of the patients (in years, median)</td>
<td>63</td>
<td>53 and 45</td>
<td>64</td>
</tr>
<tr>
<td>Indication</td>
<td>Recurrent UTI</td>
<td>Uncomplicated UTI</td>
<td>Febrile UTI</td>
</tr>
<tr>
<td>Antimicrobial used</td>
<td>TMP_SMX (160/800mg, twice daily)</td>
<td>Lomefloxacin (400mg, once daily), Norfloxacin (400 mg, twice daily)</td>
<td>Ciprofloxacin (500 mg, twice daily)</td>
</tr>
<tr>
<td>Comorbidities reported</td>
<td>Yes, diabetes (10)</td>
<td>No</td>
<td>Yes, diabetes (9), urological and heart conditions</td>
</tr>
<tr>
<td>Study setting and country</td>
<td>Urology outpatient clinic, USA</td>
<td>Outpatients in medical centres, USA</td>
<td>Primary care centres, the Netherlands</td>
</tr>
</tbody>
</table>
Table 2: Comparison of UTI clinical and bacteriological cure at the end of treatment, and recurrence

<table>
<thead>
<tr>
<th>Studies</th>
<th>Antimicrobial</th>
<th>Dose*</th>
<th>Duration</th>
<th>N</th>
<th>Clinical cure</th>
<th>Recurrence</th>
<th>Bacteriological cure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Gleckman 1979</td>
<td>TMP SMX+ Placebo</td>
<td>160/800 BD</td>
<td>14 days</td>
<td>21</td>
<td>13</td>
<td>62</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>TMP SMX</td>
<td>160/800 BD</td>
<td>42 days</td>
<td>21</td>
<td>6</td>
<td>29</td>
<td>13</td>
</tr>
<tr>
<td>Iravani 1992</td>
<td>Lomefloxacin</td>
<td>400mg QD</td>
<td>7-10 days</td>
<td>10</td>
<td>10</td>
<td>100</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Norfloxacin</td>
<td>400mg BD</td>
<td>7-10 days</td>
<td>11</td>
<td>11</td>
<td>100</td>
<td>10</td>
</tr>
<tr>
<td>van Nieuwkoop 2017</td>
<td>Ciprofloxacin</td>
<td>500mg BD</td>
<td>7 days</td>
<td>19</td>
<td>17</td>
<td>90</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin</td>
<td>500mg BD</td>
<td>14-days</td>
<td>19</td>
<td>19</td>
<td>100</td>
<td>2</td>
</tr>
</tbody>
</table>

*BD: twice a day. QD: once a day. ** one missing urine sample
Table 3: Risk of bias assessment

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sequence Generation</strong></td>
<td>Low ‘Table of random digits’</td>
<td>Low</td>
<td>Low ‘Randomised stratified per centre and gender. Computer generated randomisation list’</td>
</tr>
<tr>
<td><strong>Allocation</strong></td>
<td>Unclear ‘No information provided’</td>
<td>No comment</td>
<td>Low ‘Treatment allocation completed after urine culture results. Restricted access to independent pharmacy’</td>
</tr>
<tr>
<td><strong>Concealment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Blinding of</strong></td>
<td>Unclear ‘No description of the blinding provided’</td>
<td>High ‘No blinding of the participants or personnel only investigators’</td>
<td>Low ‘Double blinding’</td>
</tr>
<tr>
<td>participants and</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>personnel for all</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>**Blinding of outcome</td>
<td>Unclear ‘No description of the blinding provided’</td>
<td>Low ‘Investigators were blinded through third party. “The drugs were dispensed by an independent third party to ensure investigator blinding.”</td>
<td>Low ‘Analysis based on intention to treat population’</td>
</tr>
<tr>
<td>assessors for all</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Source of Bias</td>
<td>Quality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------</td>
<td>---------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data for all outcomes</td>
<td>High</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High 'Data not reported for two patients in each group suffering adverse events'</td>
<td>Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The main outcome (clinical recovery) is reported for 436/727 patients only</td>
<td>Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective outcome reporting</td>
<td>Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unclear 'Both outcomes assessed were reported, but no pre-published protocol is available to control this with the initial design'</td>
<td>Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other sources of bias</td>
<td>Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High 'Men is just 5% of population and a subgroup of the study. Dropout is about 50% for bacteriological cure and unclear for clinical cure'</td>
<td>Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None identified</td>
<td>Low</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>