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Research Paper

Three versus five days of pivmecillinam for community-acquired uncomplicated lower urinary tract infection: A randomised, double-blind, placebo-controlled superiority trial[☆]

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ABSTRACT

Background: To investigate if a 5-day course pivmecillinam (amdinocillin pivoxil) 400 mg three times daily is superior to a 3-day course in women with uncomplicated urinary tract infection (UTI).

Methods: A randomised, double-blind, placebo-controlled trial conducted at nine primary care centres in Denmark. 368 women (18–70 years) with symptoms compatible with UTI were randomised to blinded therapy of 5 days [5d] or 3 days followed by 2 days of placebo [3d] from May 2015 to November 2017. Clinical data were assessed using a validated questionnaire at inclusion (day-0), daily the following 7 days and once again within the 2nd to 6th week after intervention. Bacteriological data were collected prior to intervention and twice between day 7 and 42. Main clinical endpoints were days to symptom resolution within 7 days after inclusion and proportions with clinical success at the end of intervention. Main bacteriological endpoint was proportion of participants with significant reduction of bacteriuria ($\geq 10^2$ CFU/mL) in 1st control urine sample. ClinicalTrialsRegister.eu: 2014-001321-32.

Findings: 180 (5d) and 188 (3d) participants were included in the study (mean age: 35.4 [5d] and 34.9 [3d]). Of these, 125 (70% [5d]) and 122 (66% [3d]) had a positive baseline urine culture. Forty-four participants were lost to follow-up, leaving 161 [5d] and 163 [3d] participants for analysis, respectively. Mean time to symptom resolution was 2.91 (SD 1.46; [5d]) days and 2.94 (SD 1.42; [3d]) days ($P = .894$). Clinical success at the end of treatment occurred for 117 of 153 (76%) receiving the 5d-course and for 115 of 157 (73%) receiving the 3d course (difference 3.2% [95% CI -7.1% - 13.5%]; $P = .601$). Bacteriological success was seen in 92 of 104 (88%) participants given the 5d course and in 86 of 99 (87%) given the 3d course (difference 1.6% [95% CI -8.4%-11.6%]; $P = .895$).

Interpretations: A 5-day course of pivmecillinam was not superior to a 3-day course in clinical or bacteriological outcomes for UTI.

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[☆] **Panel: research in context** Pivmecillinam is an excellent oral antibiotic for uncomplicated urinary tract infection (UTI), but the claimed superiority of a 5-day course over a 3-day course has not been investigated. In this randomised clinical trial of 368 women with UTI there was no significant difference in neither clinical nor bacteriological outcomes between the two courses. Both groups achieved clinical success in less than 3 days and the success rates by the end of treatment were 76% and 73% in the 5-day and 3-day course, respectively. A 5-day course of pivmecillinam was not clinically superior to a 3-day course for UTI. To reduce antibiotic use, a 3-day course is the most rational option for UTI.

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1. Introduction

Uncomplicated lower urinary tract infection (UTI) is the most common bacterial infection in otherwise healthy women with an annual incidence of about 10% [1]. UTI causes considerable short-term morbidity and decreased quality of life, especially if the prescribed antimicrobial therapy is inappropriate [2,3].

Pivmecillinam (amdinocillin pivoxil) is the oral pro-drug of the antimicrobially active mecillinam (amdinocillin), a unique narrow-spectrum beta-lactam antibiotic that is highly effective against the majority of Enterobacteriaceae, including *Escherichia coli* that is the most common pathogen to cause UTI [4,5]. Pivmecillinam is safe and effective in the treatment of UTI [6–11]. Rates of resistance remain low (<6%) in countries where pivmecillinam has been used for decades [12–14]. Further, pivmecillinam has clinical effect against extended-spectrum beta-lactamase (ESBL) producing Enterobacteriaceae [15,16].

Current recommendations suggest pivmecillinam for 3 to 7 days for UTI and suggest that a 5- or 7-day course is probably superior to a 3-day course [5]. However, this recommendation refers to a single randomised controlled trial that showed that a 7-day course was superior to a 3-day course in bacteriological effectiveness at day 8–10 [9]. Thus, a 5-day course has never been studied in a controlled trial and the claimed superiority over a 3-day course has not been investigated. There is little and insufficient evidence to inform the optimal dosage, frequency and duration of pivmecillinam for UTI [7]. Therefore, we conducted a superiority study of pivmecillinam for 5-days compared to 3-days for UTI.

2. Methods

The study protocol was previously published [17]. During the trial the following amendments were made: the study period was extended to 30 months due to slow participant accrual; and the control urine sample arrival timeframes were redefined because the participants secured their first and second urine sample with a wider range than predefined: the first urine sample from 9 to 11 to 7–21 days and the second from 28 to 30 to 15–42 days post-inclusion (after the first), respectively. The study ended in November 2017 when study medication expired.

2.1. Study design and population

This multicentre, parallel randomised placebo-controlled, double-blind, clinical phase IV trial was performed from May 12th 2015 to November 30th 2017 at nine general practice clinics in Denmark. Females (18–70 years) presenting with symptoms of dysuria, frequency (pollakiuria) and/or urgency were screened according to study criteria and asked to participate based on clinical symptoms. Follow-up ended one month after the last participant was included. Participants were included after providing written consent. Common symptoms of UTI (dysuria, frequency or urgency) [18] were assessed based on a validated questionnaire [19]. Each symptom was scored from 0 to 3 (none, mild, moderate or severe) and a cumulative score of ≥ 2 points was required for participation. The presence of these inclusion symptoms and absence of vaginal symptoms has an estimated 90% positive predictive value for uncomplicated UTI, with no clear diagnostic value for urine-dipstick or culture [18]. Exclusion criteria included allergy to beta-lactam antibiotics, current antibiotic therapy, vaginal discharge or pain, pregnancy or lactation, or clear signs (high fever ≥ 38.5 °C or flank pain/tenderness) or high suspicion of pyelonephritis, complicated UTI (indwelling urinary catheter, immunosuppressive therapy, abnormal urinary tracts, recurrent UTI within the last month, serious neurological disease affecting the bladder) or sexually transmitted urethritis. Participants received free antimicrobial treatment. The study was independently reviewed and approved by the Danish Committee on Health Research Ethics (No. H-4-2014-072) and the Danish Health and

Medicine Authority (2014–001321–32). The study was monitored by the Good Clinical Practice Unit (Copenhagen, Denmark).

2.2. Randomisation and blinding

Randomisation was done by block randomisation with 25 blocks of 20 kits each (randomly arranged with 10 kits with a 5-day course of pivmecillinam and 10 kits with a 3-day course of pivmecillinam followed by two days of placebo) by the statistician (TK) using R [20]. Placebo tablets were indistinguishable from the pivmecillinam tablets by colour, taste and design, and packaged in identical blister-packages by the manufacturer (Recipharm AB, Sweden). Each blister package was numbered day 1 to 5 by the hospital pharmacy to ensure that placebo tablets were taken on days 4 and 5. The study participants, treating physicians and the investigators were all blinded. The statistician had no part in collecting the data and only knew that treatments were labelled A or B. What treatment duration A and B referred to was decided by the pharmacy personnel responsible for handing out the tablets and assignments were concealed via sealed nontransparent envelopes at the University Hospital Pharmacy from all investigators and assessors.

2.3. Intervention and procedures

Participants were randomised to a double-blind 5-day or 3-day pivmecillinam course (400 mg three times daily) and instructed to contact the investigators in the absence of improvement. The treating physician completed an inclusion questionnaire together with the participant at day-0 (inclusion day) and a urine sample was secured, analysed by dipstick and forwarded by courier service to culture and susceptibility testing at the Department of Clinical Microbiology, Hvidovre University Hospital, Denmark (DCM). A symptom diary (day 0–7), a long-term follow-up questionnaire (day 8–42), and two follow-up urine sample kits were provided by DCM for each participant to secure and submit for microbiological diagnostics. Detection of non-susceptible urinary pathogens prompted a message to the participant to see her physician, to change treatment if symptoms were still present (considered treatment failure). The data source can be viewed in Appendix Table 1.

2.4. Clinical outcomes

Clinical outcomes were participant reported and predefined [17]. In brief, clinical success was defined as a symptom score of < 2 and clinical relapse was defined as a resolution of symptom score to < 2 followed by a score of ≥ 2 . The primary clinical outcome was mean number of days to symptom resolution within 7 days post-inclusion and proportion of participants cured at the last day of treatment. Secondary clinical outcomes analysed were proportion (%) of participants with relapse of a new UTI occurring 8–42 days post-intervention (reported as “new UTI” or symptom-score ≥ 2 in the long-term follow-up questionnaire) and number of participants that acquired pyelonephritis.

2.5. Bacteriological outcomes

The outcomes were predefined [17]. In brief, bacteriological success was defined as either no growth or a significant reduction ($\geq 10^2$ decrease in colony-forming units/mL) in the first control urine sample. Bacteriological relapse was defined as initial bacteriological success followed by significant growth in the second control urine sample with the same bacterial species.

2.6. Ancillary outcomes

Adverse reactions and clinical efficacy at day-7 were analysed as ancillary outcomes. Adherence rates were also measured daily as “full adherence” (taken all tablets every 8th hour), “corrected adherence failure” (forgotten to take one tablet but retrieved it later the same day), or “adherence failure” (forgotten to take at least one tablet). We also observed the impact and retrieval in quality of life (QoL) for the participants before, during and after intervention.

2.7. Laboratory methods

Urine samples were processed at the DCM according to standard procedures by spreading 10 µL on each of a chrome-agar and 5% blood agar plate. Susceptibility testing performed on Mueller-Hilton agar (Substrate production, DCM, Herlev University Hospital, Denmark) according to the European Committee on Antimicrobial Susceptibility Testing [21]. Presence of significant bacteriuria was defined as $\geq 10^3$ bacteria/mL for *E. coli* and *Staphylococcus saprophyticus*, and $\geq 10^4$ bacteria/mL for other typical urinary tract pathogens [22]. Since these cut-offs could exclude patients with uncomplicated UTI [23] and laboratory examinations do not seem to alter the diagnosis [18], the presence of significant bacteriuria was not a inclusion criteria.

2.8. Statistical methods

2.8.1. Sample size

In the predefined sample size calculation [17] the superiority hypothesis of 15% was based on previous studies on pivmecillinam [9, 11]. Assuming an efficacy of 90% for the 5-day course and 75% for the 3-day course, an alpha of 0.05, a beta of 0.2, 30% loss to follow up and 30% culture negative rate at baseline, targeted enrolment was 460 participants with symptoms of UTI, of which 322 participants were evaluable for clinical outcomes and at least 226 with microbiologically confirmed UTI.

2.8.2. Analyses

The statistician was blinded through the analyses and all data remained blinded as group A and B until all statistical analyses were completed. Baseline characteristics were described as proportions or means with standard deviation. Categorical outcomes were analysed by χ^2 test or Fisher exact. Adjusted analyses were done by logistic regression models (adjusted variables are listed in the result tables). Models were also stratified according to positive or negative baseline urine, with estimates presented as odds ratio (OR) with 95% confidence intervals (95% CI). Continuous outcomes were analysed by independent two-sample t-test or the Wilcoxon sum-rank test if the normality assumption was rejected. Days to clinical success was also modelled by a linear regression, the model was adjusted and stratified similarly to the logistic regression models with estimates presented as mean differences with 95% CI. The statistical methods were defined prior to unblinding and analysis (Supplementary Appendix 1). Post-hoc sub-analysis on participants with *E. coli* baseline bacteriuria was introduced to assess the outcomes for the most common pathogen in UTI. Post-hoc sensitivity analysis was done by replacing all missing outcomes with either failure (worst case) or success (best case) and repeating the analysis with this new data. All analyses were performed using R 3.2.2 [20]. $P < .05$ were considered statistically significant.

3. Results

In total, 372 participants with clinical symptoms of UTI were included (Fig. 1). Three participants were excluded because of *Chlamydomphila trachomatis* urethritis and one for genital herpes. Of the remaining 368 participants (80% of the planned intention to treat sample size), 180 were randomised to a 5-day and 188 to 3-day course of

pivmecillinam, respectively. However, complete loss to follow-up was significantly lower (12%) than anticipated (30%) (19 and 25 participants, respectively), resulting in an evaluable per-protocol population of 161 and 163 in the 5-day and 3-day course, that was one participant above the calculated sample size of 322. Similarly, the number of culture positive cases ($n = 247$) was above the target of 226. However, not all participants were fully evaluable for all outcomes because of incomplete follow-up data.

3.1. Baseline demographics

The groups were similar in baseline characteristics with average age of 35.4 and 34.9 years in the 5-day and 3-day course, respectively (Table 1). Baseline characteristics, stratified by urine culture finding were similar between groups (Appendix Table 2).

3.2. Baseline urine cultures

Baseline urine cultures yielded significant growth in 125 (69.4%) and 122 (64.9%) in the 5-day and 3-day course, respectively. *E. coli* was the most frequent pathogen (95 [76%] and 105 [86%]) followed by *S. saprophyticus* in 16 (12.8%) and 6 (4.9%) episodes (Appendix Table 3). Ten *E. coli* were ESBL-producers: 3 cases in the 5-day and 7 cases in the 3-day course. One *E. coli* was resistant to mecillinam (3-day). The proportion of mecillinam non-susceptible gram-positive bacteria was 23 (18.4%) and 6 (4.9%) in the 5-day and 3-day course, respectively.

3.3. Clinical outcomes

The mean time to symptom resolution was 2.91 (1.46) and 2.94 (1.42) days for the 5-day and 3-day course, respectively (difference – 0.02 [95% CI -0.4 – 0.3]; $P = .894$; Table 2 & Fig. 2). Adjusted analyses were comparable with difference estimates ranging from –0.17 to 0.27 (Appendix Table 4).

Clinical success at end of treatment occurred for 117 of 153 participants (76%) receiving the 5-day course and in 115 of 157 participants (73%) receiving the 3-day course (difference 3.2% [95% CI -7.1% - 13.5%]; $P = .601$). Adjusted analyses were comparable with OR ranging from 0.84 to 1.75. In participants with *E. coli* UTI (Appendix Table 5), clinical success occurred in 69 of 86 (80%) and 68 of 90 (76%) participants (difference 4.7% [95% CI -8.7%-18%]; $P = .572$). The adjusted OR was 1.36 (95% CI 0.65–2.86; $P = .41$).

Clinical success at day-7 occurred in 116 of 148 participants (78%) receiving the 5-day course and in 127 of 152 participants (84%) receiving the 3-day course (difference – 5.2% [95% CI -14.7% - 4.4%]; $P = .320$). Ten participants in each group relapsed after initial clinical success at the end of treatment.

Clinical success at the long-term follow-up (day-28) occurred in 95 of 128 participants (74%) receiving the 5-day course and in 109 of 129 participants (84%) receiving the 3-day course (difference – 10% [95% CI -21%-0.3%]; $P = .060$). Mean time to clinical relapse was 20.1 days (SD 8.7) and 23.1 days (SD 9.48) for the 33 and 20 participants in the 5-day and 3-day course, respectively. The results did not change between the groups when participants with missing data at day-28, but clinical failure on day-7 ($n = 13$ [5d]; $n = 11$ [3d]), were included as clinical failure at day-28 in the post-hoc analysis. Mean time to long-term follow-up was 29 days (SD 4).

For clinical success at day-7 and day-28, respectively, the adjusted analyses were comparable (Appendix Table 4).

The post-hoc analysis on missing data for worst- or best-case models did not alter the comparative findings or interpretation of the results (results not shown).

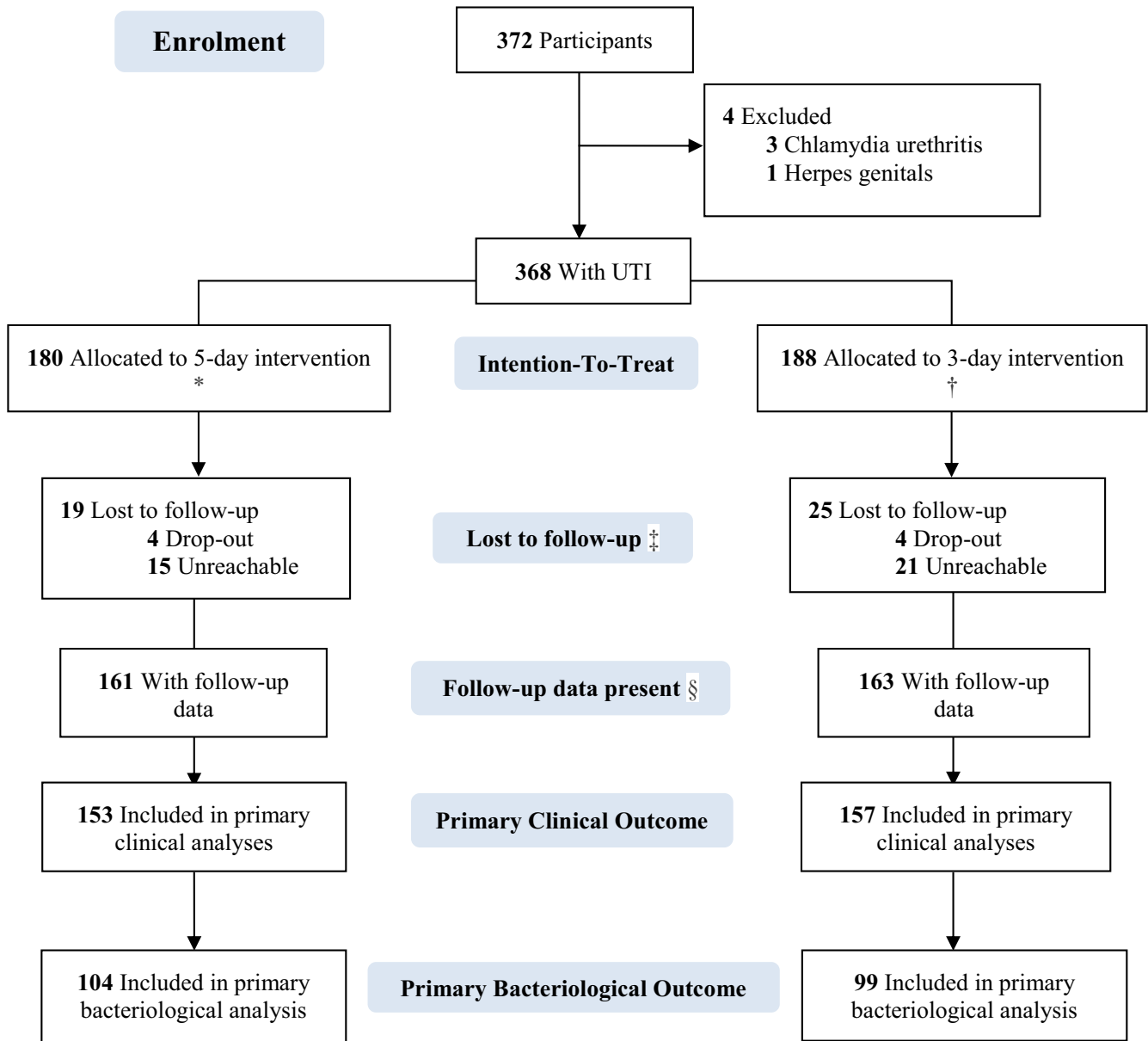


Fig. 1. Study flowchart * 125 With baseline bacteriuria (69.4%), † 122 With baseline bacteriuria (64.9%), ‡ No clinical nor bacteriological follow-up data received. § Follow-up questionnaire missing in 8 and 6 participants in 5-day and 3-day arm, respectively. Note: The number of cases assessed for eligibility at General Practitioner Clinics were not recorded because of financial and logistics imitations.

3.4. Bacteriological outcomes

Bacteriological success in the first control urine sample occurred in 92 of 104 (88%) and in 86 of 99 (87%) participants in the 5-day and 3-day course, respectively (difference 1.6% [95% CI -8.4% - 11.6%]; $P = .895$; Table 3). Clinical failure on day-7 occurred in 63% (7/11) with concomitant bacteriological failure and in 38% (5/13) of the participants with bacteriological success ($P = .22$). The adjusted OR was 0.85 (95% CI 0.35–2.06; $P = .72$) for bacteriological success (Appendix Table 6).

Bacteriological success in the second control urine sample occurred in 82 of 90 (91%) and in 75 of 89 (84%) participants in the 5-day and 3-day course, respectively (difference 6.8% [95% CI -3.9% - 17.5%]; $P = .244$). Of the participants with bacteriological failure 4 out of 8 [5d] and 10 out of 14 [3d] cases were with the same bacterial species ($P = .63$). Ten urine samples arrived in the overlapping window (15–21 days post inclusion); the exclusion of these did not alter the results.

Sub-analysis of *E. coli* UTI (Appendix Table 5–6) demonstrated early bacteriological success in 71 of 81 (88%) and 76 of 88 (86%) receiving the 5-day course and the 3-day course, respectively (difference 1.3% [95% CI -10% - 12.6%]; $P = .984$) with an adjusted OR of 0.86 (95% CI 0.34–2.16; $P = .74$).

3.5. Resistant bacteria

All but one ESBL-producing *E. coli* were susceptible to mecillinam and all, except one, had clinical success at day-7. Three participants had significant growth of the ESBL-producing isolate in the first urine sample, and of these, two were asymptomatic and the symptomatic participant was successfully retreated with 5-day pivmecillinam course.

Of the 21 *S. saprophyticus* (presumed non-susceptible to mecillinam), 13 of the 15 participants (87%) had bacteriological success in first control urine sample and 11 of the 17 participants (65%) had clinical success at day-7 (including the two bacteriological failures in

Table 1
Baseline characteristics.

| All allocated participants | Mean(SD)/No.(%) | | p-value |
|-----------------------------------|--------------------------|--------------------------|---------|
| | 5-day course (n = 180 *) | 3-day course (n = 188 †) | |
| Mean age | 35.4 (13.6) | 34.9 (12.9) | 0.724 |
| No. 18–49 years | 148 (82.2) | 161 (85.6) | 0.453 |
| No. 50–70 years | 32 (17.8) | 27 (14.4) | |
| No. significant bacteriuria | 125‡ (69.4) | 122§ (64.9) | 0.413 |
| No. positive leucocyte esterase | 164 (96.5) | 174 (94.6) | 0.544 |
| Weight < 70 kg | 102 (69.9) | 114 (73.1) | 0.624 |
| Weight > 70 kg | 44 (30.1) | 42 (26.9) | |
| Mean symptom score | 6.40 (1.83) | 6.25 (1.85) | 0.476 |
| Mean symptom score ¶ | 6.03 (1.77) | 6.05 (1.71) | 0.913 |
| Frequency (97%) ** | 2.05 (0.62) | 2.02 (0.75) | 0.687 |
| Urgency (94%) ** | 2.02 (0.84) | 2.01 (0.83) | 0.945 |
| Dysuria (93%) ** | 1.97 (0.82) | 2.02 (0.81) | 0.522 |
| No. symptom score 2–5 points | 62 (34.4) | 55 (29.3) | 0.339 |
| No. symptom score > 5 points | 118 (65.6) | 133 (70.7) | |
| Mean days with symptoms | 3.6 (4.2) | 3.6 (4.3) | 0.913 |
| No. with no UTI the previous year | 91 (51.7) | 99 (53.2) | 0.607 |
| No. ≥ 1 UTI the previous year | 85 (48.3) | 87 (46.8) | |
| Mean annual UTI incidence | 1.1 (2.0) | 1.1 (2.0) | 0.864 |

Per-protocol analyses: *161 (89.4%) one with only bacteriological data; †163 (86.7%) two with only bacteriological data; ‡114 (91.2%); §107 (87.7%). || Participant reported. ¶ Physician reported. ** Proportions of all included participants that had the symptom.

first control urine sample). The failures were evenly distributed among the treatment groups.

Two of four participants with *Enterococcus* spp. in their baseline urine sample had bacteriological failure, but none were clinical failures. Bacteriuria with *Enterococcus* spp. increased from 1.1% to 6.1% (n = 14) in baseline urine to first control urine sample.

There was only one case in each treatment group (n = 2) with acquired mecillinam resistance (both *E. coli*) in the follow-up urine samples.

Table 2
Clinical outcomes.

| Clinical outcomes | No./Total No. (%) | | Difference (95% CI) | P-value |
|--|--|---|---------------------|---------|
| | 5-day course (n = 180) [Urine sample negative:positive]† | 3-day course (n = 188) [Urine sample negative:positive] | | |
| Primary | | | | |
| Time to clinical success (Mean, days [SD]) | 2.91 (SD 1.46) | 2.94 (SD 1.42) | −0.02 (−0.4–0.3) | 0.894 |
| Clinical success (End of intervention) | 117/153 (76) | 115/157 (73) | 3.2% (−7.1–13.5) | 0.601 |
| Clinical failure (End of intervention) | 36/153 (24) | 42/157 (27) | | |
| Missing data | 27/180 (15) | 31/188 (16) | | |
| Ancillary (day-7) | | | | |
| Clinical success | 116/148 (78) [98: 12] | 127/152 (84) [102: 18] | −5.2% (−14.7–4.4) | 0.320 |
| Clinical failure | 22/148 (15) [15: 4] ‡ | 15/152 (10) [9: 4] § | | |
| Clinical relapse (After initial success) | 10/148 (7) [6: 4] ‡ | 10/152 (7) [8: 1] § | | |
| Secondary (day-28) * | | | | |
| Clinical success | 95/128 (74) [87: 1] | 109/129 (84) [96: 8] | −10% (−21.0–0.3) | 0.060 |
| Clinical failure/relapse | 33/128 (26) [22: 10] | 20/129 (16) [11: 7] ¶ | | |
| Time to relapse (Mean, days [SD]) | 20.1 (SD 8.7) | 23.1 (SD 9.5) | | |
| Missing data | 52/180 (29) | 59/188 (31) | | |

* Participants with continues clinical success or recurrence of symptoms reported in day-28 questionnaire. † Negative urine: eradication or contamination. Bacteriuria: Significant growth of uropathogenic bacteria (see in material/methods). ‡ 2 with continues clinical failure had a new bacteria in the 1st control urine sample and 2 had the same bacteria as in pre-treatment urine sample. All 4 with clinical relapse had the same *E. coli* bacteria as in pre-treatment urine sample. One participant had symptoms of pyelonephritis. § Clinical failures with concomitant bacteriuria had the same bacteria as in the pre-treatment urine sample. || 4/10 with bacteriuria had the same bacteria in the 2nd control urine sample as in the pre-treatment urine sample, however, all but 1 (asymptomatic) had been vanished in the 1st control urine sample. ¶ 4/7 with bacteriuria in the 2nd control urine sample had the same bacteria as in the pre-treatment urine sample, which had been vanished in the 1st control urine sample. Definitions: Confidence interval (CI). Last day in diary (day-7).

3.6. Pyelonephritis

Three (1.8%) and four (2.1%) participants developed symptoms suggestive of pyelonephritis (fever, chills and/or flank-pain) in the 5-day and 3-day course, respectively. They all had *E. coli* in their baseline urine sample and 5 of 7 participants also yielded *E. coli* in their control urine sample. They were all re-treated by their primary care provider.

3.7. Adherence to intervention

Data on adherence was reported by 304 participants, of these 50 (16.4%) reported having forgotten at least one dose. Full adherence varied between 77.3% to 92.5% (highest in the beginning), corrected adherence failure between 4 and 17% and adherence failure from 4 to 10% (highest in the end), and evenly distributed between the two groups (Appendix Table 7).

3.8. Symptoms and impact on quality of life, QoL

The five measurements of QoL were negatively affected by the UTI at day-0 and improved in accordance with symptom resolution (Appendix Fig. 1).

3.9. Possible adverse reactions

A total of 306 participants reported on adverse events in the diary (Appendix Table 8). There were no serious adverse events and no reported cases of *Clostridium difficile* associated diarrhoea. Fifty-one of 150 (34%) and 66 of 156 (42%) of the participants in the 5-day and 3-day course, respectively, experienced one or more adverse reactions (difference = 8.3% [95% CI −20%–3.2%; P = .168]). Four participants in each group of 216 (3.7%) with follow-up data on day-28 reported adverse reactions.

4. Discussion

In this controlled study of participants treated in primary care, superiority of pivmecillinam 400 mg three times daily for 5-days versus 3-

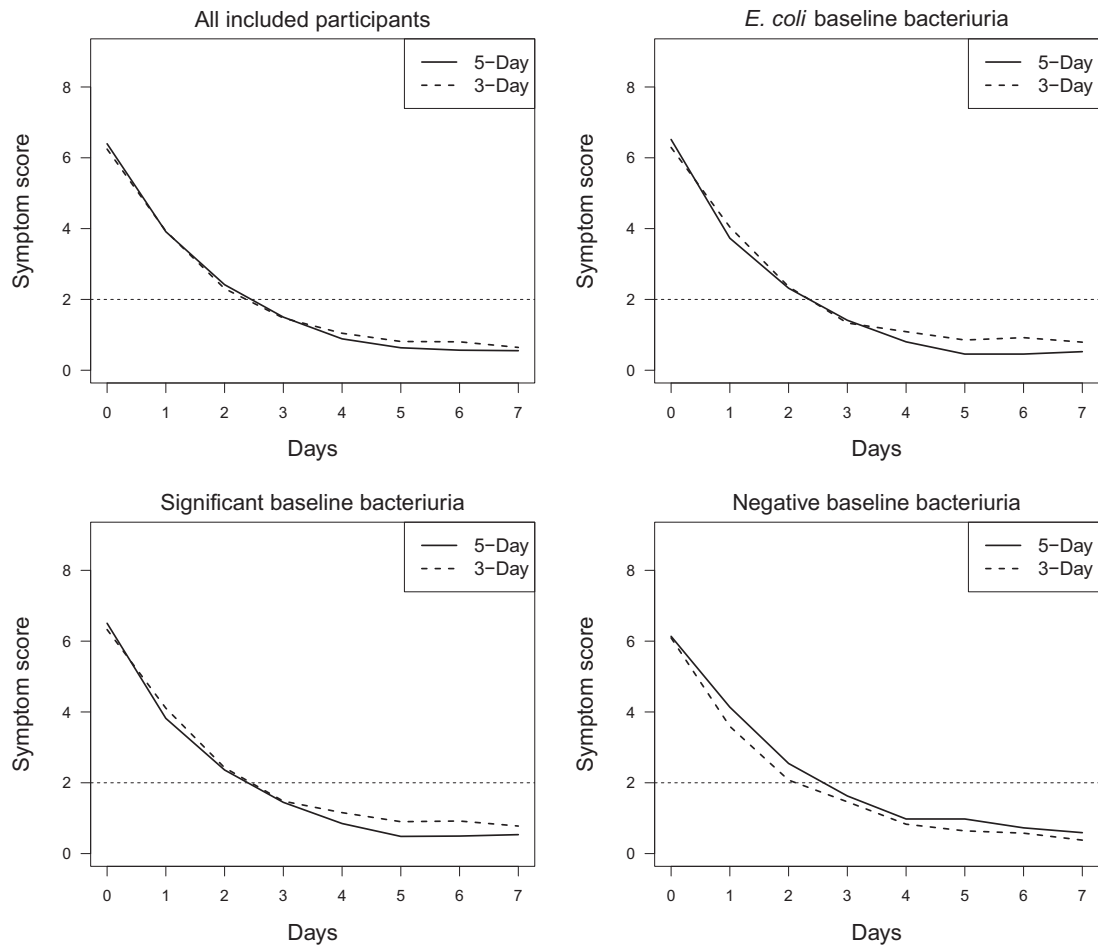


Fig. 2. Symptom resolution over time. The cumulative UTI symptom score (i.e. for the symptoms dysuria, frequency and urgency) was calculated daily. Each symptom was scored 0–3 points (i.e. none, mild, moderate or severe) daily in the participant reported diary.

days was not demonstrated for neither clinical nor bacteriological outcomes from uncomplicated urinary tract infection. Clinical and bacteriological efficacy was high at 81% and 88%, respectively. The primary clinical outcome at the end of intervention only differed 3.2% in favour of the 5-day course, whereas the secondary clinical outcome at day-28 yielded a 10% difference in favour of the 3-day course.

Compared to the two studies of pivmecillinam by Ferry et al. [9] and Nicolle et al. [11], included in the European and North American guidelines for antibiotic treatment of UTI [5], our study found similar clinical outcomes of the 3-day course around day-7 at 84% as Nicolle et al., but higher than Ferry et al. (55%). Our finding of 87% early bacteriological success was higher than Ferry et al. (84%) and Nicolle et al. (75%), respectively. Both studies used a lower dose of pivmecillinam (400 mg twice daily) suggesting that dosing thrice daily may be more effective. This is supported by a recent randomised controlled trial of pivmecillinam compared to ibuprofen for UTI, where a thrice daily course of pivmecillinam 200 mg for 3 days demonstrated a 91% clinical success rate at day-7 [24]. This study only had one ESBL-producing *E. coli*. ESBL-producing *E. coli* have a higher MIC for mecillinam [25]. In a settings of high prevalence of ESBL-producing *E. coli*, pivmecillinam 400 mg thrice daily is recommended based on observational data that showed high and even comparable outcomes for UTI caused by ESBL-producing and non-producing *E. coli* when a dose of 400 mg thrice daily was used [15,16], but not with a 200 mg dose [15,26]. The treatment success of ESBL-producing *E. coli* was also high in our study, with only one failure out of ten cases.

Pivmecillinam is assumed to have inferior efficacy to other first-line alternatives such as nitrofurantoin and fosfomycin [5]. However, a

recent study, that was comparable to ours, found cure rates of nitrofurantoin that were very similar to ours (70%), while cure rates were lower for fosfomycin [27]. Further, the time to symptom resolution was similar in both studies, while long-term clinical success of pivmecillinam was higher than for nitrofurantoin course (84% vs. 70%). A randomised controlled study comparing pivmecillinam and nitrofurantoin would determine the best option for treatment of uncomplicated UTI. In the meantime, pivmecillinam for 3 days or nitrofurantoin for 5 days appears to have comparable effect for treatment of uncomplicated UTI.

S. saprophyticus is frequently found in UTI and resistant to mecillinam in vitro [1,6]. However, the bacteriological success (87%) and clinical (65%) success were both high in our study. Previously findings have also shown that pivmecillinam seems effective for UTI caused by bacteria not presumed susceptible to mecillinam [6,10].

There was no significant difference in reported adverse events between the groups. The reported adverse events were mild and mostly gastro-intestinal (24%). The reported rate of AR was higher than expected compared to other studies with pivmecillinam [8,9,11]. A possible explanation may be that participants in our study recorded adverse events daily and also received a higher daily dose compared to most participants in the other studies.

A shorter duration than three days could be sufficient, however, this study and others [24] found a time to symptom resolution to around three days. The findings supporting a 3-day course are in line with the recent antibiotic mantra that “shorter is better” [28] and the utility of narrow-spectrum antimicrobial chemotherapies; both important in the context of fighting antimicrobial resistance.

Table 3
Bacteriological outcomes.

| Bacteriological outcomes | No./Total No. (%) [Clinical: failure, success] | | Difference % (95% CI) | P- Value |
|---|--|---------------------------|-----------------------|----------|
| | 5-day course (n = 180) | 3-day course (n = 188) | | |
| First control urine sample | | | | |
| Control cultures obtained/positive baseline culture | 104/125 (83) [20, 77] | 99/122 (81) [17, 79] | | |
| Primary outcome | | | | |
| Bacteriological success * | 92/104 (88) [13, 73] | 86/99 (87) [12, 71] | 1.6 (−8.4–11.6) | 0.895 |
| Bacteriological failure | 12/104 (13) [4, 7] | 13/99 (13) [5, 8] | | |
| Missing data | 21/125 (17) | 23/122 (19) | | |
| Control cultures obtained/negative baseline culture | 42/53 (81) [9, 32] | 50/62 (81) [6, 37] | | |
| New significant bacteriuria in first control urine | 4/42 (10) [1, 2] | 5/50 (10) [1, 4] | | |
| Second control urine sample† | | | | |
| Control cultures obtained/positive baseline culture | 90/125 (72) [13, 71] ¶ | 89/122 (73) [10, 69] | | |
| Secondary outcome | | | | |
| Bacteriological success ‡ | 82/90 (91) [7, 70] | 75/89 (84) [4, 65] | 6.8 (−3.9–17.5) | 0.244 |
| Relapse bacteriuria | 4/90 (4) [4, 0] | 10/89 (11) [3, 4] | | |
| New bacteriuria | 2/90 (2) [2, 0] | 2/89 (2) [2, 0] | | |
| Continuous bacteriuria § | 2/90 (2) [0, 1] | 2/89 (2) [0, 1] | | |
| Missing data | 35/125 (28) | 33/122 (27) | | |
| Control cultures obtained/negative baseline culture | 38/53 (71) [7, 27] | 43/62 (69) [3, 39] | | |
| New significant bacteriuria in first control urine | 3/39 (8) [1, 2] | 3/43 (7) [1, 2] | | |

* Between day 7–21. The 5-day course: 84/92 eradication, 2/92 $\geq 10^2$ reduction pathogenic bacteria, 6/92 contamination. The 3-day course: 80/86 eradication, 1/86 $\geq 10^2$ reduction of pathogenic bacteria, 5/86 contamination; † Not including first urine samples from day 15–21. ‡ Between day 15–42. The 5-day course: 75/82 eradication, 7/82 contamination (asymptomatic). The 3-day course: 70/75 eradication, 5/75 contamination (asymptomatic); § Significant growth of same pathogenic bacteria as in pre-treatment and first control urine sample. || Reported as symptom-score ≥ 2 (symptomatic) or < 2 (asymptomatic) in the last day in the diary (day-7; inclusion-day + 7 days). ¶ Symptomatic reported as symptom-score ≥ 2 and/or recurrence of UTI in the 28-day questionnaire. Asymptomatic reported as symptom-score < 2 and/or no recurrent UTI in the 28-day questionnaire. Definitions – Contamination: insignificant growth of bacteria; Eradication: Sterile urine or mix flora.

This study has several limitations. First, a lower rate of eligible participants than anticipated and expiration of the study drug necessitated premature study termination when only 80% of the planned sample size had been recruited. However, the lost to follow-up rates was lower than expected. Thus, 97.5% of the 5-day group and 95% of the 3-day group projected for the primary clinical outcome analysis was reached. Secondly, no data were collected on previous antibiotic therapy (ongoing was an exclusion criteria), intra-cervical-devices, or hormonal therapy. Lastly, the study was designed to demonstrate superiority but not non-inferiority or equivalence between the two treatment arms. However, the boundaries of the 95% CI for clinical success of the 5-day course compare to the 3-day course at the end of treatment (13.5%), day-7 (4.4%) and day-28 (0.3%) were all within our pre-estimated 15% difference; thus, showing some evidence supporting a clinical relevant non-inferiority of the 3-day course compared to the 5-day course.

In summary, a 5-day course of pivmecillinam was not superior to a 3-day course of pivmecillinam for uncomplicated lower urinary tract infection. Given the risk of adverse events, development of antimicrobial resistance and collateral damage associated with the length of antibiotic use, this study did not find evidence supporting that a 5 days course should be preferred over a 3 days course.

Trial registration

ClinicalTrialsRegister.eu: 2014–001321–32.

Protocol

The protocol has previously been published in an open-access journal in 2016 [17]. Original study protocol and amendments will be available on reasonable request from corresponding author.

Ethical considerations

The study was approved by the Danish committee on biomedical research ethics for the capitol region of Denmark (No. H-4-2014-072) and informed consent will be obtained from all participants prior to enrolment.

Authors' contribution

FJ was the primary investigator and JDK was the primary supervisor of the project. *Concept and design:* NFM, JDK and FJ. *Acquisition of data:* FJ, JV, LB and ST. *Translating raw data to electronic database:* FBH. *Analysis or interpretation of data:* FJ, ST, TLB, TK, NFM and JDK. *Drafting of the manuscript:* FJ. *Critical revision of the manuscript for important intellectual content:* ST, TLB, NFM, JDK, FBH and LB. *Statistical analysis:* TK. *Obtained funding:* NFM, JDK and FJ. *Administrative, technical, or material support:* JV, ST, JDK and FBH. *Supervision:* JDK, TLB and NFM. All authors take responsibility for the integrity of the data and the accuracy analysis and interpretation of data and have approved the final version of the manuscript.

Consent to publish

Given prior to enrolment in the study.

Potential conflicts of interest

All authors have completed the ICMJE uniform disclosure form (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the

submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Transparency declaration

All authors affirm that this manuscript is conducted honest, accurate, and transparent.

Availability of data and materials

Online Supplementary Appendix 2 contains the analysed electronic raw dataset from which the results derived. All the anonymous raw data and statistical code used to generate results will be available on reasonable request from corresponding author.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.eclinm.2019.06.009>.

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