

Treatment duration of febrile urinary tract infection: a pragmatic randomized, double-blind, placebo-controlled non-inferiority trial in men and women

BACKGROUND:

- Recommendations upon optimal treatment duration of UTIs in men, the elderly, hospitalized patients, and patients with comorbidities or bacteremia, remain unclear.
- fUTI as the clinical syndrome of interest was used because it is a broadly recognized specific clinical presentation of patients.

OBJECTIVE

- To compare clinical and bacteriological cure both short and long term in patients with febrile UTI (fUTI) on antibiotics (ciprofloxacin) for 7 or 14 days.

METHODS

- **Study design:** randomized, placebo-controlled, double-blind, multicenter, non-inferiority trial
- **Study duration:** 14 days
- **Inclusion criteria:** fever 38.2 °C and/or a history of feeling feverish with shivering or rigors in the past 24 hours, one or more symptoms suggestive of UTI, and positive urine nitrate test and/or pyuria
- **Exclusion criteria:** known allergy for fluoroquinolones, pregnancy or lactation, polycystic kidney disease, permanent renal replacement therapy, kidney transplantation, residence outside The Netherlands, and inability to speak or read Dutch.
- **# of patients enrolled:** 357 subjects were assessed for study participation. 200 subjects underwent randomization.
- **Drug regimens/dosages used:** 1st week of treatment was open label. 2nd week, treatment was continued double-blinded with either ciprofloxacin 500 mg or placebo PO BID
- **Primary outcome measure:** clinical cure rate through the 10- to 18-day post-treatment visit
- **Secondary outcome measures:** bacteriological cure through the 10- to 18- day post-treatment visit, clinical cure rate through the 70- to 84-day post-treatment visit, all-cause mortality, adverse event rate determined at 10-18 days and 70-84 days post-treatment, and rate of UTI relapses.
- **Power:** Assuming a non-inferiority margin of 0.10, 1-tailed alpha of 0.05, and a power of 0.90, the required sample size per group was 200
- **Data handling method:** Both intention-to-treat and per-protocol analyses

RESULTS

- **# patients completed the study:**
 - **ITT Analysis:** 94 in the 7 day antibiotic treatment and 100 in the 14 day treatment
 - **Per-Protocol Analysis:** 92 in the 7 day antibiotic treatment and 93 in the 14 day treatment
- **Primary outcome measure:**
 - The difference in short-term clinical cure rate between both treatment arms was 4.5% (90% CI, -10.7 to 1.7, $P_{\text{non-inferiority}} = 0.072$).
 - In women, short-term clinical cures for the 7- and 14-day arms were 47 of 50 (94%) versus 54 of 58 (93%), respectively. The difference in cure rate was 0.9% (90% CI, -6.9 to 8.7, $P_{\text{non-inferiority}} = 0.011$, non-inferiority confirmed).

- In men, clinical cure rates differed significantly between those treated for 7 or 14 days (38 of 44; 86% vs. 40 of 41; 98%). The difference in cure rate was -11.2 (90% CI, -20.6 to -1.8, $P_{\text{non-inferiority}} = 0.417$, $P_{\text{superiority 2-sided}} = 0.050$, superiority of 14-days treatment confirmed.
- **Secondary outcome measures:** For cumulative clinical cure rate (70 to 84 days post-treatment), 94 patients were evaluable in each treatment arm. Clinical cure rates were high: 93% vs. 91% in patients treated for 7 or 14 days; difference 1.1% (90% CI, -5.5 to 7.6, $P_{\text{non-inferiority}} = 0.005$, non-inferiority confirmed.
- **Author's conclusion:** Women with fUTI can be treated successfully with antibiotics for 7 days. In men, 7 days of antibiotic treatment for fUTI is inferior to 14 days during short-term follow-up but it is non-inferior when looking at longer follow-up.

STRENGTHS

- Proper randomization achieved
- Per-protocol was used
- Proper inclusion and exclusion criteria

LIMITATIONS

- Short study duration
- No statistical analysis for adverse events nor baseline characteristics
- No data provided to account for adherence
- Not 100% confirmation of positive urine cultures
- Wrong interpretation for conclusion in men
- Sample size per group was lower than expected

CONCLUSION

- The study's findings show that women with fUTI can be treated successfully with antibiotics for 7 days. In men, 7 days of antibiotic treatment for fUTI is inferior to 14 days during short-term follow-up and long-term follow-up.
 - According to the IDSA for pyelonephritis in women, ciprofloxacin (500 mg BID) for 7 days, with or without an initial 400-mg dose of intravenous ciprofloxacin, is an appropriate choice for therapy in patients not requiring hospitalization.
 - 7 day treatment of antibiotics would be more cost-effective compared to 14 day treatment. A better chance of adherence for the 7 day treatment also applies.
- Future research:
 - More studies on the optimal treatment duration for men with fUTI along with a higher percent of patients with positive urine cultures for bacteria.

Reference: van Nieuwkoop, van der Starre WE, Stalenhoef JE, et al. Treatment duration of febrile urinary tract infection: a pragmatic randomized, double-blind, placebo-controlled non-inferiority trial in men and women. *BMC Med.* 2017;15(1):1-9.