Ciprofloxacin for 7 days versus 14 days in women with acute pyelonephritis: a randomised, open-label and double-blind, placebo-controlled, non-inferiority trial

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Summary

Background Acute pyelonephritis is a common infection in adult women, but there is a paucity of controlled trials of its treatment and the optimum duration of antibiotic treatment has not been properly defined. We compared the efficacy of ciprofloxacin for 7 days and 14 days in women with community-acquired acute pyelonephritis.

Methods In a prospective, non-inferiority trial undertaken at 21 centres of infectious diseases in Sweden, women (aged ≥18 years) who were not pregnant and had a presumptive diagnosis of acute pyelonephritis were randomly assigned to oral treatment with ciprofloxacin 500 mg twice daily for 7 days or 14 days. The first week was open label. A computer-generated randomisation list in block sizes of two was used for treatment allocation in a 1:1 ratio. The study was double-blind and placebo-controlled during the second week of treatment, which was either continuation of ciprofloxacin 500 mg or placebo tablets twice daily according to the randomisation code. Patients, carers, site investigators, and trial coordinating centre staff were masked to group assignment. The primary endpoint was the clinical and bacteriological outcome 10–14 days after completion of treatment with active drug. Analysis was by per protocol. This trial is registered with EudraCT, number 2005-004992-39, and ClinicalTrials.gov, number ISRCTN73338924.

Findings 126 of 248 patients were randomly assigned to 7 days and 122 to 14 days of ciprofloxacin. 73 and 83 patients, respectively, were analysed. Short-term clinical cure occurred in 71 (97%) patients treated with ciprofloxacin for 7 days and 80 (96%) treated for 14 days (difference –0·9%; 90% CI –6·5 to 4·8; p=0·004; non-inferiority test). Cumulative efficacy at long-term follow-up was 93% in each group (68 of 73 *vs* 78 of 84; –0·3%; –7·4 to 7·2; p=0·015). Both regimens were well tolerated. Two patients discontinued ciprofloxacin because of myalgia with 7 days of treatment and itching exanthema with 14 days. Four (5%) of 86 patients assigned to 7 days of treatment who complied with study criteria and six (6%) of 93 assigned to 14 days reported an adverse event after the first week of treatment that was possibly or probably related to the study drug. In those assigned to 7 days, no patient had mucosal candida infection after the first week versus five treated for 14 days (p=0·036).

Interpretation Our results show that acute pyelonephritis in women, including older women and those with a more severe infection, can be treated successfully and safely with oral ciprofloxacin for 7 days. Short courses of antibiotics should be favoured in an era of increasing resistance.

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Introduction

The antibiotic resistance of Enterobacteriaceae, the most common cause of urinary tract infections, has increased worldwide.[1,2] The treatment options are becoming increasingly few and thus are a public health concern. An important way to tackle antibiotic resistance is to reduce antibiotic consumption—eg, by shortening the duration of treatment.[3,4] Controlled, randomised studies are needed to define the minimum treatment regimens for common infectious diseases.[3,4]

Acute pyelonephritis is a common and potentially serious infection affecting women of all ages. Few controlled trials have been done to assess the optimum duration of treatment for this infection.[5] A 2 week regimen of trimethoprim-sulfamethoxazole (co-trimoxazole)[6] or a fluoroquinolone[7] resulted in high rates of clinical and bacteriological cure. Therefore, 14 days of antimicrobial treatment is thought to be appropriate. In young women with mild, uncomplicated pyelonephritis who were managed on an outpatient basis, ciprofloxacin for 7 days was more efficacious than 14 days of co-trimoxazole.[8] This finding was, however, ascribed to a higher frequency of resistant bacteria in women treated with co-trimoxazole.[8]

In our investigator-initiated study, adult women with community-acquired acute pyelonephritis were treated with ciprofloxacin for 7 days or 14 days. The primary objective was to compare the short-term clinical and bacteriological efficacy and safety of the two regimens. Secondary aims were to assess the long-term cumulative efficacy and the consequences of not treating patients who had asymptomatic bacteriuria at short-term follow-up after completion of treatment.

Methods

Study design and patients

This study was a prospective, randomised, double-blind, non-inferiority trial with parallel groups. It was undertaken at 21 centres of infectious diseases in Sweden. Women aged 18 years or older with a presumptive diagnosis of community-acquired acute pyelonephritis were recruited to the study. Eligible patients had fever of at least 38·0°C (measured at home or in the emergency department) and at least one symptom or sign relating to the urinary tract such as flank pain, costovertebral angle tenderness, dysuria, urgency, or frequency.

A detailed medical history was obtained and a physical examination was done to assess eligibility. Symptoms and signs, a history of urinary tract infections and genitourinary disorders, concomitant diseases, and current medication were recorded. The infection was classified as sporadic (one previous episode of urinary tract infection during the past 6 months or no more than two during the past 12 months) or recurrent infection. The current episode was also classified as uncomplicated or complicated (diabetes mellitus or known structural or functional abnormalities of the urinary tract that might predispose to infections). The patients were initially hospitalised or directly managed on an outpatient basis at the discretion of the attending physician.

Patients were excluded from enrolment for any of the following reasons: pregnancy or lactation; inadequate contraception for women of childbearing age; known hypersensitivity to fluoroquinolones; systemic antibiotic treatment within the preceding 72 h; presence of an indwelling urinary catheter or clean intermittent catheterisation of the bladder; estimated creatinine clearance of less than 0·5 mL/s; convulsive disease; concomitant treatment with antacids, sucralfate, zinc, or theophylline; or previous inclusion in this study.

The Medical Products Agency, Uppsala, Sweden, and the ethical review committee at the University of Gothenburg approved the study protocol. The study was done in accordance with the ethical principles of the Declaration of Helsinki and the Guidelines for Good Clinical Practice. Written informed consent to participate in the trial was obtained from all patients.

Randomisation and masking

Patients were allocated to oral treatment in a 1:1 ratio. For comparison of the efficacy of different periods of antibiotic treatment, identical daily doses were used. The first week of treatment was open-label and all patients were given oral ciprofloxacin 500 mg twice daily. At the start of treatment, the investigator could administer discretionary ciprofloxacin 400 mg intravenously. The second week was double-blind and placebo-controlled and treatment was continued with either ciprofloxacin 500 mg or placebo tablets twice daily according to the randomisation code. Apoteket Produktion and Laboratorier AB (Stockholm, Sweden) computer-generated the allocation sequence for randomisation with block sizes of two for each study site. Trial drugs were packaged and assigned a randomisation number by Apoteket Produktion and Laboratorier AB and delivered to each participating centre. Enrolled patients thus were given by the investigator two blister packets of study medication in numerical order, one containing ciprofloxacin for the first week of treatment and another containing either ciprofloxacin or placebo tablets for the second week. Ciprofloxacin 500 mg and placebo tablets were identical with respect to shape, colour, taste, and odour and were provided by Bayer AB, Solna, Sweden. Patients, carers, site investigators, and trial coordinating centre staff were masked to group assignment.

Procedures

One or two clinical investigators were involved at each participating centre. Investigators and a coordinating committee met before and twice during the study to discuss all procedures. Members of the coordinating committee convened regularly to discuss any problems or inconsistencies that arose during the trial.

We obtained a voided midstream urine sample for culture and screening for the presence of nitrite and granulocyte esterase as an indicator of pyuria, blood specimens for culture and measurement of C-reactive protein (CRP), and creatinine after randomisation but before the start of antibiotic treatment. Women of childbearing age were given a pregnancy test.

Early follow-up was scheduled 10–14 days after the end of treatment with ciprofloxacin. Since the second week of treatment was masked, each patient had to be seen at two early visits—ie, days 17–21 and 24–28. For patients given ciprofloxacin for 7 days, results from days 17–21 were used and, for those who were given a 14 day course, data from days 24–28 were used. Long-term outcome was assessed with a late follow-up visit on days 42–63. Clinical assessments with focus on genitourinary symptoms and enquiry about further episodes of systemic antibiotic treatment were done at each visit. Repeat urine cultures and blood samples for measurement of serum CRP and serum creatinine concentrations were also obtained. Compliance with treatment was ascertained through enquiry and counting the unused tablets of the trial drug at the first follow-up visit. Patients were encouraged to consult the outpatient clinic if symptoms of urinary tract infection recurred during follow-up and all procedures were repeated.

The urine was cultured with standard microbiological methods by use of the calibrated loop technique at local laboratories. Clinically significant growth was defined as at least 10^3 colony-forming units (cfu) per mL of urine of *Escherichia coli* or *Staphylococcus saprophyticus* and at least 10^4 cfu per mL of other uropathogens. Urine samples containing more than two bacterial species were judged to be contaminated. Susceptibility testing against ciprofloxacin was done with disc diffusion and minimum inhibitory concentration (MIC; E-test,

For more on **disc diffusion for susceptibility testing** see http://www.srga.org/

bioMerieux, Lyon, France) and breakpoints from the European Committee on Antimicrobial Susceptibility Testing. The breakpoints used for Enterobacteriaceae and *Pseudomonas aeruginosa* were defined as susceptible when less or equal to 0·5 mg/L and resistant when greater than 1·0 mg/L and for *S saprophyticus* susceptible was defined as less or equal to 1 mg/L and resistant when greater than 1 mg/L. Two sets of blood cultures, obtained before treatment, were incubated both aerobically and anaerobically. All isolates were stored for ascertaining MIC at a reference laboratory.

Patients were randomly assigned before a definite diagnosis of acute pyelonephritis was established. Thus, patients were excluded from the study if they did not have acute pyelonephritis; if a pretreatment urine culture was missing, showed non-significant bacteriuria, or grew more than two bacterial species; if isolated bacteria were resistant or showed reduced susceptibility to ciprofloxacin; or if other antibiotics were given with ciprofloxacin when treatment was started. Patients were not eligible for per-protocol analysis for the following reasons: no follow-up visit; systemic treatment with other antimicrobial drugs up to day 28 (visit three); or missing more than one dose of the study drug during the first week of treatment or more than two doses during the whole treatment period.

Clinical cure was defined as complete resolution of symptoms during treatment with no recurrence of symptoms or signs of urinary tract infection during follow-up. Discontinuation of treatment because of worsened or persistent symptoms or the occurrence of adverse events was designated a clinical failure. The clinical failure or recurrence of symptoms of urinary tract infection (acute cystitis or acute pyelonephritis) during follow-up was judged to be a definite endpoint for participation in the study.

Bacteriological cure was defined as eradication of the infecting strain with no recurrence of bacteriuria ($<10^4$ cfu per mL) during follow-up. Bacteriological recurrence ($\geq10^5$ cfu per mL) without symptoms from the urinary tract at short-term follow-up was designated an asymptomatic bacteriuria and was left untreated.

Results are presented as short-term efficacy (10–14 days after treatment with active drug) and cumulative efficacy (at long-term follow-up on days 42–63). Patients who met the entry criteria and were given at least one dose of ciprofloxacin were included in the safety analysis. Adverse events were reported spontaneously by the patient and were also recorded by asking the patient a non-leading question. Adverse events were classified according to severity (mild, moderate, or severe) and relation to the study drug (probable, possible, or unlikely).

Statistical analysis

The primary objective was the short-term clinical and bacteriological efficacy 10–14 days after completion of treatment with ciprofloxacin. The secondary outcome was the long-term cumulative efficacy of ciprofloxacin. The size of the study sample was calculated on the basis of a cure rate of 10 percentage points lower at short-term follow-up with 7 days of therapy,[9] with the assumption of a 92% cure rate in patients treated for 14 days. The chosen margin of non-inferiority is quite wide because the expected gain from reducing the use of antibiotics is important. If there was a high risk that the infection could be life-threatening after the first week of treatment, the margin would have to be smaller because any advantages of the shorter treatment course must not be offset by an unacceptable increase in serious deterioration. The required sample size per group for a non-inferiority test for two binomial populations, with type 1 error 0·05, power 0·8, and non-inferiority margin 0·10, is 90 by use of the Wald test. Assuming that an estimated 30% of the randomly assigned patients would for various reasons be excluded from the efficacy analysis, we planned to recruit about 260 patients to the study.

The exact method was used to test the hypothesis of non-inferiority for the prespecified non-inferiority margin of 10 percentage points. The result of the test is significant if the 95% upper bound is less than 10 percentage points, or, equivalently, the one-sided p value is less than our significance level of 0·05. For illustrative reasons, double-sided CIs are presented. These 90% CIs were based on the inversion of two one-sided tests. This ensures that the upper bounds of the test and the interval coincide. For additional analyses, one-sided Mann-Whitney and Fisher's exact tests were used for numerical and categorical data, respectively. The p values from these tests should be interpreted descriptively because of the multiple testing.

This trial is registered with EudraCT, number 2005-004992-39 and ClinicalTrials.gov, ISRCTN73338924.

Role of the funding source

The Swedish Strategic Programme against Antibiotic Resistance (Strama) initiated and sponsored the study
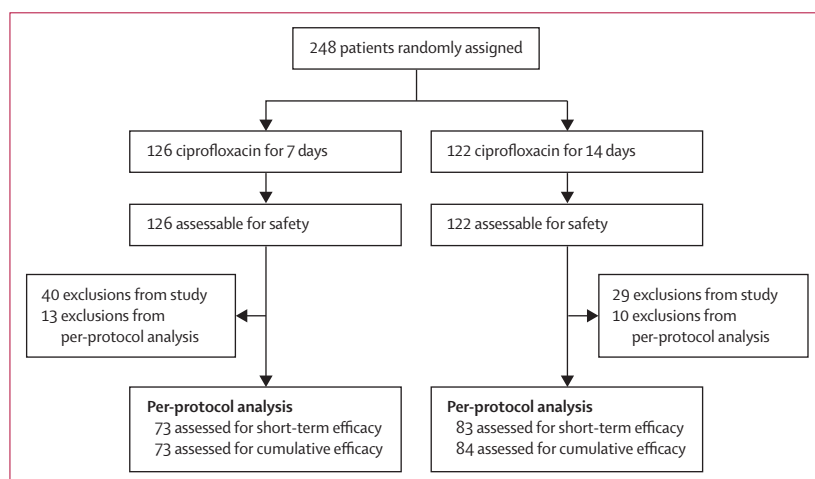

Figure: Trial profile

and was involved in study design, collection, analysis, and interpretation of data, reviewing the report, and the decision to submit the report for publication. All authors had full access to the data and decided to submit for publication.

Results

248 patients with a presumptive diagnosis of acute pyelonephritis were enrolled into the study and were randomly assigned to ciprofloxacin for 1 week or 2 weeks from Feb 1, 2006, until Dec 31, 2008 (figure). 69 (28%) randomly assigned patients were excluded from the study because the initial diagnosis of acute pyelonephritis was wrong (n=17); a pretreatment urine culture was missing, showed non-significant bacteriuria, or showed growth of more than two bacterial species (n=25); causative bacteria were resistant to or showed reduced susceptibility to ciprofloxacin (n=20); or other antibiotics were administered with ciprofloxacin during the first days of treatment (n=7; table 1). 23 (13%) of 179 remaining patients were withdrawn from efficacy assessment because they did not meet the criteria for the per-protocol analysis (table 1).

Characteristics of the 156 patients in the per-protocol population are summarised in table 2.

In the 248 randomly assigned patients, 192 strains of *E coli* were recovered in initial urine samples and 15 (8%) showed reduced susceptibility or were resistant to ciprofloxacin. *E coli* was the predominant urinary pathogen, accounting for 143 (92%) of 156 isolates in the per-protocol population (table 2). The range of MICs for *E coli* was 0·004–0·32 mg/L. Urine samples from four (3%) patients, grew 10^4 cfu per mL of a uropathogen and in all other cases at least 10^5 cfu per mL.

Blood samples for culture were obtained from 155 patients, of whom 42 (27%) had positive cultures with growth of *E coli* in all cases. Patients with positive blood cultures were older than were those with negative cultures (median age 58 years [IQR 39–66] *vs* 35 years [22–55]; estimated median difference 14 years; p=0·0002).

Four patients (two per group) did not attend the short-term follow-up but could be assessed at the last follow-up visit and thus were assessable with respect to cumulative efficacy. Three patients (two assigned to ciprofloxacin for 7 days and one for 14 days) who had a short-term assessment did not attend the late follow-up.

Both treatment regimens resulted in high clinical cure rates at short-term follow-up (table 3). Two patients assigned to ciprofloxacin for 7 days discontinued because of treatment failure (persistent symptoms on day 3; n=1) and myalgia (n=1). In the group assigned to 14 days of treatment, one patient stopped treatment on day 9 because of an itching exanthema and two patients had a recurrent episode of acute cystitis after the end of treatment. The short-term efficacy of 7 days of ciprofloxacin was not inferior to that of a 14 days (table 3).

During late follow-up, three patients assigned to 7 days of ciprofloxacin had an episode of acute cystitis, whereas

	Ciprofloxacin for 7 days (n=53)	Ciprofloxacin for 14 days (n=39)
Study criteria violations		
Diagnosis other than pyelonephritis*	8 (15%)	9 (23%)
Initial urine culture missing, showed non-significant growth, or growth of more than two bacterial species	14 (26%)	11 (28%)
Causative bacteria resistant or with reduced susceptibility to ciprofloxacin	9 (17%)/4 (8%)	7 (18%)/0
Initial treatment with other antibiotics	5 (9%)	2 (5%)
Per-protocol criteria violations		
Not turning up at second or third visit	2 (4%)	2 (5%)
No follow-up visit	2 (4%)	2 (5%)
Treatment with other antibiotics up to day 28 (visit 3)	6 (11%)	3 (8%)
Having missed too many doses of trial drug	0	2 (5%)
Refusal to continue the study	3 (6%)	1 (3%)

Data are number (%). *These patients were excluded because of pneumonia (n=6), viral disease (3), gastroenteritis (3), diverticulitis (2), endometriosis (1), salpingitis (1), and renal stone disease (1).

Table 1: **Reasons for exclusion from the study and per-protocol analysis at short-term follow-up**

	Ciprofloxacin for 7 days (n=73)	Ciprofloxacin for 14 days (n=83)
Age (years)	46 (27–62)	41 (23–58)
Recurrent urinary tract infections	11 (15%)	10 (12%)
Complicated urinary tract infections	4 (5%)	10 (12%)
Diabetes mellitus	2 (3%)	7 (8%)
Temperature (°C)	39·2 (38·7–39·7)	39·0 (38·5–39·6)
Flank pain or costovertebral angle tenderness	69 (95%)	79 (95%)
Serum CRP concentrations (mg/L)	100 (56–199)	125 (68–227)
Pyuria	70 (96%)	78 (94%)
Bacteria isolated from pretreatment urine cultures		
Escherichia coli	64 (88%)	79 (95%)
Staphylococcus saprophyticus	3 (4%)	1 (1%)
Klebsiella pneumoniae	3 (4%)	0
Others	3 (4%)	3 (4%)
Positive blood culture	16 (22%)	26 (32%)*
Initial intravenous dose(s) of ciprofloxacin	14 (19%)	11 (13%)

Data are number (%) or median (IQR). All blood cultures grew *Escherichia coli*. *Blood cultures missing for one patient.

Table 2: **Baseline characteristics of the per-protocol population**

	Ciprofloxacin for 7 days	Ciprofloxacin for 14 days	Difference (90% CI)	Non-inferiority test p value
Short-term efficacy	73	83		
Cure	71 (97%)	80 (96%)	–0·9% (–6·5 to 4·8)	0·004
Clinical failure or recurrent symptomatic urinary tract infections	2 (3%)	3 (4%)	..	
Cumulative efficacy	73	84		
Cure	68 (93%)	78 (93%)	–0·3% (–7·4 to 7·2)	0·015
Clinical failure or recurrent symptomatic urinary tract infections	5 (7%)	6 (7%)	..	

Data are number (%), unless otherwise indicated.

Table 3: **Clinical outcomes in the per-protocol population**

one patient in the group assigned to 14 days of treatment had an additional episode of acute pyelonephritis and two patients, one of whom had diabetes mellitus, had an episode of acute cystitis. Thus, in patients treated for 7 days and 14 days, the cumulative cure rates were similarly high, thus further supporting the findings of the short-term follow-up that a 7 day course of ciprofloxacin was not inferior to a 14 day course (table 3). No differences were noted in cure rates between patients with or without positive blood cultures (40 [95%] of 42 *vs* 110 [97%] of 113; p=0·412), or in patients with positive blood cultures treated for 7 days or 14 days (15 [94%] of 16 *vs* 25 [96%] of 26; p=0·623).

Four patients treated with ciprofloxacin for 7 days had asymptomatic bacteriuria at short-term follow-up (group B streptococci in two cases and one each with *E coli* and *Enterococcus faecalis*). These patients were left untreated and no strain persisted at the last follow-up visit.

In the group assigned to 14 days of ciprofloxacin, four patients had asymptomatic bacteriuria at the first follow-up visit (two with group B streptococci and one each with *E coli* and α-haemolytic streptococci). The patient with urinary *E coli* had cystitis caused by this bacterium during late follow-up whereas the other patients remained asymptomatic.

Both treatment regimens were well tolerated. Two patients discontinued treatment because of myalgia (day 2, ciprofloxacin for 7 days) and itching exanthema

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Panel: Research in context

Systematic review

We identified references for this study by searching PubMed with the terms "acute pyelonephritis" with "treatment", "clinical trials", and "female". Few controlled trials have been done to define the optimum duration of treatment for women with acute pyelonephritis. For many years, 10–14 days was the appropriate treatment as per guideline recommendations. Shorter duration is desirable in an era of increasing antibiotic resistance. In one study, a ciprofloxacin course of 7 days was efficacious for treatment of young women with uncomplicated pyelonephritis in an outpatient setting. Whether short treatment courses are applicable to older women or those with a more severe infection has not been settled.

Interpretation

The results of this randomised, double-blind, and placebo-controlled trial confirm and extend the findings from a previous study of young women with uncomplicated pyelonephritis. Our findings show that a regimen of ciprofloxacin 500 mg twice daily for 7 days was not inferior to a course of 14 days in women with acute pyelonephritis, neither at early or long-term follow-up. Our results are also valid for older women in whom positive blood cultures were more common and for those with a more severe infection. The findings should not be extrapolated to other classes of antibiotics.

(day 9, ciprofloxacin for 14 days), respectively. Four (5%) of 86 patients assigned to 7 days of treatment who complied with study criteria and six (6%) of 93 assigned to 14 days reported an adverse event after the first week of treatment that had a possible or probable association with the study drug. During this period, no patient given ciprofloxacin for 7 days had mucosal candida infection compared with five patients treated for 14 days (p=0·036).

Discussion

Our results show that community-acquired acute pyelonephritis in women can be treated successfully and safely with oral ciprofloxacin for 7 days and even in older patients and those with a more severe infection (panel). This randomised, controlled, non-inferiority study is the first in which the same antibiotic was administered in identical daily doses for different durations for the treatment of women with acute pyelonephritis. In previous studies, either different antibiotics and different treatment durations were compared[8] or different antibiotics were given for the same period.[6,7] To establish the efficacy and safety of a short treatment, we assessed patients according to a predefined protocol rather than an intention-to-treat mode.[9] Careless or inaccurate measurement, poor follow-up of patients, and poor compliance with study procedures and medication all tend to bias results towards no difference between treatment groups. This bias implies that an intention-to-treat analysis is unlikely to be appropriate because poor logistical procedures might hide treatment differences. To achieve quality in non-inferiority trials, especially high compliance by patients with respect to the treatment protocol is needed. However, an intention-to-treat analysis supports our findings.

Our results show that 7 days of ciprofloxacin was not inferior to 14 days of treatment. The clinical and bacteriological cure rates were high for both regimens at short-term and long-term follow-up. Even in patients with high fever and an intense inflammatory response to the infection as measured by serum CRP concentrations or the occurrence of positive blood cultures, the shorter treatment course was safe and highly effective. These results support and extend the findings from a previous study that showed a similar short-term cure rate after 7 days of treatment with ciprofloxacin for young women with uncomplicated acute pyelonephritis in an outpatient setting (panel).[8] However, in that study only 3% of the patients had positive blood cultures compared with 27% in our study. Furthermore, our results are also valid for middle-aged and older women (median age 46 years compared with 25 years in the earlier study). For many years, 10–14 days was thought of as an appropriate treatment for acute pyelonephritis. Based on the results of the earlier study,[8] updated guidelines recommend oral ciprofloxacin for 7 days in patients with acute pyelonephritis not requiring hospitalisation.[5] Positive blood

cultures were more common in older patients, which agrees with the findings of others.[10] Pyelonephritis with bacteraemia in the elderly is associated with a risk that the infection might take a more severe course but is not necessarily associated with treatment failure,[11] also shown in our study.

Patients recruited to this trial are most likely to be representative of women with community-acquired acute pyelonephritis, which is supported by the low occurrence of complicated (9%) and recurrent (13%) infections (table 2). A selection bias towards a more severe disease that did not allow treatment at home might be assumed because the patients arrived at the emergency depart-ments of the hospitals. Whether short courses of anti-biotics are as effective in settings where patients have more complicated infections could not be ascertained in this study. The presence of underlying anatomical and functional abnormalities of the urinary tract are well known predisposing factors to recurrent infections. A successful treatment outcome in patients with compli-cated acute pyelonephritis will therefore depend on the possibility to eliminate the complicating factor.

One advantage with short courses of antibiotics might be a lower frequency of adverse events. Both regimens were well tolerated but somewhat more patients who received ciprofloxacin for 14 days reported symptomatic overgrowth of candida after the first week of treatment. Ecological disturbances of this kind can be expected to increase with longer treatment courses.

Asymptomatic bacteriuria was an infrequent finding at early follow-up and only two patients, one in each treatment group, had a urine culture that grew *E coli*. When left untreated, none of them had recurrent acute pyelonephritis during long-term follow-up. Conse-quently, post-treatment urine cultures can safely be omitted for clinically cured patients.

The high cure rate obtained with a 7 day course of ciprofloxacin should not be extrapolated to other classes of antibiotics. The fluoroquinolones have the advantage of effectively eradicating susceptible enterobacteria from the rectal and vaginal flora,[12,13] resulting in a low frequency of recurrent urinary tract infections during the first months after completion of treatment. By contrast, high recurrence rates have been repeatedly reported after treatment with β-lactam antibotics,[6,7,14–16] and might be attributable to the ability of these drugs to promote vaginal colonisation with uropathogens.[17]

Fluoroquinolones like ciprofloxacin are recommended as a first-line choice for empirical oral treatment of acute pyelonephritis as long as the resistance rate of uropathogens does not exceed 10%.[5] Our data showed that 8% of *E coli* strains recovered from randomly assigned patients had reduced susceptibility or were resistant to ciprofloxacin. However, the prevalence of resistance to ciprofloxacin among urinary isolates of *E coli* in Sweden now amounts to about 13%.[18] A great concern is that even higher resistance rates have been reported in other countries.[19] Nonetheless, if the use of ciprofloxacin can be restricted to febrile or complicated urinary tract infections and if the length of treatment is reduced as shown in this study, the trends in increasing resistance might be impeded. Therefore, short courses of antibiotics should be the preferred option.

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References
1. Livermore D. Has the era of untreatable infections arrived? *J Antimicrob Chemother* 2009; **64** (suppl 1): i29–36.
2. Kumarasamy KK, Toleman MA, Walsh TR, et al. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. *Lancet Infect Dis* 2010; **10**: 597–602.
3. Rice LB. The Maxwell Finland lecture: for the duration–rational antibiotic administration in an era of antimicrobial resistance and *Clostridium difficile*. *Clin Infect Dis* 2008; **46**: 491–96.
4. Infectious Diseases Society of America (IDSA). Combating antimicrobial resistance: policy recommendations to save lives. *Clin Infect Dis* 2011; **52** (suppl 5): S397–428.
5. Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society of Microbiology and Infectious Diseases. *Clin Infect Dis* 2011; **52**: e103–20.
6. Stamm WE, McKevitt M, Counts GW. Acute renal infection in women: treatment with trimethoprim-sulfamethoxazole or ampicillin for two or six weeks. *Ann Intern Med* 1987; **160**: 341–45.
7. Sandberg T, Englund G, Lincoln K, Nilsson L-G. Randomised double-blind study of norfloxacin and cefadroxil in the treatment of acute pyelonephritis. *Eur J Clin Microbiol Infect Dis* 1990; **9**: 317–23.
8. Talan DA, Stamm WE, Hooton TM, et al. Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute uncomplicated pyelonephritis in women. A randomized trial. *JAMA* 2000; **283**: 1583–90.
9. D'Agostino RB Sr, Massaro JM, Sullivan LM. Non-inferiority trials: design concepts and issues–the encounters of academic consultants in statistics. *Statist Med* 2003; **22**: 169–86.

10   Sandberg T, Alestig K, Eilard T, et al. Aminoglycosides do not improve the efficacy of cephalosporins for treatment of acute pyelonephritis in women. *Scand J Infect Dis* 1997; **29:** 175–79.

11   van Nieuwkoop C, van't Wout JW, Spelt IC, et al. Prospective cohort study of acute pyelonephritis in adults: safety of triage towards home based oral antimicrobial treatment. *J Infect* 2010; **60:** 114–21.

12   Edlund C, Nord CE. A review on the impact of 4-quinolones on the normal oropharyngeal and intestinal human microflora. *Infection* 1988; **16:** 8–12.

13   Tartaglione TA, Johnson CR, Brust P, Opheim K, Hooton TM, Stamm WE. Pharmacodynamic evaluation of ofloxacin and trimethoprim-sulfamethoxazole in vaginal fluid of women treated for acute cystitis. *Antimicrob Agents Chemother* 1988; **32:** 1640–43.

14   Jernelius H, Zbornik J, Bauer C-A. One or three weeks' treatment of acute pyelonephritis. *Acta Med Scand* 1988; **223:** 469–77.

15   Eriksson S, Zbornik J, Dahnsjö H, et al. The combination of pivampicillin and pivmecillinam versus pivampicillin alone in the treatment of acute pyelonephritis. *Scand J Infect Dis* 1986; **18:** 431–38.

16   Cronberg S, Banke S, Bergman B, et al. Fewer bacterial relapses after oral treatment with norfloxacin than with ceftibuten in acute pyelonephritis initially treated with intravenous cefuroxime. *Scand J Infect Dis* 2001; **33:** 339–43.

17   Winberg J, Herthelius-Elman M, Möllby R, Nord CE. Pathogenesis of urinary tract infection—experimental studies of vaginal resistance to colonization. *Pediatr Nephrol* 1993; **7:** 509–14.

18   SWEDRES (2010). A report on Swedish antibiotic utilisation and resistance in human medicine. http://www.smittskyddsinstitutet.se/publikationer/arsrapporter-och-verksamhetsberattelser/swedres/swedres-2010 (accessed Aug 1, 2011).

19   Antimicrobial resistance surveillance in Europe 2009. Annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). http://www.ecdc.europa.eu/publications/Publicatins/Forms/ECDC_DispForm.aspx?ID=580 (accessed Aug 1, 2011).