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ORIGINAL ARTICLE

Clinical and bacteriological outcome of different doses and duration of pivmecillinam compared with placebo therapy of uncomplicated lower urinary tract infection in women: The LUTIW project

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Abstract

Objective. To analyse associations between symptoms and bacteriuria in uncomplicated lower urinary tract infection in women (LUTIW) and to evaluate outcome of therapy with three different regimens of pivmecillinam or placebo. *Design*. Prospective, multicentre, randomized, double-blind, and placebo-controlled therapy study. Symptoms registered at inclusion, during therapy and at follow-up visits after 8−10 and 35−49 days. Significant bacteriuria defined according to current European guidelines. *Setting*. A total of 18 primary healthcare centres in northern Sweden. *Subjects*. Women aged 18 years and above with symptoms of urgency, dysuria, suprapubic or loin pain. *Main outcome measures*. Symptoms and bacteriuria at inclusion and course of symptoms, bacteriuria, and their combinations during and post-therapy. *Results*. At inclusion, no associations or significant differences were found between symptom scores and bacteriuria, bacterial counts, or species. The 884 patients (77%) with significant bacteriuria were followed up. All pivmecillinam therapies were superior to placebo (p<0.001). From day six until first follow-up, the mean values of all symptoms were higher and the bacteriological cure was lower at first follow-up in the three days (84%) compared with the seven days regimens (93−94%, p<0.001). At final follow-up clinical cure was similar in all pivmecillinam regimens (65−72%) as was bacteriological cure (83−89%). Pivmecillinam had few low to mild adverse reactions, comparable to placebo. *Conclusions*. Symptoms are not conclusive for diagnosis of LUTIW. Pivmecillinam therapies are superior to placebo and seven days regimens are more efficient than three days. Pivmecillinam 200 mg $\times 2 \times 7$ days is recommended as a first-line therapy for LUTIW.

Key Words: *Bacteriuria, family practice, pivmecillinam, placebo, symptoms, therapy study, urinary tract infection*

About half of all women suffer at least once in their lifetime from urinary tract infection (UTI) [1]. In Sweden approximately one million patients annually visit mainly primary healthcare because of lower UTI in women (LUTIW) [2], and 14% of all antibiotics prescribed to outpatients are due to UTI [3]. Common symptoms of LUTIW are urgency/frequency, dysuria, suprapubic pain and loin pain without signs of pyelonephritis [4,5]. The definition of uropathogens and cut-off limits for significant bacteriuria have been debated [6], and different guidelines have been used, which vary between 10^3

and 10^5 colony forming units/ mL depending on uropathogens, sex, and type of urine sample [7−9].

Among UTI therapies pivmecillinam has shown good efficacy, few ecological side effects as adverse reactions [10,11], and low induction of antibiotic resistance [12]. The increasing resistance to many antibiotics commonly prescribed is often associated with high consumption of antibiotics [13,14] and may cause therapeutic problems. Optimal doses and length of pivmecillinam therapy have not been established [10,15], though empirical treatment of uncomplicated cystitis for three days has been

Literature on lower urinary tract infection in women (LUTIW) is usually focused on bacteriology and bacteriological outcome of antimicrobial therapy, while symptoms and clinical outcome and the natural course by placebo therapy are sparsely documented.

- Symptoms are not conclusive for the diagnosis of LUTIW.
- Outcomes of pivmecillinam therapies are superior to placebo therapy.
- Seven days of pivmecillinam therapies are more efficient than three days and pivmecillinam 200 mg $\times 2 \times 7$ days is recommended as a first-line therapy for LUTIW.

recommended for most common antibiotics including pivmecillinam [16].

The aims of the present study were to analyse the associations between symptoms and bacteriuria and to evaluate the effect on symptoms, bacteriuria, and their combinations by three different regimens of pivmecillinam compared with placebo during and 5–7 weeks post-therapy in patients with significant bacteriuria at inclusion.

Material and methods

Study design

A prospective, multicentre, randomized, double-blind, and placebo-controlled therapy study was performed at 18 primary healthcare centres in the county of Västerbotten in northern Sweden with inclusion period from April 1995 to December 1997. Women aged 18 years and above with symptoms suggestive of lower UTI – urgency, dysuria, suprapubic pain, or loin pain – were eligible to participate. The severity of each symptom was graded as none, light, moderate, or severe (score 0–3), and a total symptom score of ≥ 2 was required for inclusion. Patients were randomized to three different regimens of pivmecillinam (Selexid®): 200 mg $\times 3 \times 7$ days, 200 mg $\times 2 \times 7$ days or 400 mg $\times 2 \times 3$ days or placebo (i.e. all patients were given $2 + 1 + 2$ identical tablets each day for 7 days). Prior to inclusion patients gave informed written consent to participate. Patients with significant bacteriuria were followed up at two visits, after 8–10 days and 35–49 days, respectively.

Exclusion criteria

Antibiotic therapy for UTI within the last month, participation in other studies within last three months, known/suspected penicillin allergy, genital infection, complicating factors (diabetes or abnormality of the urinary tract), one or more signs of pyelonephritis (pyrexia $\geq 38.5°C$, CRP ≥ 25 mg/L, kidney tenderness by palpation), urine incontinence requiring catheter/pads, pregnancy/planned pregnancy, or previous participation in the study form the exclusion criteria.

Controls

Patients fulfilling the inclusion criteria but who rejected participation in the study were voluntarily registered as controls (reject log) at consultation, when compared with the included patients.

Bacteriological methods

After spreading of the labia, a mid-stream urine sample was collected and transported at $<6°$ C within 24 h to the Laboratory of Clinical Bacteriology, University Hospital of Umeå [17]. The uropathogens were quantified in colony-forming units/mL, and significant bacteriuria was defined according to current European guidelines in patients with symptoms as $\geq 10^3$/mL for primary pathogens, $\geq 10^4$ for secondary pathogens, and $\geq 10^5$ for doubtful pathogens, and as $\geq 10^5$ for all species in patients without symptoms [9] (see Table II). Samples without bacteriuria or with nonsignificant bacterial counts were classified as negative cultures as were samples with mixed flora without one dominating species. In cultures with mixed flora and one species dominating (i.e. at least 10 times higher than any other species and in significant bacterial counts), this species was denoted as a uropathogen. Bacterial species in significant counts were registered at inclusion and at the follow-up visits.

Adverse events

At both follow-up visits suspected adverse events were registered.

Outcome of therapy

Symptom scores for each symptom were registered at inclusion, at medication three times daily in diaries during therapy (days 1–7) when the mean value for all symptom scores was calculated daily, and at the follow-up visits. The clinical effect of therapy was illustrated by mean values for all symptom scores or proportion of symptom-free patients daily during therapy and at the follow-up visits. Clinical cure was defined as no persisting symptoms during and post-therapy. Bacteriological cure was defined as eradication of initial bacteriuria at the follow-up visits.

Sample size calculation

Assuming a clinical cure rate of 80% at last follow-up in the 200 mg $\times 3 \times 7$ days regimen, a total of 250 patients per treatment group were required, in order to ensure with 80% certainty that the upper 95% (one-alpha) confidence limit for difference in cure rates between the 200 mg $\times 3 \times 7$ days and the other pivmecillinam regimens was less than 10%.

Statistics

Comparison of proportions was done using the chi-squared test. P-values <0.05 were considered significant. Analysis of variance with post hoc tests and Bonferroni correction was used when mean values were compared [18]. The software used for statistical calculation was SPSS 11.0 (SPSS Inc., Chicago, IL).

Results

Patients included and controls

A total of 1605 women were eligible for recruitment of which 443 rejected participation but accepted to serve as controls (Figure 1). Of the 1162 patients, 19 were excluded due to total symptom scores <2 (n $=8$) or missing cultures (n $=11$), as were 18 controls, resulting in 1143 included patients and 425 controls. The patients had a mean age of 43 years, mean symptom duration of 10 days, mean value for all symptom scores of 5.3 points (Table I), urgency in 96%, dysuria in 88%, suprapubic pain in 60%, and loin pain in 40%. E. coli was the most common bacterial species (62.1% of cultures, Table II), followed by coagulase negative staphylococci other than S. saprophyticus (3.8%) and S. saprophyticus (2.6%). Among cultures, 67% had $\geq 10^5$ colony forming units/mL, 7% had 10^4, 3% had 10^3, and 23% were negative. The controls had similar characteristics except that they were older (mean value 47 years, p <0.001) and had shorter symptom duration (mean value 7 days, p <0.001). No associations or significant differences were found between mean values for all symptom scores, bacteriuria, bacterial counts, or species (Table II).

Patients with significant bacteriuria were studied further

Of the 1143 included patients, 884 had significant bacteriuria (77%, see Table II) and were studied further. At the first follow-up, 97% of these participated (see Figure 1) but patients with unbearable
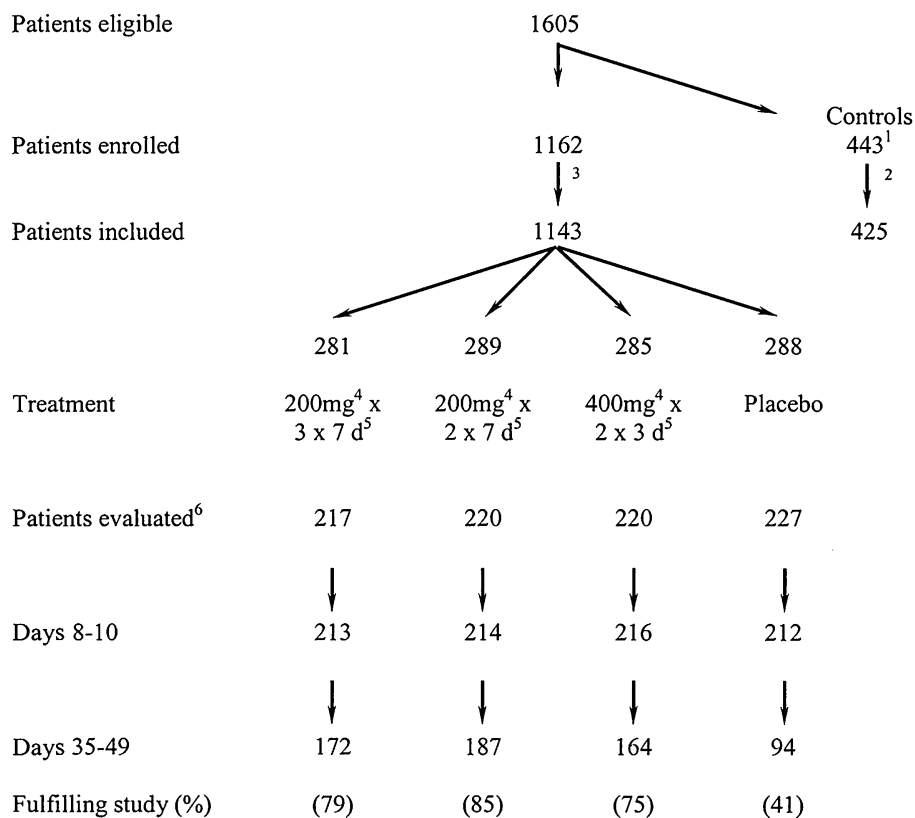
	200mg[4] x 3 x 7 d[5]	200mg[4] x 2 x 7 d[5]	400mg[4] x 2 x 3 d[5]	Placebo
Patients eligible		1605		
Patients enrolled		1162	Controls 443[1]	
Patients included		1143	425	
	281	289	285	288
Treatment	200mg[4] x 3 x 7 d[5]	200mg[4] x 2 x 7 d[5]	400mg[4] x 2 x 3 d[5]	Placebo
Patients evaluated[6]	217	220	220	227
Days 8-10	213	214	216	212
Days 35-49	172	187	164	94
Fulfilling study (%)	(79)	(85)	(75)	(41)

Figure 1. Flow chart of patients receiving pivmecillinam or placebo treatment and controls. [1]443 patients fulfilled the inclusion criteria but rejected participation (reject log); [2]18 patients excluded at consultation (missing cultures) resulting in 425 controls; [3]19 patients excluded at consultation (11 missing cultures, 8 with symptom score <2); [4]pivmecillinam; [5]days of treatment; [6]patients with significant bacteriuria according to current European guidelines.

Table I. Characteristics at inclusion of different patient groups and controls (reject log).

	Placebo group	Pivmecillinam 200mg ×3 ×7d[1]	Pivmecillinam 200mg ×2 ×7d[1]	Pivmecillinam 400mg ×2 ×3d[1]	Controls
Number of patients	288	281	289	285	425
Age mean value (years)	42 (±17)	44 (±18)	43 (±18)	44 (±18)	47 (±19)
Age median and range (years)	41 (18−82)	44 (18−85)	42 (18−88)	40 (18−83)	46 (18−89)
Age distribution (%) ≤24 years	23	22	20	21	17
25−54 years	52	47	51	50	48
≥55 years	25	31	29	29	35
Symptom duration (days)					
Mean value (SD)	9 (±16)	11 (±22)	9 (±21.0)	10 (±18)	7 (±12)
Median	4	4	4	5	3
Mean value of symptom scores (SD)	5.3 (±2.0)	5.5 (±2.0)	5.2 (±2.0)	5.3 (±2.0)	5.5 (±.2.1)
Mean bladder incubation time (hours)	4 (±2)	4 (±3)	4 (±2)	4 (±3)	4 (±3)
Significant bacteriuria (%)					
E. coli	59	67	61	62	62
Other species	20	11	15	15	15
Negative culture	22	23	24	23	23

[1]Days of treatment.

symptoms received antibiotics other than pivmecillinam and left the study. Significantly fewer placebo-treated patients fulfilled the study (41%) compared with patients receiving pivmecillinam (75−85%, p< 0.001), among whom fewer patients fulfilled the 3 days (75%) compared with the 200 mg ×2 ×7 days regimen (85%, p =0.006).

Clinical outcome

The symptoms disappeared gradually and faster among all pivmecillinam regimens compared with placebo (Figure 2, p <0.001), with higher clinical cure rates post-therapy (Table III, p <0.001). The proportion of pivmecillinam treated patients free from symptoms was 44%, 55−65%, and 65−72% at day five, first, and final follow-up, respectively (Figure 2). Comparable figures for placebo-treated patients were 12%, 26%, and 51%. From day six until first follow-up, the proportion of symptom-free patients tended to be lower (Figure 2), and mean values for all symptom scores were higher in the 3-day compared with the 200 mg ×3 ×7 days and 200 mg ×2 ×7 days regimens (day 6: 1.32, 1.00 and 0.93, respectively, p =0.045, and first follow-up: 1.33, 1.03 and 0.85, p =0.024). At final follow-up, these differences in clinical outcome between the pivmecillinam regimens had disappeared. Clinical cure at both follow-up visits was similar in 59−62% in the pivmecillinam regimens compared with 37% after placebo therapy (Table III, p <0.001). Clinical recurrence of symptoms at last follow-up was similar in 12−13% of all pivmecillinam- as placebo-treated patients.

Bacteriological outcome

Bacteriological cure was more efficient for all pivmecillinam regimens compared with placebo (see Table III, p <0.001) and more successful at first follow-up in the 7 days regimens (93−94%) compared with 3 days regimens (84%, p <0.001). However, at final
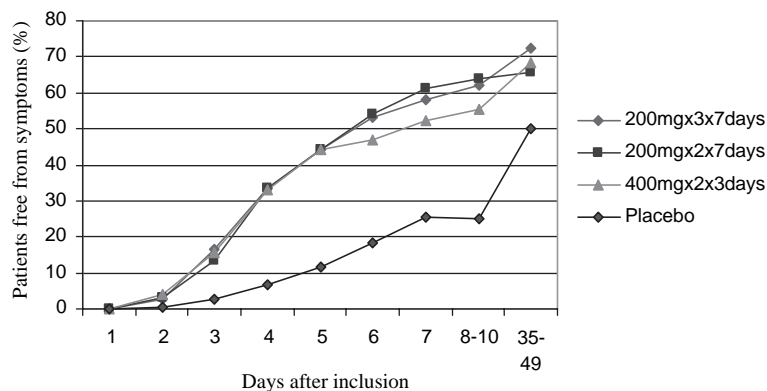

Figure 2. Eradication of symptoms during and post-therapy among pivmecillinam- and placebo-treated patients.

Table II. Relation between bacteriuria according to current European guidelines and mean values of all symptom scores at inclusion.

Species	Bacteria CFU/ mL										
	Negative [1]		10^3		10^4		$\geq 10^5$		Total		
	Symptom score [2]	n	Symptom score [2]	n	Symptom score [2]	n	Symptom score [2]	n	Symptom score [2]	n	%
E. coli [3]			5.7	38	5.5	70	5.3	602	5.3	710	62.1
CNS [5, 6]							5.8	43	5.8	43	3.8
S. saprophyticus [3]					5.0	4	5.9	26	5.8	30	2.6
Klebsiella species [4]					4.0	1	4.8	28	4.8	29	2.5
Enterococcus species [4]					6.2	6	6.0	16	6.1	22	1.9
Citrobacter species [4]							5.6	14	5.6	14	1.2
Enterobacter species [4]							6.1	13	6.1	13	1.1
S. aureus [4]					5.0	2	4.8	5	4.9	7	0.6
Group B streptococci [5]							3.8	6	3.8	6	0.5
Proteus species [4]					5.0	2	6.0	4	5.7	6	0.5
Pseudomonas species [5]							6.0	2	6.0	2	0.2
Gram negative rods [5]							4.0	2	4.0	2	0.2
Gram positive rods [5]							5.0	1	5.0	1	0.1
Negative culture [1]	5.1	258							5.1	258	22.7
Total	5.1	258	5.7	38	5.5	85	5.4	762	5.3	1143	
% of total		23		3		7		67			100

[1]Non-significant bacteriuria, see Material and methods; [2]mean value of symptom scores, see Material and methods; [3]primary pathogen; [4]secondary pathogen; [5]doubtful pathogen; [6]coagulase-negative staphylococci other than S. saprophyticus.

follow-up, the bacteriological cure rates were similar in all pivmecillinam regimens (83–89%).

Clinical and bacteriological outcome

Clinical and bacteriological cure at both follow-up visits was 56–58% in the pivmecillinam regimens (see Table III) compared with 21% after placebo therapy (p <0.001). At first follow-up after pivmecillinam therapy, 96–97% of patients free from symptoms were also free from bacteriuria (Table IV). Among patients with symptoms, 10–30% also had persisting bacteriuria. At final follow-up after pivmecillinam therapy, 93–98% of patients free from symptoms were also bacteriologically cured, and 25–48% of the patients with symptoms also had persisting bacteriuria (Table IV).

Adverse drug reactions

The most common adverse drug reactions were gastrointestinal (5–8% of pivmecillinam- and 4% of placebo-treated patients) and only seven patients (<1%) given pivmecillinam withdrew from treatment due to adverse reactions. The majority of adverse reactions were mild to moderate and similar in the pivmecillinam regimens as in placebo (17% in 200 mg × 3 × 7 days, 12% in 200 mg × 2 × 7 days, 14% in 3 days, and 12% in placebo, respectively, p = 0.17). The risk of complications was low and two patients developed pyelonephritis, one receiving placebo and one pivmecillinam for seven days.

Discussion

The LUTIW project is to our knowledge the largest prospective, multicentre, randomized, double-blind, and placebo-controlled therapy study of UTI. The patients included were representative of uncomplicated LUTIW consulting primary healthcare with similar symptoms and bacteriology to the controls. The majority of clinical trials of UTI focus on bacteriological cure [19], but in the present study we also highlight symptoms and clinical outcome. This study is unique as current international ethical recommendations do not support placebo therapy [20].

In accordance with other studies [9], E coli was the dominating bacterial species. The low incidence of S. saprophyticus (2.6%) may have been due to a high concentration of novobiocin in agar plates used in the multipoint inoculation tests for identification. Hence a number of S. saprophyticus (novobiocin resistant) may have been misidentified as other coagulase negative staphylococci (sensitive) [17]. However, the present distribution of staphylococci had no significant influence on outcome of therapy, as both staphylococcal groups had similar spontaneous clinical and bacterial cure [17] and similar outcome of pivmecillinam therapy to E. coli, despite in vitro resistance to pivmecillinam for staphylococci (data not shown). These results can partly be explained by the low predictive values of antibiotic resistance for outcome of LUTIW therapy [21,22].

No associations or significant differences between mean symptom scores and bacteriuria, bacterial counts, or species were found at inclusion, and 23% of the patients did not have significant bacteriuria, indicating that suggestive symptoms only are not conclusive for diagnosis of LUTIW. In order to prevent unnecessary consumption of antibiotics we consider that antibiotics should be prescribed for symptomatic bacteriuria and not for symptoms only, and therefore we focus outcome of therapy on

Table III. Clinical and bacteriological cure of treatment in different pivmecillinam and placebo regimens (%).

| | Pivmecillinam | | | Placebo | p-values comparison | |
	200mg × 3 × 7d[1] (A) n = 217	200mg × 2 × 7d[1] (B) n = 220	400mg × 2 × 3d[1] (C) n = 220	(P) n = 227	A vs. B vs. C vs. P	A vs. B vs. C
Outcome of therapy						
Clinical cure						
Days 8–10	62	64	55	25	<0.001	0.16
Days 35–49	72	65	68	51	0.006	0.37
Days 8–10 and 35–49	62	59	60	37	<0.001	0.80
Bacteriological cure						
Days 8–10	93	94	84	34	<0.001	<0.001[2]
Days 35–49	89	83	86	70	<0.001	0.21
Days 8–10 and 35–49	86	80	80	44	<0.001	0.25
Clinical and bacteriological cure at days 8–10 and 35–49	58	57	56	21	<0.001	0.96

[1]Days of treatment; [2]p-values comparing A vs. B: p = 0.18; A vs. C: p = 0.01; B vs. C: p = 0.003.

Table IV. Bacteriological outcome in relation to clinical outcome in different regimens of pivmecillinam and placebo therapy.

Outcome of therapy: Bacteriological response in relation to clinical response	Pivmecillinam			Placebo
	200mg $\times 3 \times 7d^1$ (A) n = 217	200mg $\times 2 \times 7d^1$ (B) n = 220	400mg $\times 2 \times 3d^1$ (C) n = 220	(P) n = 227
Days 8–10	n (%)	n (%)	n (%)	n (%)
Clinically cured	132 (62)	136 (64)	119 (55)	54 (25)
Bacteriologically cured among clinically cured	128 (97)	132 (97)	114 (96)	30 (56)
Clinical failure	81 (38)	78 (36)	97 (45)	158 (76)
Bacteriological failure among clinical failure	10 (12) [2]	8 (10) [2]	29 (30) [2]	117 (74)
Days 35–49				
Clinically cured	124 (72)	122 (65)	111 (68)	48 (51)
Bacteriologically cured among clinical cured	115 (93)	119 (98)	105 (95)	40 (83)
Clinical failure	48 (28)	65 (35)	53 (32)	46 (49)
Bacteriological failure among clinical failure (%)	12 (25) [3]	31 (48) [3]	20 (38) [3]	24 (52)

[1]Days of treatment; [2]p-values comparing A vs. B: p = 1.0; A vs. C: p = 0.015; B vs. C: p = 0.005; [3]p-values comparing A vs. B: p = 0.042; A vs. C: p = 0.510; B vs. C: p = 0.840.

patients with significant bacteriuria. This is supported by Belgian, Dutch, and German guidelines [23], which advise both symptoms and urinalysis for diagnosis and therapy of UTI, but is opposed by Norwegian guidelines [24], which recommend empirical therapy for symptoms only. This also contradicts the increasing tendency in clinical practice to prescribe antibiotics for symptoms only, which has been reported to be cost-effective [25] and has been proposed in the US [26]. Moreover, equal relief of symptoms was found in women with bacterial cystitis or urethral syndrome given empirical antibiotic therapy [27], and trimethoprim was reported as more efficient than placebo in relieving urgency in women with urethral syndrome [28]. However, these studies had few patients and short follow-up times and are not conclusive for prescribing antibiotics in the case of symptoms only.

In a recent meta-analysis of 32 studies of LUTIW the efficacy of 3 days therapies was compared with 5 days and longer therapies [29]. No significant differences in clinical cure rates were found at short- and long-term follow-up, but 3 days therapies were less effective in bacteriological outcome at both short- and long-term follow-up. However, comparison and assessment of outcome between different studies are difficult due to differences in: definitions of significant bacteriuria, evaluation of symptoms and clinical outcome, and times for follow-up. For instance, the bacteriological failure rate for norfloxacin could vary between 1% and 43% due to different cut-off limits used for significant bacteriuria [30].

In the present study, we used four-graded symptom scores and patient diaries, which probably contributed to lower clinical cure rates and illustrated the clinical course of LUTIW better, since mild symptoms were also considered. Recently, the benefit of using graded symptom scores was reported concluding that moderate or severe symptoms had higher predictive values of diagnosing UTI than slight symptoms [31]. We found that symptoms disappeared gradually and similarly during the first five days in most patients given pivmecillinam. At days 6–10, the clinical outcome in the 3 days regimen was less efficient with higher symptom scores compared with the 7 days regimen, which probably contributed to a higher dropout frequency in the 3 days regimen. At final follow-up, no differences in clinical efficacy were seen among all pivmecillinam regimens. The clinical cure after placebo therapy was 51% at final follow-up, but this result was highly biased due to many dropouts. If dropouts were considered as clinical failures, the clinical cure was 21%.

Traditionally, outcome of therapy focus on bacteriological cure, of which the 7 days pivmecillinam regimens were more effective than the 3 days at first but not at final follow-up. However, as asymptomatic bacteriuria is harmless unless during pregnancy [32], only symptomatic bacteriuria needs to be diagnosed and treated with antibiotics. In the present study almost all clinically cured patients were also bacteriologically cured (96–97% at first and 93–98% at final follow-up, respectively), which also supports that outcome of therapy should focus more on clinical cure.

We found that the 7 days regimens were more effective than the 3 days, especially between days 6–10 in respect of relief of symptoms and bacteriological cure. The 200 mg $\times 2 \times 7$ days dosage had similar efficacy to the 200 mg $\times 3 \times 7$ days, which could be explained by the high concentrations and long half-life of mecillinam in urine (T½ = 17 h) [33]. Hence, the 200 mg $\times 2 \times 7$ days regimen is preferred with 1/3

reduction of antibiotic consumption compared with the traditional Swedish 200 mg ×3 ×7 days dosage.

From the present project we have published a study of the natural course of LUTIW illustrated by placebo therapy [17], which had previously been only sparsely documented [34–36]. Also, at a symposium a preliminary summary of the outcomes of therapies has been reported [10]. The results in that preliminary report differed from this study due to bacteriuria defined according to modified American guidelines [7] and a less strict definition of "free from symptoms" (score ≤ 1). However, we consider that the present evaluation of the study is more comprehensive and clinically relevant.

In summary, symptoms are not conclusive for diagnosis of LUTIW. Pivmecillinam therapies are superior to placebo and 7 days regimens are more efficient than 3 days regimens. We recommend pivmecillinam 200 mg ×2 ×7 days as a first-line therapy for LUTIW.

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