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Comparison of Single-Dose Administration and Three-Day Course of Amoxicillin with Those of Clavulanic Acid for Treatment of Uncomplicated Urinary Tract Infection in Women

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In a double-blind randomized study we compared a single-dose amoxicillin-clavulanate combination with a regular 3-day regimen in 109 women with cystitis. Clinical cure rates at 7 and 28 days posttreatment were 78 versus 87% and 67 versus 78%, respectively. The 3-day regimen was significantly better ($P < 0.001$) only in women with recurrent urinary tract infections.

The preferred treatment for uncomplicated cystitis in nonpregnant women is controversial. Single-dose regimens have been shown to be as effective as 7- to 10-day courses (10). The advantages of single-dose therapy include lower cost, better compliance, fewer side effects, and a diminished pressure on the intestinal and vaginal flora (4). However, several studies have shown that the rate of recurrent infection following single-dose treatment is significantly higher than after longer courses (8, 9). The high rate of resistance to amoxicillin found among urinary isolates in Israel (approximately 70%) limits its use, and new antimicrobial agents must be tested. The combination of amoxicillin and clavulanic acid broadens the antimicrobial spectrum of amoxicillin and consequently has demonstrated excellent results in the treatment of urinary tract infections (UTIs) (1). The aims of the present study were to evaluate the efficacy of a single-dose of amoxicillin-clavulanic acid and to compare it with that of a 3-day regimen in the treatment of uncomplicated cystitis.

Women 16 years of age or older who had been referred to three of our out-patient clinics with the diagnosis of uncomplicated UTI were eligible for enrollment in this study. The diagnosis of UTI was based upon both clinical symptoms of dysuria, frequency of urination, and absence of fever or flank pain, in addition to laboratory findings of pyuria (at least eight leukocytes per high-power field) and a positive urine culture yielding $\geq 10^5$ CFU/ml on pure growth. Patients with a history of pyelonephritis or nephrolithiasis or who were currently pregnant or immunocompromised were excluded from the study. Cases in which the initial culture yielded organisms resistant to amoxicillin-clavulanic acid were also excluded. The severity of recent symptoms was rated subjectively, according to the women's complaints, from mild to severe. Also, women with three or more episodes of UTI during the last year were defined as having recurrent UTI, and the use of contraceptive methods by and the menstrual status of the patients were recorded.

Clean, voided midstream urine specimens were collected and cultured on the Uritest system (Hylab dip slides; Hylab, Rehovot, Israel). All isolates were identified by standard procedures and tested for susceptibility to antimicrobial drugs by the Kirby-Bauer method. A 30-μg amoxicillin-clavulanic acid disk was used for susceptibility testing, and a zone diameter of less than 19 mm was considered to be indicative of resistance.

Treatment was given on a randomized and double-blind basis. Women in the single-dose group received five caplets of amoxicillin (500 mg each) plus one caplet of augmentin containing 500 mg of amoxicillin plus 125 mg of clavulanic acid. This was followed by single placebo caplets every 8 h for 3 days. Women in the second group received one caplet of augmentin containing 250 mg of amoxicillin plus 125 mg of clavulanic acid and five placebo caplets; this was followed by augmentin (250 mg) every 8 h for 3 days. Each patient was monitored clinically and bacteriologically at 7 and 28 days. Women with persistent bacteriuria and sensitive organisms were further evaluated by intravenous pyelogram or renal ultrasound.

Statistical analysis was performed by the chi-square test with Yates' correction where appropriate, and P values of <0.005 were considered statistically significant.

A total of 109 patients completed the treatment and both follow-up points; 55 received the single-dose regimen, and 54

TABLE 1. Clinical characteristics[a]

Characteristic	Single-dose augmentin	3-day augmentin
No. of patients	55	54
Avg age (yr) (range)	41.8 (18–82)	41.6 (18–87)
UTI status		
Single episode	30	21
Recurrent	25	33
UTI severity		
Mild	14	9
Moderate	36	37
Severe	5	8
Menstrual status		
Premenopausal	34	38
Postmenopausal	21	16
Contraceptive use	38	35
Intrauterine device	29	26
Oral contraceptive	9	9

[a] Unless otherwise indicated, values represent the number of patients with each characteristic.

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TABLE 2. Microbiological findings

Strains found	No. of patients on:	
	Single-dose augmentin	3-day augmentin
On enrollment		
E. coli	43	49
K. pneumoniae	4	1
Enterobacter spp.	3	1
Enterococcus spp.	3	
P. mirabilis	1	1
M. morganii	1	2
Failures or relapses		
E. coli	10	6
K. pneumoniae	1	1
M. morganii	1	

received the 3-day treatment with amoxicillin-clavulanic acid. Enrollment parameters in both groups were similar (Table 1). The etiological agents are listed in Table 2.

Clinical cure at 7 days was achieved in 43 women (78.1%) in the first group and in 47 women (87%) in the second group ($P = 0.33$). At the 28-day follow-up (Table 3), 37 and 42 women (67.3 and 77.7%) of the two groups continued to be symptom free ($P = 0.31$). Complete eradication of the organisms 7 days after treatment was achieved in 39 patients (70.9%) in the single-dose group and 45 patients (83.3%) in the 3-day treatment group ($P = 0.18$). Negative urine cultures at 28 days posttreatment were found in 36 and 41 women (65.5 and 75.9%), respectively ($P = 0.32$). The persistent microorganisms in the single-dose group were *Escherichia coli* (10 cases), *Klebsiella pneumoniae* (1 case), and *Morganella morganii* (1 case) and in the 3-day group were *E. coli* (6 cases) and *K. pneumoniae* (1 case). Resistance to amoxicillin-clavulanic acid after treatment appeared in one *E. coli* isolate in the 3-day-treated women.

The clinical and microbiological cure rates were analyzed in relation to the severity of infection, menstrual status, contraception, and recurrency; the only significant finding was limited to women who had recurrent UTIs (Table 4). Women in this category had a significantly higher microbiological failure rate at 7 and 28 days when treated with the single-dose regimen ($P < 0.001$ and $P = 0.07$).

TABLE 3. Clinical and microbiological responses

Response type and time of follow-up	No. (%) of patients on:	
	Single-dose augmentin	3-day augmentin
Clinical		
7 days		
Cure	43 (78.1)	47 (87.0)
Failure	12 (21.8)	7 (12.9)
4 wks		
Cure	37 (67.2)	42 (77.7)
Failure/relapse	6 (10.9)	5 (9.2)
Microbiological		
7 days		
Cure	39 (70.9)	45 (83.3)
Failure	16 (29.6)	9 (16.6)
4 wks		
Cure	36 (65.5)	41 (75.9)
Failure/relapse	3 (5.5)	4 (7.4)

TABLE 4. Clinical and microbiological response according to recurrency[a]

Response type and time of follow-up	No. (%) of patients with:			
	Single UTI episode on:		Recurrent UTI on:	
	Single-dose augmentin	3-day augmentin	Single-dose augmentin	3-day augmentin
Clinical				
7 days				
Cure	25 (86.2)	21 (95.7)	18 (69.2)	27 (84.3)
Failure/relapse	4 (13.8)	1 (4.3)	8 (30.8)	5 (15.7)
4 wks*				
Cure	24 (82.7)	21 (91.3)	16 (61.5)	24 (75.0)
Failure/relapse	1 (3.4)	0	2 (7.6)	3 (9.3)
Microbiological				
7 days				
Cure	26 (89.7)*	21 (95.7)	14 (53.8)*	24 (75.0)
Failure/relapse	3 (10.3)	1 (4.3)	12 (46.2)	8 (25.0)
4 wks				
Cure	25 (86.2)**	20 (90.9)	13 (50.0)**	21 (65.6)
Failure/relapse	1 (3.4)	1 (4.5)	1 (3.8)	3 (9.3)

[a] *, $P < 0.001$; **, $P = 0.07$.

Side effects, mostly gastrointestinal, were minor and occurred in similar rates in both groups (Table 5).

The efficacy of amoxicillin-clavulanic acid in the treatment of both complicated and uncomplicated UTI has been well established (1), but its use in single-dose regimens still remains to be proved. Fang et al. (2) showed in 1978 that a single dose of 3 g of amoxicillin or 250 mg three times a day for 10 days were comparably successful in women with antibody-coated bacterium-negative tests. Other oral antimicrobial agents used as a single dose, such as cotrimoxazole, trimethoprim, nitrofurantoin, and tetracycline, achieved similar cure rates (7).

In the last few years, several studies showed a higher rate of relapse or reinfection in women treated with a single dose (7). We recently showed that using either a single dose of 100 mg of ofloxacin or 250 mg of ciprofloxacin in women with recurrent UTI produces significantly higher rates of reinfection (5, 6).

This study is the first to use a single dose of amoxicillin-clavulanic acid and the first to compare its efficacy with that of a 3-day treatment. The use of high doses of amoxicillin-clavulanic acid at the usual ratio of amoxicillin to clavulanic acid is limited because of the possible high rate of side effects, especially gastrointestinal, attributed to the high concentration of clavulanic acid. This is the reason that a special formula containing only 125 mg of clavulanic acid in combination with 3 g of amoxicillin was used. Our results

TABLE 5. Side effects

Side effect	No. of patients on:	
	Single-dose augmentin	3-day augmentin
Diarrhea	2	3
Abdominal pain	1	
Nausea	2	2
Vomiting	1	
Pruritis		1
Total	5 (9%)	6 (11.1%)

suggest that this combination may be enough to inhibit the β-lactamase produced by the gram-negative bacteria in the bladder (1a, 2, 3).

In this study both regimens achieved high clinical and microbiological cure rates (approximately 80%), but when the results were analyzed by contributing factors, we found that women with a history of recurrent UTI had a significantly higher failure rate, probably because of an early recolonization in the vagina with uropathogens.

This study corroborates previous works that recommended management of women with uncomplicated cystitis with a short-course therapy. When amoxicillin-clavulanic acid is chosen, a combination of 3 g of amoxicillin plus 125 g of clavulanic acid seems efficacious and well tolerated. For women with three or more episodes of UTI in the last year, we would advocate a 3-day regimen.

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