Comparative Efficacy and Safety of Nalidixic Acid Versus Trimethoprim/Sulfamethoxazole in Treatment of Acute Urinary Tract Infections in College-Age Women

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One hundred and thirty-five college-age women with acute urinary tract infections caused by gram-negative *Enterobacteriaceae* were treated by random allocation with either nalidixic acid (NA), 1 g every 6 h for 7 days, or trimethoprim/sulfamethoxazole (TMP/SMZ), 160/800 mg every 12 h for 10 days. The clinical and bacteriological cure rates were 98.0% in each group on the last day of therapy. At 1 and 4 weeks posttherapy, both the clinical and bacteriological cure rates for NA declined to 90.0 and 74.0%, respectively; for TMP/SMZ, they declined to 93.0 and 72.0%, respectively. By 4 weeks posttherapy, 96.0% of the TMP/SMZ group and 93.0% of the NA group had remained free of the initial urinary pathogens. Neither drug was associated with emergence of resistant bacterial mutants in urine. The antibody-coated bacteria test (ACBT) localized 31.5% of the infections to the kidney and 67.7% to the bladder. Upper tract symptoms did not correlate with the presence of a positive ACBT. The response to therapy was similar for the two regimens regardless of ACBT results. After treatment, the emergence of resistant *Enterobacteriaceae* in fecal flora was 1.1% in the NA group and 2.3% in the TMP/SMZ group. The incidences of drug reactions were 7.0% with NA and 6.3% with TMP/SMZ.

Trimethoprim/sulfamethoxazole (TMP/SMZ) has been shown to be effective against most gram-negative and gram-positive organisms except *Pseudomonas* species (5, 10, 22). Nalidixic acid (NA) has a broad spectrum of activity against gram-negative *Enterobacteriaceae*. *Pseudomonas* species and gram-positive cocci are resistant to this agent (6, 23, 24). Oral doses of both drugs produce bactericidal urinary levels well in excess of the minimal inhibitory concentration for most urinary pathogens (20). TMP/SMZ is considered an effective drug for the treatment of urinary tract infections (UTIs) (5, 9, 13, 21, 28, 35). However, because of conflicting reports and controversy over the emergence of bacterial resistance, NA has been used less frequently (8, 25, 28).

In this study, the efficacy of NA was compared with that of TMP/SMZ for treatment of acute UTIs in young women. The antibody-coated bacteria test (ACBT) was used to localize the site of the infections (32, 33). Criteria were established to allow recurrences to be subdivided into reinfections and relapses. The effects of these drugs on the ecology of the fecal flora, as well as the emergence of resistant urinary pathogens, were assessed.

MATERIALS AND METHODS

The patient population was comprised of college women who entered the University of Florida Outpatient Clinic with symptoms of acute UTI. The criterion for inclusion in the study was the presence of more than 10^5 colonies of the same gram-negative *Enterobacteriaceae* per ml in each of three consecutive urine samples obtained within 24 h of initiating therapy. Lower urinary tract symptoms were monitored by the use of a patient diary. The time of each voiding and the degree of severity of each symptom were recorded in the diary during the first 3 days of therapy. Women with asymptomatic infections were included in the study. They were identified from a group of students who were having monthly urine cultures done as follow-up for previous UTIs.

Patients excluded from the study were those with allergy to NA or TMP/SMZ, infections due to gram-positive cocci, gonorrhea, catheter-induced UTIs, renal calculi, and radiographically proven obstructive uropathies.

Bacteriology. Quantitative bacterial counts were performed with a calibrated platinum loop delivering 0.001 ml of urine onto blood agar and MacConkey agar plates. The culture was incubated at 37°C and examined after 24 h for growth and colony counts. The species of infecting pathogens were identified by standard microbiological methods. Antibiotic susceptibility testing of each pathogen was done by the disk

diffusion method of Bauer et al. (2), using a 30- μ g NA and 1.25- μ g TMP/23.75- μ g SMZ disk. Serotyping of O antigen was done on *Escherichia coli* isolates (36).

Pretherapy and 1-week posttherapy fecal cultures were obtained with rectal swabs, which were placed in a Culturette (Scientific Products, Evanston, Ill.) and immediately refrigerated at 4°C. Within 24 h, they were streaked onto MacConkey and blood agar plates and incubated at 37°C overnight. Isolates of gram-negative rods were tested biochemically and transferred to Mueller-Hinton medium for antibiotic susceptibility testing. Twenty-four age-matched volunteers who had not received any antibacterial agent for the preceding 8 weeks served as controls. Fecal cultures were obtained from each control initially and 2 weeks later.

Patients were screened for vaginal gonorrhea, trichomonas, and monilia before therapy and at 1 week after therapy.

Localization of infection. The site of infection was determined in vitro by the fluorescent ACBT as modified by Thomas et al. (32, 33). The sediment from 10 ml of pretherapy urine was examined for ACB with 0.55 ml of a 1:10 dilution of fluorescence-conjugated anti-human globulin of goat origin (Hayland Diagnostics, Deerfield, Ill.). The test was considered positive when at least two fluorescent bacteria were found in each of 10 high-power fields ($\times 400$). The test was considered negative if no ACB were seen after multiple fields had been examined for approximately 5 min. A positive ACBT was defined as a kidney infection; a negative one was defined as a bladder infection (15, 18, 27, 32, 33). Each positive ACBT specimen was examined for nonspecific fluorescence by testing a washed subculture of the bacterial isolates. The test was considered nonspecific if the positive ACBT persisted in the subcultured isolates.

Therapy. Patients were randomly allocated to either NA, 1.0 g every 6 h for 7 days, or TMP/SMZ, 160/800 mg every 12 h for 10 days. Patients with concurrent vaginal monilia or trichomonas infections were simultaneously treated with either miconazole nitrate 2% vaginal cream or metronidazole oral tablets, respectively.

Assessment of therapy. Clinical and bacteriological evaluations were conducted at 2 days after initiating therapy and on the last day of therapy. Post-therapy evaluations were done at 1, 2, and 4 weeks and thereafter at 4-week intervals through 6 months. Colony counts of less than 10^3 /ml were considered a bacteriological cure; greater than 10^5 /ml, a bacteriological failure; and between 10^3 and 10^5 /ml, bacteriologically suspicious. All patients with bacteriologically suspicious and positive urines were reassessed with two urine cultures. Criteria were established to separate recurrences into either relapses or reinfections. Reinfections were limited to any or all of the following: (i) recurrence with a different bacterium; (ii) recurrence with a different *E. coli* serotype; (iii) recurrence at or beyond 4 weeks posttherapy; and (iv) recurrence with the same bacteria but with conversion of a positive ACBT to a negative ACBT. The last case applies if one accepts the premise that a positive ACBT indicates a kidney infection and a negative ACBT indicates a bladder infection. Therefore, if the initial

urinary pathogen survived in the kidney after therapy, causing a recurrence (relapse), the ACBT would have remained positive, whereas conversion of a positive ACBT to a negative ACBT would imply a new infection. A relapse was considered when all of the following criteria were met: (i) recurrence with a bacterium of the same species and antibiotic susceptibility; (ii) recurrence with *E. coli* of the same serotype; (iii) recurrence with the same bacterium without conversion of a positive ACBT to a negative ACBT; and (iv) recurrence with the same bacterium within 4 weeks posttherapy. Clinical cure was defined as disappearance of all presenting signs and symptoms by the completion of therapy, and an unsatisfactory clinical response or failure was defined as no appreciable change in signs and symptoms by the completion of therapy.

The study received prior approval of the University of Florida College of Medicine Human Experimentation Committee. The procedures were fully explained to each patient, and informed consent was obtained before therapy was begun. The data were analyzed in consultation with the Health Center biostatistician. The life table method (11) was used to determine the percentage cumulative rate of bacteriological recurrence (PCRR) and cure. This method incorporates all patients entered in the study and takes into account those lost to follow-up as well as treatment failures.

RESULTS

A total of 135 female college students were entered in the study. Seventy-one randomly chosen patients were treated with NA, and 64 were treated with TMP/SMZ. The presenting clinical characteristics of the patients were similar in both treatment groups. The mean age was 23 ± 4.0 years. Of the total, 129 (95.6%) expressed some combination of dysuria, frequency, urgency, and suprapubic pain. Fifteen patients (11.1%), six in the NA group and nine in the TMP/SMZ group, had costovertebral angle tenderness. Twenty-three patients (17.0%), 10 in the NA group and 13 in the TMP/SMZ group, had a mild fever (37.5 to 38.0°C). The mean duration of symptoms before therapy was 3.0 ± 2.5 days. Only six patients (4.4%) were asymptomatic, two in the NA group and four in the TMP/SMZ group. Pretherapy vaginal candida was isolated in 24 patients (17.8%), 12 in each treatment group. Pretherapy trichomonas was isolated in two patients (1.5%), both in the NA group. After therapy with NA, three other patients (4.2%) developed vaginal candida infection.

Thirty-five patients (26.0%), 16 in the NA group and 19 in the TMP/SMZ group, had no history of UTI within the preceding 12 months. Seventy-two patients (53.3%), 42 in NA group and 30 in the TMP/SMZ group, had one to two UTIs within that same period. Twenty-eight patients (20.7%), 13 in the NA group and 15 in the TMP/SMZ group, had three or more UTIs

during the preceding 12 months. Radiological and urological studies were limited to those with a history of previous recurrent infections. These included 56 intravenous pyelograms, 9 voiding cystourethrograms, and 13 cystoscopic examinations. All of these procedures were reported normal.

Pretherapy bacteriology. *E. coli* was the most common primary urinary pathogen (74.8%) isolated (Table 1). Of these isolates 53.3% were identifiable by O-antigen serotyping. The most common serotypes were O6 (38.9%) and O75 (20.4%). Of the 135 *Enterobacteriaceae* isolated, 98.5% were susceptible to NA and 99.3% were susceptible to TMP/SMZ. The resistant organisms consisted of an NA-resistant strain of *E. coli* in the TMP/SMZ group and a strain of *Klebsiella pneumoniae* resistant to both TMP/SMZ and NA, but showing good therapeutic response with NA. Novobiocin-resistant *Staphylococcus saprophyticus* was isolated in 17 patients (11.2%), who were excluded from the study.

Bacteriology at 2 days of therapy. Of the 71 patients in the NA group, 67 completed the first 2 days of therapy and were bacteriologically cured. In four others, NA was discontinued because of drug reactions. Of the 64 patients in the TMP/SMZ group, 63 completed the first 2 days of therapy and exhibited bacteriological cure. One patient did not return for follow-up. In both treatment groups, personal interviews and review of the diaries of each patient showed that a clinical cure had been produced within 48 h of therapy.

Last day of therapy. In the NA group, 65 of 67 patients completed 7 days of therapy. Of these, 64 (98.5%) showed a clinical and bacteriological cure, and one developed a reinfection with a strain of *S. saprophyticus*. Of the remaining two, NA was discontinued in one more patient because of a drug reaction, and one patient failed to return for follow-up. In the TMP/SMZ group, 58 of 63 patients completed 10 days of therapy. Of these, 57 (98.3%) continued to show a clinical and bacteriological cure, and one became reinfected with a resistant strain of *K.*

pneumoniae. Of the other five patients, TMP/SMZ was discontinued in four because of drug reactions and in one because of concomitant gonorrhea.

Posttherapy follow-up. In the NA group, the initial urinary pathogens remained eradicated at 1 and 4 weeks posttherapy in 100 and 93.0% of the patients, respectively. In the TMP/SMZ group, the original pathogens remained eradicated at 1 and 4 weeks posttherapy in 98.0 and 96.0% of the patients, respectively.

By 4 weeks posttherapy, reinfections accounted for 75.0% (12 of 16) of the recurrences in the NA group and 87.5% (14 of 16) of those in the TMP/SMZ group. The remainder of the recurrences were relapses. In the NA group, 31.3% (5 of 16) of the recurrences were reinfections with NA-resistant isolates. Four of the five were *S. saprophyticus* organisms, and one was an *E. coli*. In the TMP/SMZ group, 6.3% (1 of 16) of the recurrences were reinfections with a TMP/SMZ-resistant *K. pneumoniae*. There was no statistically significant difference in the number of reinfections with *S. saprophyticus* during the 4 weeks of posttherapy follow-up between the NA group (4 of 16) and the TMP/SMZ group (2 of 16).

In the NA group, PCRR values at 1, 4, and 24 weeks posttherapy were 10.0, 26.0, and 42.0%, respectively; in the TMP/SMZ group, values were 7.0, 28.0, and 45.0%, respectively (Fig. 1).

ACBT. The ACBT was performed in 126 patients. Of these, 31.7% were ACBT positive and 68.3% were ACBT negative. Of the patients with upper urinary tract symptoms, 71.4% were ACBT negative and 28.6% were ACBT positive. This distribution was similar to that seen in patients with lower urinary tract symptoms, of

TABLE 1. Distribution of initial bacteria by treatment group

Bacteria	Distribution			
	NA	TMP/SMZ	Total	%
<i>E. coli</i>	52	49	101	74.8
<i>K. pneumoniae</i>	12	7	19	14.1
<i>Proteus</i> sp.	4	6	10	7.4
<i>Enterobacter</i> sp.	3	2	5	3.7
Total	71	64	135	100.0

FIG. 1. PCRR in NA versus TMP/SMZ groups.

which 67.9% were ACBT negative and 32.1% were ACBT positive.

Of the 24 positive ACBT patients in the NA group, 23 completed 7 days of therapy with clinical and bacteriological cure rates of 100 and 95.7% at the 2nd and last days of therapy, respectively. In this group, 100% of the initial urinary pathogens remained eradicated at 1 week and 95.0% remained eradicated at 4 weeks posttherapy. The PCRR values at 1, 4, and 24 weeks posttherapy were 17.0, 26.0, and 46.0%, respectively (Fig. 2).

Thirty-nine of the 43 negative ACBT patients in the NA group who completed 7 days of therapy had clinical and bacteriological cure rates of 100% at both the 2nd and last days of therapy. In this group, 100% of the initial urinary pathogens remained eradicated at 1 week and 91.9% remained eradicated at 4 weeks posttherapy. The PCRR values at 1, 4, and 24 weeks posttherapy were 3.0, 23.0, and 32.0%, respectively (Fig. 2).

The clinical and bacteriological cure rates were 100% at both the 2nd and last days of TMP/SMZ therapy in the 16 positive ACBT patients. In this group, 100% of the urine cultures remained free of the initial urinary pathogens at 1 and 4 weeks posttherapy. The PCRR values at 1, 4, and 24 weeks posttherapy were 7.0, 20.0, and 34.0%, respectively (Fig. 2).

Thirty-nine of 42 negative ACBT patients completed 10 days of TMP/SMZ therapy with clinical and bacteriological cure rates of 100 and 97.4% at the 2nd and last days of therapy, respectively. In this group, the initial urinary pathogens remained eradicated in 100 and 97.0% of the patients at 1 and 4 weeks posttherapy, re-

spectively. The PCRR values at 1, 4, and 24 weeks posttherapy were 2.0, 23.0, and 44.0%, respectively (Fig. 2).

By 4 weeks posttherapy in the positive ACBT patients, reinfections accounted for 83.3% (five of six) of the recurrences in the NA group and 100% (three of three) of those in the TMP/SMZ group. During the same follow-up period of the negative ACBT patients, reinfections contributed to 62.5% (five of eight) of the recurrences in NA group and 88.9% (eight of nine) of those in the TMP/SMZ group. The remainder of the recurrences in each subgroup were considered relapses.

Fecal flora. During 2 weeks of observation, the rectal cultures of the 24 uninfected, age-matched controls showed no evidence of a significant change in the number or types of *Enterobacteriaceae* colonizing the bowel flora. Neither NA- nor TMP/SMZ-resistant organisms were found in these fecal isolates.

Sixty patients in the NA group and 58 in the TMP/SMZ group had both pretherapy and 7-day posttherapy fecal cultures. All the pretherapy fecal bacterial isolates were susceptible to both agents in vitro, except for a strain of *Pseudomonas* species which was resistant to both drugs. Therapy with NA and TMP/SMZ reduced the number of *E. coli* strains colonizing the bowel flora by 67.2% (45 of 67) and 57.4% (31 of 54), respectively. *Enterobacteriaceae* were cleared from the bowel flora by NA therapy in 15.0% (9 of 60) and by TMP/SMZ therapy in 22.4% (13 of 58) of the patients. One NA-resistant strain of *E. coli* (1.1%) was isolated from a patient after therapy with this drug. After therapy with TMP/SMZ, a resistant strain emerged in two patients (2.3%). *K. pneumoniae* was isolated from the first patient, and *Pseudomonas* species was isolated from the second.

Adverse reactions. Drug reactions occurred in 7.0% (5 of 71) of the NA group and 6.3% (4 of 64) of the TMP/SMZ group. Untoward symptoms in the NA group consisted of a combination of a mild to moderate degree of photophobia in four patients, blurred vision and nausea in three, dizziness in two, and loss of balance, malaise, vomiting, and flushing of the face in one. The blood pressures and eye examinations, including eye grounds, of these patients were normal. The symptoms became apparent in two patients within 2 h of the first dose of NA and in two others within 2 h of the second dose. All of the untoward symptoms spontaneously resolved within 2 h after NA was discontinued. In the fifth patient, mild symptoms occurred on the 3rd day of therapy and abated within 4 days after treatment was stopped.

FIG. 2. PCRR in NA versus TMP/SMZ-treated ACB subgroups.

Adverse reactions to TMP/SMZ occurred in four patients. The first patient complained of moderate nausea and dizziness on the 4th day of therapy. A second patient was bothered by mild to moderate insomnia, vertigo, diarrhea, chills, and perspiration on the 5th day of therapy. The third patient experienced shakiness, malaise, palpitation, puffy eyes, and a paresthetic area of 4 to 6 cm in diameter on the median side of her right leg on the 7th day of therapy. The fourth patient developed a generalized nonpruritic maculopapular rash on the 9th day of therapy. All of the untoward symptoms resolved within 2 to 3 days after TMP/SMZ was discontinued.

DISCUSSION

In this study, the four treatment subgroups were clinically and bacteriologically comparable; therefore, the efficacy of NA and TMP/SMZ could be reliably evaluated. The majority of the initial *Enterobacteriaceae* responsible for the infections were susceptible to NA (98.5%) and TMP/SMZ (99.3%) by in vitro susceptibility testing. Both agents produced a rapid resolution of clinical symptoms and elimination of the urinary pathogens by the 2nd day of therapy, independent of the sites of infection. Through 4 weeks posttherapy, the urine culture remained free of the initial urinary pathogens in 93.0% of the NA group and 96.0% of the TMP/SMZ group. Therefore, in vitro susceptibility testing of both drugs correlated well with the clinical and bacteriological cure rates. The combination TMP/SMZ has been reported to be effective in the treatment of both acute and chronic infections in all age groups (5, 9, 13, 21, 35). However, there has been controversy in the literature regarding the value of susceptibility testing of NA in predicting the outcome of therapy. Some investigators have reported rapid emergence of resistant bacterial mutants and development of resistant superinfections during NA therapy (7, 16, 25), whereas others have reported a lesser degree of bacterial resistance with good success in the treatment of UTI (4, 28, 29, 34). The results of this study agree with those of the latter group; our data showed that in vitro susceptibility testing was reliable for predicting results of treatment with either NA or TMP/SMZ in patients with uncomplicated UTI.

Neither NA nor TMP/SMZ caused persistence of the UTIs with resistant bacterial mutants of the initial pathogens. Development of reinfections with resistant *Enterobacteriaceae* was not a problem in either therapeutic regimen. By 4 weeks posttherapy, two reinfections with resistant *Enterobacteriaceae* had occurred, an *E. coli* in the NA group and a *K. pneumoniae* in the TMP/SMZ group.

Toivonen et al. (34) compared NA and ampicillin in 67 patients with acute and chronic infections. In the group with acute infection, the cure rate was 93.0% with ampicillin and 95.0% with NA. In those with chronic infections, the cure rate was 82.0% with ampicillin and 77.0% with NA. Before therapy was begun, 19.0% of the organisms were resistant to ampicillin and none were resistant to NA. Posttherapy, the resistance to NA was 2.3%. Brown et al. (4) reported a 94.0% cure rate with NA and 81.0% with sulfadimidine in 177 patients. Before therapy, urinary bacterial isolates resistant to sulfa and NA were 10.0 and 1.0%, respectively. Posttherapy resistance was 11.3% to sulfa and 3.2% for NA. Of interest, 5.4% of the patients who had received sulfadimidine developed superinfections with different sulfa-resistant organisms. Cederberg et al. (8) found an 86.0% cure rate and a posttherapy bacterial resistance of 8.0% in 100 patients treated with NA. The majority of these patients had asymptomatic infections. Ronald et al. (25) reported a 50.0% cure rate after NA treatment of 50 patients with chronic UTI. The emergence of bacterial resistance to NA was 25.0%. Harrison and Cox (16) found an 88.5% cure rate and an 11.5% emergence of bacterial resistance in 26 patients treated with NA. Sleet et al. (26) reported failure with NA therapy in 75.0% (26 of 35) of patients with renal insufficiency, complicated chronic infections or both. Buchbinder et al. (7) found a 73.0% cure rate and 27.0% incidence of subsequent bacterial resistance to NA in 15 pyelonephritic patients.

Conditions that appear to enhance the development of bacterial resistance to NA are inadequate dosage, complicated chronic pyelonephritis, renal failure, urinary foreign bodies, and indwelling urinary catheters (28). The therapeutic effectiveness of NA and lack of emergence of the bacterial resistance in our study as compared with previous studies might be attributed to the absence of these factors in our patients.

Four of the recurrences in the NA group and two in the TMP/SMZ group were considered relapses. The initial pathogen might have survived in the urinary tract if sufficient drug levels had not been maintained in the kidney and the urine. However, oral administration of NA or TMP/SMZ at the recommended dosage has been reported to attain renal and urinary concentrations adequate to eliminate susceptible bacterial pathogens in uncomplicated UTIs (1, 17, 30). Another explanation for the relapses might have been poor patient compliance. This is unlikely, since the relapses occurred beyond 1 week posttherapy, and patient diary records demonstrated that the patients had taken their medication at the prescribed doses and times

during the first 3 days of therapy. We would favor the view that the relapses seen in our patients were more likely reinfections with the same bacterial strains from persistent colonization within the vagina. This view is in agreement with findings of Stamey et al. (31).

Novobiocin-resistant *S. saprophyticus* was isolated in 17 patients (11.2%), who were excluded from the study. This organism comprises 10 to 13% of the urinary pathogens of uncomplicated acute UTI of young women (14, 19). *S. saprophyticus* is susceptible to TMP/SMZ and resistant to NA. Therefore, before initiating therapy with NA in young women, one should search for the presence of this organism by performing microscopic examination and Gram stain of the urine sediment or culture of the urine.

By 4 weeks posttherapy, 4 of 16 reinfections in NA and 2 of 16 reinfections in TMP/SMZ were with *S. saprophyticus*. The number of reinfections with *S. saprophyticus* were not statistically different in the two treatment groups. Since *S. saprophyticus* is resistant to NA, the rate of reinfections with NA-resistant organisms was higher (31.3%) in the NA group than in the TMP/SMZ group (6.3%).

Another interesting finding in our study was the lack of correlation of the ACBT with the presenting clinical signs and symptoms of the upper and lower tract infections. Patients were found often to have upper tract symptoms with a negative ACBT. Since these patients were seen early in the course of their illness, it is possible that there was insufficient time for antibodies to have developed. The response to therapy was similar for NA and TMP/SMZ regardless of the ACBT results. Patients with a positive ACBT did not show a propensity for higher recurrence rates than those with a negative ACBT. We feel that further studies are required to clarify the clinical significance of this test.

After therapy, the fecal flora showed that the emergence of resistant strains to NA (1.1%) and TMP/SMZ (2.3%) was minimal as compared with other antibiotics (12, 28). This finding was consistent with the low incidence of resistant isolates in the follow-up urine cultures. Both drugs significantly reduced the incidence of colonization with *E. coli* in the fecal flora. TMP/SMZ and NA eradicated the susceptible fecal *Enterobacteriaceae* in 22.4 and 15.0% of the patients, respectively. In two separate studies of 27 and 54 patients, Stamey et al. (28, 29) reported the identical emergence of 7.0 and 5.5% NA-resistant urinary and fecal organisms, respectively. NA eliminated *Enterobacteriaceae* from the fecal flora in 67.0% of their patients. These effects might have been due to the fecal

concentration of biologically active unabsorbed drugs (3).

The majority of our patients tolerated both drugs well. The incidence of drug reaction was 7.0% to NA and 6.3% to TMP/SMZ. The severity of side effects necessitated discontinuation of therapy in these patients. Photophobia and blurred vision were unique to NA, and skin rash was unique to TMP/SMZ. In each patient, the drug reactions abated soon after the test drugs were discontinued.

The overall results of this study suggest that both NA and TMP/SMZ are efficacious agents for treatment of uncomplicated acute UTI caused by gram-negative *Enterobacteriaceae* in young women.

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