ORIGINAL INVESTIGATION

Comparison of Short-Course (5 Days) and Standard (10 Days) Treatment for Uncomplicated Cellulitis

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Background: Cellulitis is a condition routinely encountered in the primary care setting. No previous study has compared a short (5 days) vs standard (10 days) course of therapy of the same antibiotic in patients with uncomplicated cellulitis.

Methods: We performed a randomized, double-blind, placebo-controlled trial to determine if 5 days of therapy has equal efficacy to 10 days of therapy for patients with cellulitis. Of 121 enrolled subjects evaluated after 5 days of therapy for cellulitis, 43 were randomized to receive 5 more days of levofloxacin therapy (10 days total antibiotic treatment), and 44 subjects to receive 5 more days of placebo therapy (5 days of total antibiotic treatment). Levofloxacin was given at a dose of 500 mg/d. Subjects were not randomized if they had worsening cellulitis, a persistent nidus of infection, a lack of any clinical improvement, or abscess formation within the first 5 days of therapy. The main outcome measure was resolution of cellulitis at 14 days, with absence of relapse by 28 days, after study enrollment.

Results: Eighty-seven subjects were randomized and analyzed by intention to treat. There was no significant difference in clinical outcome between the 2 courses of therapy (success in 42 [98%] of 43 subjects receiving 10 days of antibiotic, and 43 [98%] of 44 subjects receiving 5 days of antibiotic) at both 14 and 28 days of therapy.

Conclusion: In patients with uncomplicated cellulitis, 5 days of therapy with levofloxacin appears to be as effective as 10 days of therapy.

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CELLULITIS IS ONE OF THE most common diagnoses encountered by the primary care provider.[1] The US military alone observed 104 738 cases of cellulitis from January 1998 to December 2001.[2] Most outpatient presentations of cellulitis are uncomplicated, and improve with empiric antimicrobial therapy effective against *Streptococcus* species and *Staphylococcus aureus*.[3] The duration of therapy required for these uncomplicated cases of cellulitis remains undefined. Most studies of uncomplicated skin and soft tissue infections used 7- to 10-day courses of antibiotics for treatment.

Cellulitis appears to be a paucibacillary disease influenced by a strong inflammatory response, evidenced by the low bacterial yield of skin aspirates from involved areas.[4,5] It is conceivable that most bacteria may be eradicated from the underlying dermal layers within the first few days of antibiotic therapy, and therefore a brief course of therapy may be as effective as a standard 7- to 10-day course. Investigations into appropriate durations of therapy for other disease processes, such as acute cystitis[6] and acute sinusitis,[7] have suggested equivalent efficacy for abbreviated courses of therapy for uncomplicated infections. We hypothesized that cellulitis might also be a disease process in which short-course therapy would be successful. On literature review, we did not encounter a previous study that compared a short course (<1 week of therapy) with a standard course of therapy, using the same antibiotic, for skin and soft tissue infections. We therefore designed a trial to compare a short (5 days) and standard (10 days) course of therapy for uncomplicated cellulitis, using the same antibiotic. We hypothesized that there would be no difference in outcomes when uncomplicated cellulitis was treated with either short-course or standard-course therapy.

METHODS

PARTICIPANTS

Patients with presumed cellulitis were referred from primary care clinics and the emer-

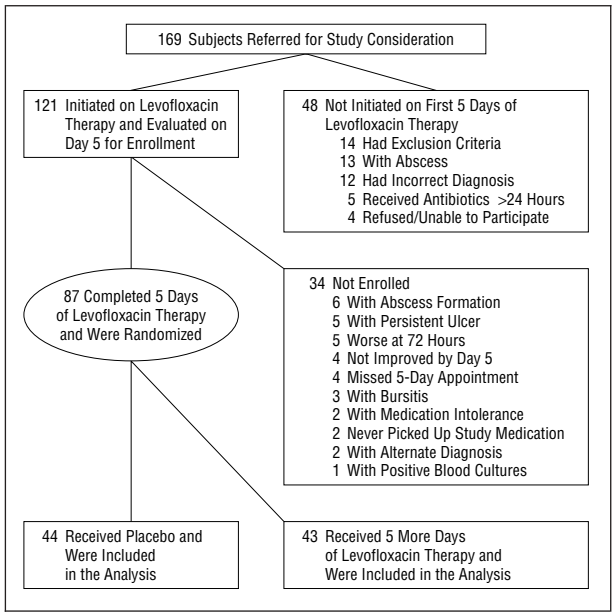

Figure 1. Study enrollment and completion.

gency department at Brooke Army Medical Center, a tertiary care military hospital in San Antonio, Tex. Patients eligible for care at our facility include active-duty personnel, military dependents, and military retirees (served for ≥20 years on active duty). After initial presentation in primary care clinics, patients were either referred immediately to the infectious disease clinic for evaluation, or were begun on treatment with antibiotics and then seen within 24 hours either as inpatients or, if not admitted, in the infectious disease clinic as outpatients. Patients were recruited for study enrollment if they fit the inclusion criteria: age 18 years and older; cellulitis involving the face, trunk, or an extremity; and presentation to the investigators for evaluation within 24 hours of initiation of antibiotic therapy. Exclusion criteria for enrollment were documented bacteremia; evidence of severe sepsis (including septic shock); clinical evidence of deep soft tissue infection (including abscess, fasciitis, myositis, osteomyelitis, or septic arthritis) or infection requiring debridement at the site; animal or human bite wound cellulitis; neutropenia; diabetic foot infections with nonviable tissue suggesting vascular insufficiency; chronic cellulitis (see criteria below); pregnancy or breastfeeding; known allergy or intolerance to levofloxacin or other fluoroquinolone antibiotics; severe renal insufficiency (serum creatinine level ≥4.0 mg/dL [354 µmol/L] or glomerular filtration rate estimated at ≤10 mL/min); or any antibiotic administration within 2 weeks before initial presentation.

Participation was voluntary, and subjects were allowed to discontinue participation in the study at any time. This study was approved by the institutional review board at Brooke Army Medical Center (C-1999-072).

DEFINITIONS

A case of cellulitis was determined using the definition from the Infectious Diseases Society of America and Food and Drug Administration for clinical trials: "Cellulitis is a general descriptive term suggesting infection and indicating the warmth, erythema, and induration of skin and/or subcutaneous tissue, with or without pain."[8] Chronic cellulitis was diagnosed when the above findings were present and stable for more than 2 weeks at presentation. Cellulitis was considered to be uncomplicated if it was not associated with any of the more severe or nonresponsive manifestations of disease as described in the exclusions above. In the setting of an insect bite, cellulitis was diagnosed if a new acceleration of an erythematous, painful, and warm reaction developed more than 48 hours after the initial bite or sting. Subjects with initial (within the first 48 hours) erythematous reactions to insect bites were considered to have allergic reactions and were not enrolled.

PROCEDURE

All study participants received antibiotics for the first 5 days of treatment (**Figure 1**). If initial antibiotics were administered intravenously, a switch to an oral antibiotic was performed as soon as 1 to 2 days of distinct improvement occurred. Most antibiotic courses, however, were entirely oral with subjects switching from the initial drug (usually a β-lactam) to levofloxacin within 24 hours after presentation. We chose to use levofloxacin as the antibiotic for this study for 3 reasons: (1) this antibiotic was one of the few available medications in the United States at the time of study initiation with a once-daily dosing schedule, thought optimal for patient adherence; (2) the antibiotic has documented efficacy in cellulitis[9-12]; and (3) the antibiotic effect of levofloxacin dissipates by 24 hours after the last dose on the fifth day of therapy. The last dose of the initial course of levofloxacin was given no later than late in the fifth day after presentation.

Subjects were assessed by one of the co-investigators within 24 hours of initial primary clinic presentation to confirm the diagnosis of cellulitis and provide an initial quantitative assessment. Wound cultures were performed only when purulent material was obtainable from a superficial site of infection. Blood cultures were performed only when either the investigators or the referring physicians determined their necessity, usually for inpatient hospitalizations. At each visit, the severity of cellulitis was graded using a clinical scoring sheet, in which the investigators assigned an assessment (none, mild, moderate, or severe) to each of the following parameters: erythema, warmth, tenderness, edema, ulceration, drainage, and fluctuance. Grading of each was standardized among investigators at the beginning of the study by simultaneous readings. The grading designations none through severe were converted into a numerical value of 0 to 3 and these numbers were added to create a physician composite score for purposes of analysis (maximum score possible, 21). Subjects also self-assessed their subjective pain and swelling on Likert scales (0-10) at each visit. Subjects initially received levofloxacin, 500 mg/d (250 mg for estimated glomerular filtration rate <50 mL/min, although only 1 subject met this criterion), for 5 days. Subjects were advised to contact the co-investigators for progression of disease or side effects of the medication at any point during the study.

The first mandatory follow-up visit, when the decision to randomize or not was made, occurred on day 5 (Figure 1). Subjects were assessed for clinical improvement of their cellulitis and medication adherence. Subjects were randomized at day 5 unless the course of treatment within the first 5 days was complicated by progression of infection requiring the continuation or reinstitution of intravenous antibiotic therapy; if there was an adverse reaction to levofloxacin; if an abscess or other nidus of infection became apparent; if further diagnostic information excluded participation (positive blood cultures, or if an alternative diagnosis became evident); or if appointments were missed. The continued presence of the clinical indicators of cellulitis (erythema, warmth, tenderness, or edema) did not exclude subjects from randomization if, in the investigator's opinion, even minimal improvement had occurred. Randomization occurred in double-blind fashion to either an additional 5 days of levofloxacin (at the subject's initial daily dose)

or placebo. The next follow-up visit occurred between days 10 and 14, when subjects were assessed for clinical resolution of their infection. A final telephone call after 28 days from the initiation of treatment was performed to monitor for evidence of recurrence.

OUTCOMES

Our primary outcome was resolution of infection at day 14, defined as disappearance of warmth and tenderness at the site of infection, with substantial improvement in erythema and edema, and without symptom recurrence by day 28. A case was considered a clinical success even with mild residual erythema, hyperpigmentation or edema, contingent upon not requiring further antibiotic therapy. Clinical failure of short-course therapy was defined as worsening signs and symptoms beyond day 5 of therapy. Any requirement for further intervention, such as abscess drainage or reinitiation of antibiotics, or the recurrence of signs of infection within 28 days of enrollment, were all classified as antibiotic failure. Secondary outcomes included comparisons of the speed and degree of improvement of clinical scores between the 5-day and 10-day treatment groups.

STATISTICAL METHODS

Power calculations were performed assuming a success rate of therapy of 98% was predicted, and that a difference of 20% (78% success rate) would be considered clinically meaningful. Eighty total subjects (40 per group) were required for a power of 80% (95% confidence) to be able to detect differences between groups.

Block randomization in groups of 10 was used. A random-numbers table was generated by our pharmacy, and randomization occurred in the pharmacy when the study medication was dispensed on day 5. The subject roster and group allocation were maintained by and known only to the pharmacy. Levofloxacin or placebo tablets were dispensed in identical gelatin capsules so that subjects and investigators were blinded to group allocation. Unblinding did not occur until the study was complete.

The primary outcome of success or failure at day 14, without relapse by day 28, was assessed as a binomial variable, and the means of groups were compared using the Fisher exact test. Intention-to-treat analysis was used to compare the 2 groups following randomization at day 5. Differences in the baseline characteristics of the 2 groups were assessed using independent sample *t* tests for interval variables (age, absolute neutrophil count, and days of symptoms before presentation), Mann-Whitney rank sum tests for ordinal variables (physician score), and Pearson χ^2 tests for categorical variables (sex, ethnicity, history of diabetes, first seen as an inpatient, and fever on presentation) as appropriate. A 2-factor analysis of variance (treatment, time) with repeated measures on one factor (time) with 2-tailed *t* tests corrected for multiple comparisons was used to compare the change in clinical scores and in subjective scores (pain and swelling) between the 2 groups on serial visits.

RESULTS

The enrollment and subsequent randomization processes, and the numbers of subjects for each, are depicted in Figure 1. There were 169 potential participants with presumed cellulitis who had been treated for less than 24 hours and referred and interviewed either in the outpatient setting (infectious disease clinic, urgent care clinic) (n=147) or after hospitalization (n=22). On review, 48 subjects refused participation, did not have cellulitis, or met exclusion criteria for enrollment (Figure 1). Of the 121 enrolled subjects, 34 were not randomized at day 5 for the listed reasons (Figure 1). The 5 potential subjects with persistent posttraumatic ulcers had significant areas of abraded skin on presentation. These subjects were excluded since their wounds were poorly reepithelialized by day 5. The 15 subjects whose condition either worsened, declared abscesses, or had no improvement by day 5 were not exposed to randomization into a short-course arm. Each of these subjects would have required reevaluation of their cellulitis, and possible modification of the therapeutic approach, if treated in the nonresearch setting. In the end, 87 subjects were randomized at day 5: 44 into the short-course arm (and then given placebo) and 43 into the standard-course arm (and then given 5 more days of levofloxacin therapy).

Table 1. Baseline Characteristics*

Characteristic	10-d Levofloxacin Group (n = 43)	5-d Levofloxacin Group (n = 44)
Age, mean, y	49	56
Male sex	19 (44)	24 (54)
Ethnicity/race		
White	30 (70)	36 (81)
Black	5 (12)	4 (9)
Hispanic	7 (16)	3 (7)
Other	1 (2)	1 (2)
Absolute neutrophil count, /μL	7303	6251
No. of days of symptoms before presentation	3.4	2.9
History of diabetes mellitus	5 (12)	7 (16)
Initially seen as inpatients	4 (9)	8 (18)
Fever on presentation	5 (12)	4 (9)
Initial physician score, aggregate†	6.8	6.3

*Data are number (percentage) of patients unless otherwise specified. *P* values were not significant for each category.
†See text for description.

Table 1 displays the baseline characteristics of the subjects who completed the trial. A total of 12 subjects were treated as inpatients, initially receiving antibiotic treatment intravenously and then orally, and 75 were treated solely as outpatients with oral antibiotics. Of the 12 inpatient subjects, 4 were randomized to the 10-day therapy group (mean duration of hospitalization, 4.5 days), and 8 were randomized to the 5-day therapy group (mean duration of hospitalization, 2.4 days). There were no significant differences in any of the demographic or clinical parameters between groups. **Table 2** lists the predisposing factors for cellulitis, if any, among study subjects. An antecedent abrasion or blister and insect bites or stings were the most common inciting factors for cellulitis. Blood cultures were obtained at presentation in only 8 subjects, only 1 of whom was excluded from randomization into the study because of a positive result (for *Streptococcus agalactiae*).

Forty-three (98%) of 44 subjects receiving 5 days of levofloxacin had resolution of their infections, while 42 (98%) of 43 subjects receiving 10 days of therapy had resolution of their infections, by 14 days and without relapse by 28 days ($P>.05$). In the standard (10 days of therapy) group, the only clinical failure was a subject with

Table 2. Predisposing Factors Associated With Cellulitis

Standard-course group (10-d levofloxacin)	
Abrasion/blister	13
Insect bite	13
Venous stasis	4
Tinea pedis	3
Lymphedema	3
Other*	7
Short-course group (5-d levofloxacin)	
Insect bite	12
Abrasion/blister	9
Lymphedema	4
Tinea pedis	4
Paronychia	4
Other†	11

*Other includes pimple (2), scar (1), paronychia (1), xerosis (1), and none (2).

†Other includes scar (3), xerosis (2), venous stasis (1), pimple (1), erysipelas (1), callus (1), and none (2).

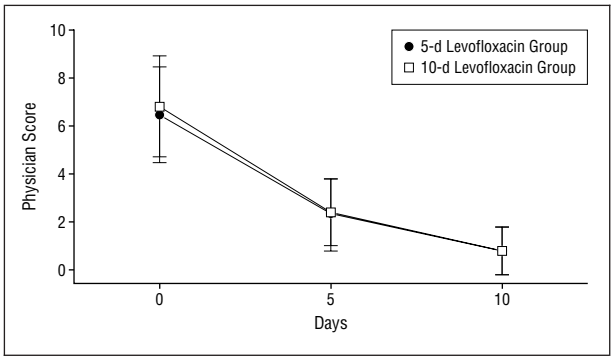

Figure 2. Serial physician composite scores for cellulitis with 5 vs 10 days of therapy. Physician composite score was a summation of 7 clinical indicators of cellulitis; maximum score 21 (see text for details). Error bars indicate SD.

a relapse of her infection less than 1 week after therapy was complete. Four subjects in the standard group had protocol violations: 2 patients missed their 10- to 14-day follow-up appointment, 1 never took the second 5 days of prescribed treatment medication, and 1 stopped her levofloxacin on day 8 due to gastrointestinal side effects. Each of these 4 subjects had full resolution of cellulitis. In the 5-day therapy group, the only clinical failure was a subject whose cellulitis did not completely improve, but instead worsened after randomization and by day 10 the patient had to resume antibiotic therapy, eventually requiring 21 days of treatment before resolution. Three subjects from the short-course (5-day) therapy group violated protocol by receiving antibiotics elsewhere for different reasons during the 14- to 28-day follow-up period (cellulitis on the contralateral extremity; reaction to a bee sting; suspected diverticulitis). Their infections resolved. If the subjects with protocol violations from each group were excluded from analysis, the results of the study did not differ from those obtained in the intention-to-treat analysis.

Each subject reported full adherence with medication when queried at follow-up appointments. No serious adverse events that were attributable to the medication or cellulitis were noted during the study. Three subjects had to discontinue levofloxacin therapy during the course of the study (2 for gastrointestinal intolerance, 1 for rash). Two of these subjects discontinued their levofloxacin before day 5 of the study and were never randomized. The third subject had gastrointestinal upset on day 8 of the study and had her medication discontinued on that day.

Physician composite clinical scores as well as the subjective pain and swelling scores significantly decreased over time as expected (for each, $P<.001$) (**Figures 2**, **3**, and **4**). The rates of decline in investigator composite scores were not different between the 5-day or 10-day group. Additionally, the rates of decline in the subjective pain and swelling measurements were also not different between the 2 groups. The investigators' composite scores on day 5 of treatment (2.3 ± 1.5 for the short-course group and 2.4 ± 1.4 for the standard-course group, both after initial scores >6) indicated that most subjects still had mild residual signs of cellulitis at the time of randomization.

COMMENT

We have observed that a short course of therapy (5 days) with a once-a-day medication dosing yields similar clinical outcomes to a standard course of therapy (10 days) for subjects with uncomplicated cellulitis. The rates of improvement, measured objectively and subjectively, between the short and standard courses of therapy were also similar, indicating that time to resolution of infection was also not affected by the duration of antibiotic therapy.

The therapy of uncomplicated cellulitis may be amenable to a shortened therapeutic course because of the paucibacillary nature of this disease.[4,5] Numerous investigations have reported disappointing yields in attempts to culture tissue aspirates from skin with cellulitis.[4,13-15] The inflammatory response to invading bacteria is thought to play a predominant role in creating the physical findings associated with cellulitis.[5] If eradication of sparse bacterial pathogens could be accomplished with a short course of therapy, the residual inflammatory response could then gradually resolve. We observed numerous subjects in both the short and standard treatment groups who still displayed substantial erythema and edema at day 5, and occasionally perceptible erythema at day 10, of therapy. These infections eventually resolved without complications. Some observers have suggested the continuation of therapy even beyond 10 to 14 days in subjects with any residual erythema, due to concerns about relapsing infection.[16] Our findings suggest that patients with residual signs of otherwise uncomplicated cellulitis will have resolution of their infection even if antibiotics are discontinued after 5 days, as long as their condition is improving within the first 5 days of treatment.

There are few formal recommendations in the literature that address the length of therapy for cellulitis.[1,2,16,17] *The Sanford Guide to Antimicrobial Therapy* suggests that treatment continue until 3 days after the acute inflammation resolves.[17] As mentioned, however, we observed many subjects with residual erythema and edema, and we are now skeptical that prolonged therapy is necessary in this subpopulation. Most clinical trials admin-

istered therapy for 7 to 10 days. To our knowledge, the only trials that have administered therapeutic courses of less than 7 days involved newer macrolides.[18-22] These medications, especially azithromycin, have prolonged functional half-lives in tissue, and introduce difficulties with interpretation of the duration of antibiotic effect. Additionally, these trials were not designed to assess duration of therapy in isolation, as they did not compare a medication with itself; rather, they compared a newer antibiotic with an older, more established antibiotic for the treatment of cellulitis. Our study was not supported by industry, and was designed such that the single variable of duration of therapy was studied in isolation.

Levofloxacin is considered a reasonable albeit expensive alternative to β-lactam antibiotics for the treatment of uncomplicated skin and soft tissue infections.[1,9,17] We elected to use levofloxacin for this study to maximize adherence, as levofloxacin can be administered once daily in an oral formulation. Subject adherence is crucial in a duration-of-therapy trial. Although fluoroquinolones with enhanced gram-positive activity may be unnecessarily expensive agents for the treatment of uncomplicated cellulitis in the United States, studies have demonstrated comparable efficacy between these fluoroquinolones and more established antibiotics.[9-12,23-25]

Our study intentionally selected subjects without complicating abscesses and with evidence of at least minimal improvement at the day 5 follow-up visit. Our findings would not support the practice of short-course therapy for all cellulitis without appropriate follow-up. A substantial portion of subjects with worsening cellulitis were not randomized at day 5 (5 subjects worse by 72 hours; 6 other subjects developing abscesses requiring drainage within 5 days of therapy). These 11 (of 121, or 9%) were considered primary antibiotic failures, a proportion similar to that reported in skin and soft tissue infection therapy trials in the literature (failure rates between 2% and 32%[9-12,20,23-25]). One recent description of therapy for uncomplicated cellulitis in an outpatient clinic noted an overall 27% failure rate for oral antibiotic therapy.[26] Four of our own subjects (out of 121, or 3%) did not show improvement at all by the fifth day of therapy, and so we excluded them from randomization. Although they eventually had resolution of their cellulitis after 10 to 14 days of therapy, we did not consider them eligible for short-course therapy. Five subjects with ulcers or extensive abrasions did not have substantial improvement in their primary lesions by day 5, suggesting short-course therapy may not be appropriate for patients with substantial predisposing lesions, such as burn wounds or extensive ulcers. We suggest that short-course therapy be reserved for subjects with some clinical improvement by the fifth day of therapy, and that, minimally, telephone contact for follow-up of patients with even uncomplicated cellulitis is prudent.

This study has several limitations. We intentionally excluded subjects with neutropenia or other conditions causing degrees of immunocompromise, and subjects with complicated skin wounds including abscesses and persistent ulcers. Although we would not advocate

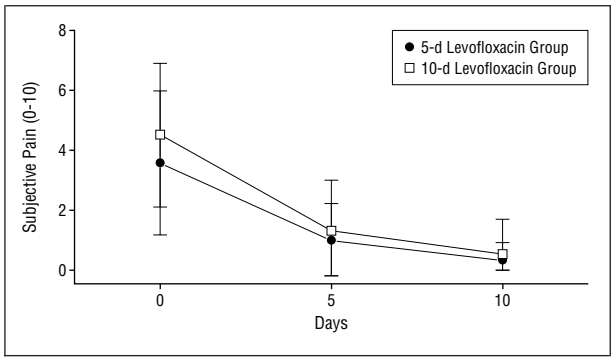

Figure 3. Serial subjective pain scores for cellulitis with 5 vs 10 days of therapy. Subjective pain was evaluated by the subjects using a 0-10 Likert scale. Error bars indicate SD.

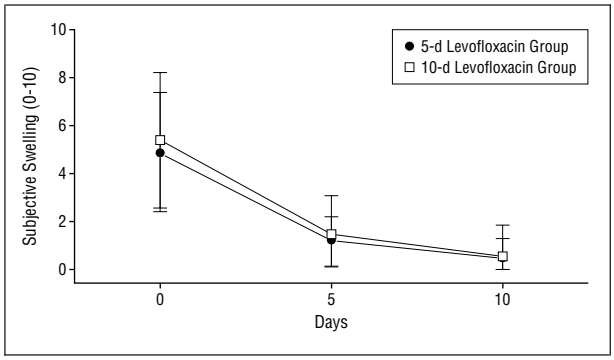

Figure 4. Serial subjective swelling scores for cellulitis with 5 vs 10 days of therapy. Subjective swelling was evaluated by the subjects using a 0-10 Likert scale. Error bars indicate SD.

short-course therapy for these populations, it is unknown how effective a short antibiotic course would be. We did not randomize our subjects to 5 vs 10 days of therapy at the time of initial clinic presentation because we considered that adherence with return visits would be worse if a "final" course of therapy was given at the outset. These data therefore do not imply equivalence between 5- and 10- day courses if these courses are given without thought to follow-up to ensure response. Finally, our results apply only to levofloxacin, and they should be confirmed with other medications.

In an era in which evidence-based medicine is increasingly emphasized, systematic study of the duration of therapy for various infectious syndromes is desirable. This study is the first to compare different durations of therapy with the same antibiotic for cellulitis. In the usual uncomplicated cellulitis that responds to initial treatment, a short course (5 days) of levofloxacin provides effective therapy.

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The opinions or assertions contained herein are those of the authors and are not to be construed as official policy or as reflecting the views of the Department of the Army or the Department of Defense.

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