# Rapid Resolution of Cellulitis in Patients Managed With Combination Antibiotic and Anti-inflammatory Therapy

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*There is some evidence to suggest that host inflammatory response has some effect on the clinical manifestations of cellulitis. The objective of this pilot study was to investigate whether the addition of oral nonsteroidal anti-inflammatory (NSAI) therapy to antibiotic treatment hastens resolution of cellulitis-related inflammation. Patients presenting in the emergency department with signs and symptoms of class II cellulitis were assigned to receive treatment with either antibiotic therapy alone (intravenous, supplemented with oral cephalexin or an equivalent) for 10 days (n=33) or antibiotic therapy for 10 days plus an oral anti-inflammatory (ibuprofen 400 mg every 6 hours) for 5 days (n=31). Patients were discharged as soon as possible to complete their therapy on an outpatient basis. The addition of an oral anti-inflammatory agent significantly (P<.05) shortened the time to regression of inflammation and complete resolution of cellulitis. Twenty-four of 29 evaluable patients (82.8%) who received supplemental anti-inflammatory treatment showed regression of inflammation within 1 to 2 days compared with only 3 of 33 patients (9.1%) treated without an anti-inflammatory in the same time frame. All patients receiving adjunctive anti-inflammatory treatment experienced complete resolution of cellulitis in 4 to 5 days or less, while 24.2% (8/33) of patients treated with antibiotic alone required 6 to 7 days, and 6.1% (2/33) required 7 days or more (P<.05). This small preliminary study provides some promising data, suggesting that the supplemental use of anti-inflammatory therapy may hasten the time to regression of inflammation and complete resolution of cellulitis.*

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Cellulitis is an acute inflammatory skin disorder, the symptoms of which include localized pain and tenderness, induration, erythema, swelling, and heat.[1,2] Some patients may display lymphangitis, regional adenopathy, or constitutional symptoms such as malaise.[3] The routine care of cellulitis invariably involves the administration of antibiotics, yet specific bacterial etiology is often difficult to pinpoint. Needle aspiration yields for causative organisms range anywhere from 4% to 42%.[4] When pathogenic bacteria are isolated, they are generally found in relatively low concentrations.[5] The low bacterial recovery rate also raises the suspicion that cellulitis-related signs and symptoms may be precipitated by secondary factors such as toxins or host inflammatory response.[6]

It has been suggested that cutaneous hypersensitivity reactions to streptococcal antigens may be causative in generating the signs and symptoms associated with cellulitis.[1] A small number of residual bacteria and bacterial fragments might precipitate

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local warmth and erythema, which are further amplified by lymphokines secreted in response to antigenic stimulation. From this supposition, we hypothesized that the use of nonsteroidal anti-inflammatory (NSAI) agents may be a logical approach in the treatment of cellulitis.

To date, little prospective research of anti-inflammatory therapy in the management of cellulitis has been undertaken. In fact, there has been some controversy regarding the safety of such a strategy, particularly as to whether anti-inflammatory agents can precipitate the onset of necrotizing fasciitis.[7,8] In one randomized double-blind study, Bergkvist and Sjöbeck[9] compared the use of antibiotics in combination with either prednisolone (titrated dosing schedule ranging from 5–30 mg/d over 8 days) or placebo in 112 patients with erysipelas. The authors reported significantly shorter healing time ($P<.01$), shorter hospital stay, and fewer days of intravenous antibiotic therapy in the prednisolone group compared with the placebo group. The addition of prednisolone was not associated with either an increased incidence of side effects or a relapse of disease after one year of follow-up.[10]

**Eron/Dall Classification System for Cellulitis**

| Class | Criteria |
|---|---|
| I | Healthy patients with cellulitis <15 cm in diameter, with or without fever |
| II | Healthy patients or patients with peripheral vascular disease, diabetes, or obesity with cellulitis >15 cm, ± fever; patients that have failed on oral antibiotics |
| III | Patients with fever and mental status changes; physical findings of gangrene, crepitus, or open draining wounds |
| IV | Patients with systemic complications of severe infection, which include hypotension, renal failure, acute respiratory distress syndrome, and more |

No studies have been done to investigate the use of NSAI agents as adjuvant therapy with antibiotics to manage cellulitis. The purpose of this analysis was to compare the outcomes, particularly the time to regression of inflammation, in patients with cellulitis treated with antibiotics with or without the adjunctive administration of oral NSAI therapy.

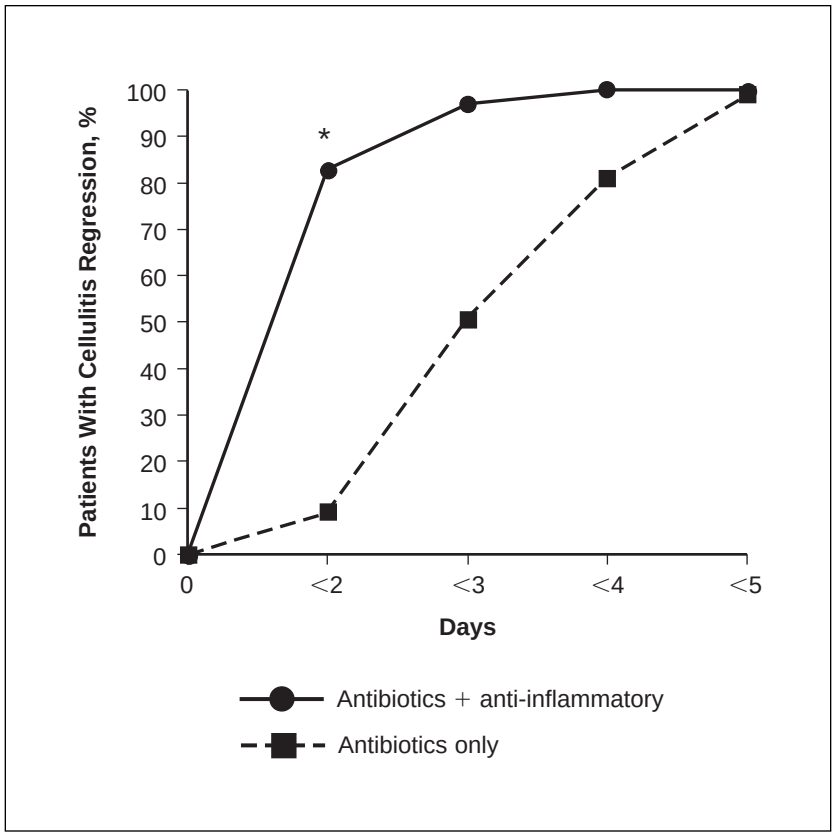
## Methods

This was a prospective study conducted by the Midwest Hospital Specialists group practice, a private group of 22 internal medicine, in-hospital physicians in metropolitan Kansas City, Missouri.

*Study Population*—The study population was gathered from patients presenting to the emergency department with signs and symptoms of cellulitis. Established prognostic criteria for cellulitis developed by Eron and Passos[11] were used to identify patients having disease characteristics appropriate for home-based treatment (Table). Patients with cellulitis of the upper or lower extremity who met class II criteria were eligible for participation. Patients who might have been immunocompromised were excluded from the study because of the greater likelihood of a higher bacterial inoculum.[12] Initial patient workups included blood cultures, complete blood cell count, and blood chemistry analysis, as well as cultures of any draining wounds. Patients with a baseline serum creatinine level of greater than 1.5 mg/dL also were excluded from the study.

*Patient Management and Assessment*—Patients were alternately assigned to receive treatment with antibiotic therapy alone or antibiotic therapy plus an oral anti-inflammatory (ibuprofen 400 mg every 6 hours) for 5 days. Ceftriaxone 1 g every 24 hours was given empirically to provide coverage against *Staphylococcus* and *Streptococcus* for at least 48 hours. An oral antibiotic (cephalexin 500 mg 4 times daily or an equivalent) also was initiated for a total treatment interval of 10 days.

The leading edge of the cellulitis was outlined using a permanent marker on admission to the study. The extent of the cellulitis was measured daily to determine regression from the original marking or progression outside of the marked area. Regression was defined as a decrease in the objectively measured total extent of cellulitis. After patients were discharged, volunteer medical students continued to perform margin measurements, beginning 24 hours after discharge. Medical students were blinded to patient treatment. Patients were discharged from the program when they had been afebrile for 24 hours and when the cellulitis had shown evidence of regression by direct measurement. Patients were contacted 72 hours after discharge from the program to ensure that the




Number of days required to first observe objective evidence of regression of cellulitis-related inflammation in patients receiving an antibiotic plus a nonsteroidal anti-inflammatory vs patients receiving an antibiotic alone. Asterisk indicates $P<.05$.

cellulitis had completely resolved. Resolution was defined as no further evidence of cellulitis.

The primary end point in this analysis was the time elapsed until regression of inflammation was noted. Complete resolution of cellulitis was a secondary, and more subjective, end point.

*Statistical Analysis*—Statistical analyses were conducted using SAS® statistical software, version 6.12. The comparative analyses were based on a 2-sample *t* test. The $\chi^2$ test was used to evaluate equality of distribution.

## Results

*Patients*—A total of 64 patients with cellulitis were enrolled between November 2001 and April 2002. All patients received antibiotic therapy, and 31 of them (48.4%) received anti-inflammatory treatment. The 2 treatment groups were similar as to demographic and clinical characteristics. Most patients were male (70%), with the most common site of infection being a lower extremity (91%). Most patients (n=58, 90.6%) were managed entirely as outpatients, while 6 patients (9.4%), 3 from each treatment group, were hospitalized briefly (for a cumulative total of 8 inpatient bed days). Two patients in the anti-inflammatory group were excluded from the efficacy analysis. One patient was excluded because of a diagnosis of gout. There was one failure that resulted in readmission in a patient found to have methicillin-resistant *Staphylococcus aureus*.

*Regression of Cellulitis*—The addition of an oral NSAI agent significantly ($P<.05$) shortened the time to regression of cellulitis (defined as any measurable decrease in the total extent of cellulitis). The Figure illustrates the number of treatment days required to achieve regression of cellulitis in both study groups. As a group, patients receiving anti-inflammatory therapy in addition to antibiotics showed a trend toward faster regression compared with patients receiving antibiotic therapy alone. Twenty-four of the 29 evaluable patients (82.8%) who received supplemental anti-inflammatory treatment showed regression of inflammation within 1 to 2 days compared with only 3 of 33 patients (9.1%) treated without an anti-inflammatory. In all patients treated with an anti-inflammatory, regression of cellulitis was observed in 4 days or less. Six of 33 patients (18.2%) treated without an anti-inflammatory required 4 to 5 days of therapy before regression was observed. No patient in either group required more than 5 days of therapy to show regression of cellulitis.

*Resolution of Cellulitis*—Complete resolution of cellulitis was attained within 2 days of therapy in 10.3% (3/29) of patients receiving both an antibiotic and an anti-inflammatory compared with 3% (1/33) of patients receiving antibiotic therapy alone during this same time frame. In the group receiving adjunctive anti-inflammatory treatment, 100% experienced complete resolution of cellulitis within a 5-day period, while 24.2% (8/33) of patients treated with antibiotics alone required 6 to 7 days, and 6.1% (2/33) of patients required 7 days or more. The difference between treatment groups in time to resolution was statistically significant ($P<.05$).

## Comment

The use of anti-inflammatory agents in the management of cellulitis is still considered experimental. The results of this pilot study support the hypothesis that the use of NSAI agents can hasten the time to regression of cellulitis without negative sequelae.

Although the study was generally conducted in a nonblinded fashion, observers who documented regression were blinded to treatment. Regression was realized when the total extent of cellulitis was less than at study entry. This end point was the primary focus because it allowed for objective assessment. Data regarding complete resolution of cellulitis were clearly more subjective and relied on patient interpretation.

Some authors have cautioned against the use of anti-inflammatory agents in patients with cellulitis, citing concerns about promoting bacterial overgrowth and possibly posing a risk for precipitating necrotizing fasciitis.[8,13,14] Smith and Berk[8] described the appearance of necrotizing fasciitis in a patient with granulocytopenia after excessive intake of an NSAI drug. Other published case reports have suggested a theoretical association between anti-inflammatory use and necrotizing cellulitis,[13,14] though a causal relationship has not been established.[15] Although our study was not large enough to rule out such a risk, it is reassuring that there were no cutaneous adverse events noted in any of our patients.

## Conclusion

This pilot study, while admittedly small and preliminary, nonetheless provides some promising data that warrant additional investigation. Further analysis of this issue will be facilitated by larger study samples and possibly longer follow-up.

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