JAMA | Original Investigation

Effect of Cephalexin Plus Trimethoprim-Sulfamethoxazole vs Cephalexin Alone on Clinical Cure of Uncomplicated Cellulitis
A Randomized Clinical Trial

Gregory J. Moran, MD; Anusha Krishnadasan, PhD; William R. Mower, MD, PhD; Fredrick M. Abrahamian, DO; Frank LoVecchio, DO; Mark T. Steele, MD; Richard E. Rothman, MD, PhD; David J. Karras, MD; Rebecca Hoagland, MS; Stephanie Pettibone, BS; David A. Talan, MD

IMPORTANCE Emergency department visits for skin infections in the United States have increased with the emergence of methicillin-resistant *Staphylococcus aureus* (MRSA). For cellulitis without purulent drainage, β-hemolytic streptococci are presumed to be the predominant pathogens. It is unknown if antimicrobial regimens possessing in vitro MRSA activity provide improved outcomes compared with treatments lacking MRSA activity.

OBJECTIVE To determine whether cephalexin plus trimethoprim-sulfamethoxazole yields a higher clinical cure rate of uncomplicated cellulitis than cephalexin alone.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, double-blind, randomized superiority trial in 5 US emergency departments among outpatients older than 12 years with cellulitis and no wound, purulent drainage, or abscess enrolled from April 2009 through June 2012. All participants had soft tissue ultrasound performed at the time of enrollment to exclude abscess. Final follow-up was August 2012.

INTERVENTIONS Cephalexin, 500 mg 4 times daily, plus trimethoprim-sulfamethoxazole, 320 mg/1600 mg twice daily, for 7 days (n = 248 participants) or cephalexin plus placebo for 7 days (n = 248 participants).

MAIN OUTCOMES AND MEASURES The primary outcome determined a priori in the per-protocol group was clinical cure, defined as absence of these clinical failure criteria at follow-up visits: fever; increase in erythema (>25%), swelling, or tenderness (days 3-4); no decrease in erythema, swelling, or tenderness (days 8-10); and more than minimal erythema, swelling, or tenderness (days 14-21). A clinically significant difference was defined as greater than 10%.

RESULTS Among 500 randomized participants, 496 (99%) were included in the modified intention-to-treat analysis and 411 (82.2%) in the per-protocol analysis (median age, 40 years [range, 15-78 years]; 58.4% male; 10.9% had diabetes). Median length and width of erythema were 13.0 cm and 10.0 cm. In the per-protocol population, clinical cure occurred in 182 (83.5%) of 218 participants in the cephalexin plus trimethoprim-sulfamethoxazole group vs 165 (85.5%) of 193 in the cephalexin group (difference, −2.0%; 95% CI, −9.7% to 5.7%; $P = .50$). In the modified intention-to-treat population, clinical cure occurred in 189 (76.2%) of 248 participants in the cephalexin plus trimethoprim–sulfamethoxazole group vs 171 (69.0%) of 248 in the cephalexin group (difference, 7.3%; 95% CI, −1.0% to 15.5%; $P = .07$). Between-group adverse event rates and secondary outcomes through 7 to 9 weeks, including overnight hospitalization, recurrent skin infections, and similar infection in household contacts, did not differ significantly.

CONCLUSIONS AND RELEVANCE Among patients with uncomplicated cellulitis, the use of cephalexin plus trimethoprim-sulfamethoxazole compared to cephalexin alone did not result in higher rates of clinical resolution of cellulitis in the per-protocol analysis. However, because imprecision around the findings in the modified intention-to-treat analysis included a clinically important difference favoring cephalexin plus trimethoprim-sulfamethoxazole, further research may be needed.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00729937

JAMA. 2017;317(20):2088-2096. doi:10.1001/jama.2017.5653

Editorial page 2070

JAMA Patient Page page 2142

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Gregory J. Moran, MD, Olive View–UCLA Medical Center, 14445 Olive View Dr, North Annex, Sylmar, CA 91342 (idnet@ucla.edu).

Emergency department visits for skin and soft tissue infections in the United States have increased with the emergence of community-associated methicillin-resistant *Staphylococcus aureus* (MRSA).[1,2] Cellulitis represents a unique type of skin and soft tissue infection for which it is usually not possible to determine the bacterial etiology because of a lack of a diagnostic specimen. Despite use of blood cultures and serology,[3,4] tissue specimens with conventional culture,[5] and molecular diagnostic testing,[6] the etiology of presumed infectious cellulitis has been difficult to determine definitively; however, β-hemolytic streptococci are presumed to be the predominant pathogens for cellulitis without purulent drainage. In a 2006 report, MRSA was the most common cause of purulent skin infections in the United States,[7] although the etiologic role and current prevalence of MRSA cellulitis are unclear.

The Infectious Diseases Society of America practice guidelines recommend that patients with cellulitis and without systemic signs of infection, penetrating trauma, evidence of MRSA elsewhere, or injection drug use should receive an antimicrobial agent active only against streptococci.[8] However, despite these guidelines, clinicians in the United States frequently prescribe regimens that include MRSA activity for cellulitis.[9]

To determine whether addition of a MRSA-active antimicrobial improves outcomes in patients with cellulitis, this randomized, double-blind trial compared cephalexin plus trimethoprim-sulfamethoxazole with cephalexin alone among emergency department patients presenting with cellulitis without a wound or abscess.

Key Points

Question Does cephalexin plus trimethoprim-sulfamethoxazole yield higher clinical cure rates than cephalexin alone for treatment of patients with uncomplicated cellulitis?

Findings In this randomized clinical trial of 500 patients with cellulitis, the clinical cure rate was not significantly different between those treated with cephalexin plus trimethoprim-sulfamethoxazole vs cephalexin plus placebo (83.5% vs 85.5% in the per-protocol analysis and 76.2% vs 69.0% in the modified intention-to-treat analysis). However, the 95% confidence interval for the difference in the intention-to-treat analysis was −1.0% to +15.5%, which included the minimal clinically important difference of 10%.

Meaning Addition of trimethoprim-sulfamethoxazole to cephalexin did not result in a statistically significant improvement in clinical cure for uncomplicated cellulitis. However, because the imprecision around the findings in the modified intention-to-treat analysis included a clinically important difference favoring the combination, further research may be needed.

Methods

Design

This study was a multicenter, double-blind, randomized trial to determine whether a 7-day course of oral cephalexin plus trimethoprim-sulfamethoxazole is superior to cephalexin alone for outpatient treatment of patients with acute cellulitis. The full protocol and statistical analysis plan are available in Supplement 1. Written informed consent was obtained from all participants. For minors, consent was obtained from a parent or guardian, with a written assent obtained from minors believed capable of understanding the assent form. Each institutional review board approved the study. Study sites are listed in the eAppendix in Supplement 2.

Study Population

From April 2009 through June 2012, patients older than 12 years with uncomplicated cellulitis, defined as presence of erythema without an abscess, purulent drainage, or wound and believed to be of infectious etiology, were enrolled. Enrollment was limited to participants with a lesion present for less than 1 week and measuring at least 2.0 cm in diameter who agreed to reevaluation and provided written informed consent. All participants had soft tissue ultrasound performed at the time of enrollment to exclude abscess. Patients with underlying skin conditions in the affected area, history of intravenous drug use with fever, concurrent infection at another site, or immunosuppression were excluded. Other exclusions are listed in the eAppendix in Supplement 2. Follow-up data were obtained through August 2012.

Interventions and Baseline Evaluation

Using double-blind web-based block randomization, participants were assigned in a 1:1 ratio to receive either a 7-day course of cephalexin (one 500-mg pill 4 times daily) plus placebo (4 pills twice daily) or cephalexin plus trimethoprim-sulfamethoxazole (4 single-strength pills, 80 mg/400 mg, twice daily). An independent contract research organization (Emmes Corporation) performed randomization; assignments were stratified by clinical site with a stratum size of 12 or 24. The randomized complete block design used randomly permuted block sizes within each stratum. Each block had a 1:1 allocation of cephalexin:cephalexin plus trimethoprim-sulfamethoxazole.

Medications were dispensed in blister packs indicating treatment day and time. Placebo and active medications were encapsulated in gel capsules with filler to give identical weight and appearance. Blinding could only be broken if a participant experienced treatment failure or an adverse event for which an acceptable alternative treatment could not be given and knowledge of the treatment assignment was needed for clinical care.

At the baseline evaluation, the study team recorded medical history and results of a physical examination and obtained detailed wound characteristics including location, presence of tenderness, and the dimensions of erythema and swelling/induration (eAppendix in Supplement 2). Information on race was collected at the time of enrollment based on participant self-report of racial identity using a form with fixed categories. Information on race was collected in this trial because assessment of skin erythema as an outcome measure could potentially be more difficult in participants with darker skin.

Table 1. Definitions of Study Populations and Outcomes Among Participants With Cellulitis Treated With Cephalexin Plus Trimethoprim-Sulfamethoxazole or Cephalexin Plus Placebo[a]

Study Population	Description	Outcome Definition
Per protocol	Participants who either took ≥75% of the total doses of study medication during the first 5 d and had an in-person test-of-clinical-cure visit or were determined to have had clinical failure before the test-of-cure visit and received ≥75% of the doses provided during the first 48 h of the treatment period	Participants were considered to have had a clinical cure if they did not meet the criteria for clinical failure at or before the test-of-clinical-cure visit. The criteria for clinical failure were as follows: fever (attributable to the infection), increase in maximal dimension of erythema by >25% from baseline, or worsening of swelling and tenderness by on-treatment visit (day 3 or 4); fever, no decrease in maximal dimension of erythema from baseline, or no decrease in swelling or tenderness by end-of-treatment visit (days 8-10); and fever or more than minimal erythema, swelling, or tenderness by the test-of-clinical-cure visit (days 14-21).
Modified intention to treat 1	Participants who took ≥1 dose of study medication and had an in-person or telephone assessment at the test-of-cure visit, as well as those who withdrew from the trial, were lost to follow-up before final classification, or had missing or unassigned outcomes	Participants were considered to have had a clinical cure if they did not meet the criteria for clinical failure (see examination criteria above) at or before the test-of-cure visit or based on no change in antibiotic therapy due to persistence or worsening of infection based on study clinician assessment, the participant's assessment, or assessment by an outside clinician. Participants who withdrew from the trial, were lost to follow-up before final classification, or had missing or unassigned outcomes were classified as having had clinical failure.
Modified intention to treat 2	Participants who took ≥1 dose of study medication and had an in-person follow-up evaluation at any time during the study	Participants were considered to have had a clinical cure if they did not meet the criteria for clinical failure (see examination criteria above) at or before the last recorded follow-up visit.
US Food and Drug Administration guidance early end point	Participants who took at ≥1 dose of study medication and completed the follow-up evaluation at 48 to 72 h after the start of treatment	A clinical cure was defined by a decrease or no increase in the length, width, and area of erythema from baseline, no worsening in swelling or induration, and absence of fever (ie, temperature <37.7°C [<99.9°F]) on the basis of a trial clinician's assessment.
Safety	Participants who underwent randomization, received study medication, and did not return 100% of the doses	Adverse events were coded according to the *Medical Dictionary for Regulatory Activities, Version 17.0*. Investigators categorized adverse events as related or not related to the study medication.

[a] These criteria were developed by investigator consensus.

Outcome Measures

Follow-up evaluations occurred in person (or if unable, by telephone) on days 3 to 4 (during therapy), days 8 to 10 (end of therapy), days 14 to 21 (test of clinical cure), and days 49 to 63 (extended follow-up) after enrollment. Treatment adherence was assessed by inspecting blister packs or, if not available, a memory aid record and participant interview.

Descriptions of study populations, including per protocol, modified intention to treat (mITT-1 and mITT-2), and US Food and Drug Administration (FDA) guidance[10] early end point, as well as definitions of clinical cure or failure are shown in **Table 1.** The primary outcome was clinical cure of cellulitis at the test-of-clinical-cure visit, 14 to 21 days after enrollment. A participant was classified as having a clinical cure if he/she did not meet failure criteria at or before the test-of-clinical-cure visit. The following criteria for failure were developed by investigator consensus prior to study initiation: fever (attributable to the infection), an increase in the maximal dimension of erythema by more than 25% from baseline, or worsening of swelling and tenderness by the visit during the treatment period (day 3 or 4); fever, no decrease in the maximal dimension of erythema from baseline or no decrease in swelling or tenderness by the visit at the end of the treatment period (days 8-10); and fever or more than minimal erythema, swelling, or tenderness by the test-of-clinical-cure visit (days 14-21). Participants meeting failure criteria had their assigned treatment stopped and another nonstudy antibiotic regimen started in addition to any surgical drainage deemed necessary. The mITT-1 group consisted of participants who took at least 1 dose of study medication and had an in-person or telephone assessment through the test-of-clinical-cure visit, as well as those who withdrew from the trial, were lost to follow-up before final classification, or had missing or unassigned outcomes. For the mITT-1 analysis, participants lost to follow-up were considered to have clinical failure; those who did not present for the test-of-clinical-cure visit but were reached by telephone were classified as having failure if they reported a change in antibiotic treatment for their cellulitis. Outcome assessment methods are described in the eAppendix and interrater agreement is described in eTable 1 in Supplement 2. Baseline cultures were not obtained but were obtained at follow-up visits if indicated clinically and material that could be cultured was present.

Secondary outcomes planned before study initiation included composite clinical cure (ie, resolution of all symptoms and signs of infection or improvement such that no additional antibiotics and/or surgical procedures were necessary), surgical drainage procedures, changes in erythema size, presence of swelling/induration and tenderness, invasive infections (ie, sepsis, bacteremia, endocarditis, osteomyelitis, septic arthritis, necrotizing fasciitis, or pneumonia), skin infections at the same or different site, hospitalizations, similar infections in household contacts, days missed from normal activities and work/school, and days of analgesic use.

Statistical Analysis

The study was designed as a superiority trial. The primary hypothesis was that the clinical cure rate with cephalexin plus trimethoprim-sulfamethoxazole would be greater than that with cephalexin alone. Assuming a 10-percentage-point effect size, type I error rate of 5%, power of 90%, using a 2-sided significance threshold, expected clinical cure rate

with cephalexin of 85%,[11] and 85% of enrolled patients with evaluable outcomes, we estimated that 500 participants would be adequate.

The primary outcome is reported as the difference in the proportion of clinical cures between patients treated with cephalexin plus trimethoprim-sulfamethoxazole and those treated with cephalexin alone in the per-protocol population. The per-protocol group was chosen as the primary outcome population to optimize the accuracy of evaluation of clinical response and best determine the effect of adding trimethoprim-sulfamethoxazole on clinical cure. A greater degree of nonadherence and lack of follow-up was anticipated in a population recruited from the emergency department. Analyses were also performed in the mITT-1, mITT-2, and FDA guidance early end-point populations.[10] Statistical superiority for the primary end point required the lower bound of the 95% confidence interval for the difference in clinical cure rates to be greater than 0, whereas the clinical superiority required the lower bound to be greater than 10%. The 10% threshold was based on consensus among investigators, who decided that in the interest of antibiotic stewardship, increasing antibiotic use for this common infection should require strong justification.

Levels of statistical significance were computed using a general linear mixed model with site as a random effect. To examine potential bias due to attrition or nonadherence, sensitivity analyses were performed by examining "best-" and "worst-case" clinical cure rates while varying the assumptions regarding outcomes among participants lost to attrition. In the "best-case" analysis, participants who were not included in the per-protocol population were assigned a clinical cure outcome if they were randomized to receive cephalexin plus trimethoprim-sulfamethoxazole and clinical failure if they were randomized to receive only cephalexin. In the "worst-case" analysis, participants who were not included in the per-protocol population were assigned a clinical failure outcome if they were randomized to receive cephalexin plus trimethoprim-sulfamethoxazole and clinical cure if they were randomized to receive only cephalexin.

Secondary outcomes were analyzed in the per-protocol population on an exploratory basis and between-group differences in outcome rates are reported with associated 95% confidence intervals. Post hoc subgroup analyses were conducted to examine clinical cure rates for participants with history of fever, diabetes, and involved skin area of 75 cm^2 or greater.

Testing was 2-sided with a significance threshold of .05. SAS version 9.3 was used for analyses. Interim analyses for safety and efficacy occurred at 50% and 75% of anticipated enrollment.

Results

Among 500 randomized participants, 248 (49.6%) received cephalexin plus trimethoprim-sulfamethoxazole, 248 received cephalexin alone, and 4 patients were excluded prior to treatment initiation; 218 (87.9%) participants who received cephalexin plus trimethoprim-sulfamethoxazole and 193 (77.8%) who received cephalexin plus placebo qualified for the per-protocol population, totaling 411 participants (82.2%) (**Figure 1**). Of 496 participants who took at least 1 dose, 257 (51.8%) were 100% adherent (137 taking cephalexin plus trimethoprim-sulfamethoxazole and 120 taking cephalexin alone) and 122 (24.6%) took 76% to 99% of doses (61 taking cephalexin plus trimethoprim-sulfamethoxazole and 61 taking cephalexin alone).

Participant characteristics in the per-protocol population are summarized in **Table 2**. Median age was 40 years (range, 15-78 years), 58.4% were male. Diabetes was present in 45 participants (10.9%). Sixteen participants (3.9%) had a history of MRSA infection and 81 (19.7%) had a history of fever. Median length and width of erythema at study entry were 13.0 cm (interquartile range [IQR], 8.0-21.0 cm; range, 2.0-63.0 cm) and 10.0 cm (IQR, 6.0-15.0 cm; range, 1.0-65.0 cm), respectively. Area of erythema was at least 75 cm^2 in 243 participants (59.1%).

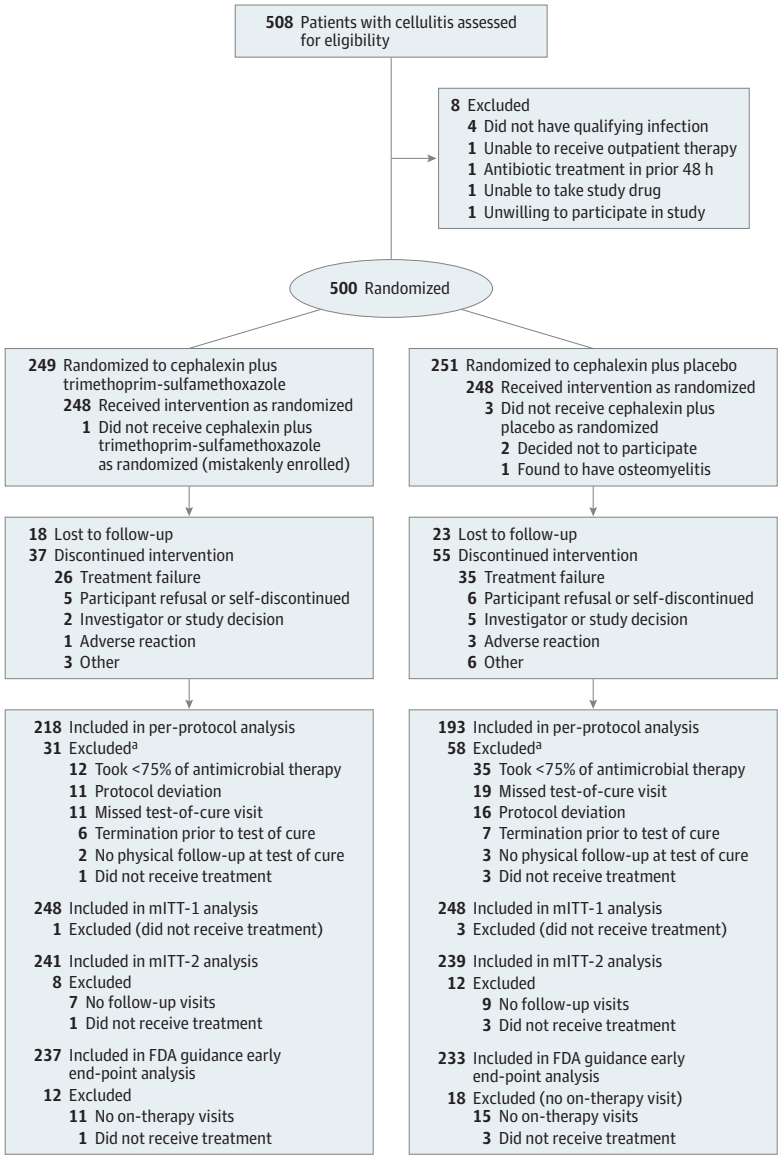
Clinical cure rates are summarized in **Figure 2**. Clinical cure occurred at 14 to 21 days after enrollment in 182 (83.5%) of 218 participants in the cephalexin plus trimethoprim-sulfamethoxazole group and 165 (85.5%) of 193 participants in the cephalexin group in the per-protocol population (difference, −2.0%; 95% CI, −9.7% to 5.7%; P = .50). In the mITT-1 population, clinical cure occurred in 189 (76.2%) of 248 participants in the cephalexin plus trimethoprim-sulfamethoxazole group and 171 (69.0%) of 248 participants in the cephalexin group (difference, 7.3%; 95% CI, −1.0% to 15.5%; P = .07). Clinical cure rates were not significantly different between the trimethoprim-sulfamethoxazole group and the cephalexin group in the mITT-2 population (83.8% and 82.8%, respectively) and the FDA guidance early end-point population (26.6% for both groups).

In the "best case" sensitivity analysis, treatment with cephalexin plus trimethoprim-sulfamethoxazole produced higher cure rates (85.5%) than treatment with cephalexin alone (65.7%; difference, 19.8%; 95% CI, 11.9%-27.7%). In the "worst case" analysis, treatment with cephalexin plus trimethoprim-sulfamethoxazole produced lower cure rates (73.1%) than treatment with cephalexin alone (88.8%; difference, −15.8%; 95% CI, −23.1% to −8.4%).

Of 36 participants who had treatment failure with cephalexin plus trimethoprim-sulfamethoxazole, 10 (27.8%) were found to have an abscess at the time of clinical failure and 9 (25.0%) developed opening of the skin and purulent drainage. Of 28 participants who had failure in the cephalexin group, 10 (35.7%) had an abscess at the time of clinical failure and 10 (35.7%) developed purulent drainage. Among 60 participants who had failure with clinical evidence of infection and had material available for culture at a follow-up visit, MRSA was isolated from 41 (68.3%), methicillin-susceptible *S aureus* from 8 (13.3%), and streptococcal species from 2 (3.3%). There was no between-group difference in the proportion with MRSA isolated during follow-up. No participant developed an invasive infection.

Post hoc subgroup analyses were conducted. Among participants with history of fever, clinical cure occurred in 38

Figure 1. Flow of Participants With Cellulitis Randomized to Treatment With Cephalexin Plus Trimethoprim-Sulfamethoxazole or Cephalexin Plus Placebo



See Table 1 for a description of the per-protocol, modified intention-to-treat (mITT-1 and mITT-2), and US Food and Drug Administration (FDA) guidance early end-point populations and outcome definitions. On-therapy, test-of-clinical-cure, and extended follow-up visits occurred on days 3 to 4, 14 to 21, and 49 to 63 after starting treatment, respectively. The primary outcome is clinical cure at the test-of-clinical-cure visit in the mITT-1 population.

[a] Some participants had more than 1 exclusion.

(82.6%) of 46 participants in the cephalexin plus trimethoprim-sulfamethoxazole group and in 28 (80.0%) of 35 participants in the cephalexin group (difference, 2.6%; 95% CI, −14.9% to 20.9%). Among participants with diabetes, clinical cure was observed in 21 (84.0%) of 25 participants in the cephalexin plus trimethoprim-sulfamethoxazole group and in 19 (95.0%) of 20 participants in the cephalexin group (difference, −11.0%; 95% CI, −19.5% to 10.9%). Among participants with an area of erythema of at least 75 cm^2, clinical cure occurred in 108 (82.4%) of 131 participants in the cephalexin plus trimethoprim-sulfamethoxazole group and 96 (85.7%) of 112 participants in the cephalexin group (difference, −3.3%; 95% CI, −12.5% to 6.8%).

Secondary outcomes were not significantly different between treatment groups, including drainage procedures, changes in erythema size and swelling/induration and tenderness, invasive infections, new skin infections at same or different site, overnight hospitalizations, similar infections in household contacts, days missed of normal activities and work/school, and analgesic use (eTable 2 in Supplement 2).

Adverse events are described in eTables 3 and 4 in Supplement 2. Between-group overall adverse event rates were not significantly different, and approximately 90% were graded as mild. The most common events were gastrointestinal, which occurred in 46.0% of the cephalexin plus trimethoprim-sulfamethoxazole group and in 38.7% of the cephalexin group (difference, 7.3%; 95% CI, −1.8% to 16.2%). One case of *Clostridium difficile* infection, attributed to clindamycin given after treatment failure, occurred in the

Table 2. Baseline Characteristics of Participants With Cellulitis Treated With Cephalexin Plus Trimethoprim-Sulfamethoxazole or Cephalexin Plus Placebo in the Per-Protocol Population[a]

Characteristics	Cephalexin Plus Trimethoprim-Sulfamethoxazole (n = 218)	Cephalexin Plus Placebo (n = 193)
Age, median (IQR) [range], y[b]	39 (29-49) [15-74]	41 (28-49) [15-78]
Male	137 (62.8)	103 (53.4)
Race		
White	123 (56.4)	111 (57.5)
Black	75 (34.4)	68 (35.2)
Asian	2 (0.9)	2 (1.0)
Hawaiian/Pacific Islander	0	0
American Indian/Alaskan Native	2 (0.9)	0
Multiracial	7 (3.2)	8 (4.1)
Other/unknown	9 (4.1)	4 (2.1)
Hispanic ethnicity	75 (34.4)	60 (31.1)
Symptom duration, median (IQR), d	3.0 (2.0-4.0)	3.0 (2.0-4.0)
History of fever in the week prior to enrollment	46 (21.1)	35 (18.1)
Comorbidities		
Diabetes	25 (11.5)	20 (10.4)
History of methicillin-resistant *Staphylococcus aureus* infection	9 (4.1)	7 (3.6)
Eczema or other chronic skin condition	7 (3.2)	11 (5.7)
Chronic peripheral edema	6 (2.8)	5 (2.6)
History of antibiotic treatment for current skin and soft tissue infection	0	2 (1.0)
Close household contact with similar infection[c]	10 (4.6)	12 (6.2)
Cellulitis location		
Head or neck	19 (8.7)	9 (4.7)
Trunk, abdomen, or back	17 (7.8)	19 (9.8)
Groin or buttocks	7 (3.2)	8 (4.1)
Upper extremity	52 (23.9)	50 (25.9)
Lower extremity	123 (56.4)	107 (55.4)
Erythema dimension, median (IQR) [range], cm		
Length[d]	13.0 (8.0-22.0) [3.0-59.0]	12.5 (8.2-18.0) [2.0-63.0]
Width	9.6 (6.0-16.0) [1.0-50.0]	10.0 (6.0-14.5) [2.0-65.0]
Area[e]	102.1 (41.2-274.9) [2.4-1946.2]	99.4 (37.7-188.5) [3.1-3216.2]
Area of erythema >75 cm^2[e]	131 (60.1)	112 (58.0)
Dimensions of swelling/induration, median (IQR) [range], cm		
Length[d]	8.0 (4.5-15.0) [1.0-55.0]	8.0 (4.5-14.0) [0.5-51.0]
Width	6.0 (4.0-12.0) [1.0-50.0]	6.0 (3.5-10.0) [0.5-47.0]
Area[e]	42.4 (14.1-150.8) [1.2-1693.3]	42.4 (12.6-117.4) [0.2-1762.4]
Temperature >38°C (>100.4°F) at baseline	3 (1.4)	2 (1.0)

Abbreviation: IQR, interquartile range.

[a] Data are expressed as No. (%) of participants unless otherwise indicated.

[b] Three participants (0.7%) were aged 13 to 17 years.

[c] Close household contact with someone with similar skin infection in last month.

[d] Length was defined as the maximal dimension.

[e] Areas of erythema and induration/swelling were calculated using formula for an ellipse (1/4 × π × length × width).

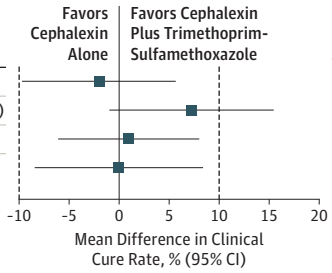
cephalexin plus trimethoprim-sulfamethoxazole group. One treatment-associated serious adverse event occurred in the cephalexin plus trimethoprim-sulfamethoxazole group, an acute-on-chronic kidney injury that resolved. Between-group rates of treatment discontinuation due to treatment-related adverse events were not significantly different (0.4% and 1.2%, respectively).

Discussion

In this randomized trial involving 500 mostly adult participants, a regimen with activity against MRSA, cephalexin plus trimethoprim-sulfamethoxazole, was not superior to a regimen lacking MRSA activity, cephalexin (plus placebo).

Figure 2. Clinical Cure Rates Among Participants With Cellulitis Treated With Cephalexin Plus Trimethoprim-Sulfamethoxazole or Cephalexin Plus Placebo in the Modified Intention-to-Treat, Per-Protocol, and FDA Guidance Early End-Point Populations

Study Population	Clinical Cure, No./Total (%)		Mean Difference, % (95% CI)	*P* Value
	Cephalexin Plus Trimethoprim-Sulfamethoxazole	Cephalexin Plus Placebo		
Per protocol	182/218 (83.5)	165/193 (85.5)	-2.0 (-9.7 to 5.7)	.50
mITT-1	189/248 (76.2)	171/248 (69.0)	7.3 (-1.0 to 15.5)	.07
mITT-2	202/241 (83.8)	198/239 (82.8)	1.0 (-6.1 to 8.1)	.85
FDA guidance early end point	63/237 (26.6)	62/233 (26.6)	0.0 (-8.4 to 8.4)	.94



See Table 1 for a description of the per-protocol, modified intention-to-treat (mITT-1 and mITT-2), and US Food and Drug Administration (FDA) guidance early end-point (response rate reported) populations and outcome definitions. Dashed lines indicate the 10% predetermined threshold of clinically significant difference.

However, the results from the mITT-1 analysis did not exclude the possibility of clinical superiority of cephalexin plus trimethoprim-sulfamethoxazole; therefore, more research may be necessary to more definitively answer this question.

Although the upper bound of the 95% confidence interval of the between-group difference in clinical cure rates favoring cephalexin plus trimethoprim-sulfamethoxazole was greater than the 10-percentage-point threshold deemed clinically significant in the mITT-1 population, the bounds of this confidence interval were within this threshold in the per-protocol and mITT-2 populations. Per-protocol criteria required a physical follow-up at 14 to 21 days after enrollment and adherence to at least 75% of the doses provided. Per-protocol analysis optimizes the accuracy of evaluating clinical response and best determines the effect of adding antimicrobial activity against MRSA on clinical cure for participants who adhere to treatment. However, per-protocol analysis may not reflect the effectiveness of a course of therapy in the clinical setting, where effects such as adherence and drug intolerance play a greater role.[12]

Because the tolerability of these antibiotics is well known from decades of experience, and adherence was lower in the cephalexin plus placebo group, it is less likely that drug intolerance led to significant postrandomization bias. Intention-to-treat analysis avoids postrandomization bias but must assign outcomes when these are unknown because of lack of follow-up. In this study, the default approach was to assign the outcome as failure if a participant could not be evaluated for their 14- to 21-day postenrollment status. Another ITT approach is to assign outcomes based on participant status at last reevaluation visit, excluding the remainder without any follow-up, which was the mITT-2 population in this study. The mITT-2 population accounted for more than 96% of the mITT-1 population, and between-group differences in this population were within the 10-percentage-point threshold. The best-case and worst-case analyses gave disparate results showing benefit for each treatment group.

Few studies have evaluated oral antibiotic regimens to treat cellulitis since the emergence of community-associated MRSA. In a randomized trial of 153 adults with cellulitis without abscess, Pallin et al[11] reported a clinical cure rate of 85% with cephalexin plus trimethoprim-sulfamethoxazole and 82% with cephalexin (difference, 2.7%). The relatively small sample size in this study allowed for a between-group difference of 15%, there was no minimum lesion size, lesions could have up to 1 mL of purulent drainage, and patients with common comorbidities were excluded. In a retrospective study in children with skin infections that were not cultured or drained, Elliott et al[13] reported that clindamycin and β-lactams were equally effective and trimethoprim-sulfamethoxazole was associated with a slightly higher failure rate. In a prospective study by Jeng et al[4] of nonculturable cellulitis among hospitalized adults, overall clinical response rate to β-lactam therapy was 96%. The outcomes in that study were not specifically defined, investigators grading outcomes were not blinded to treatment, and there was no comparison group.

In contrast, the current trial focused on patients with cellulitis without abscess or wound and no diagnostic specimen available for culture. This trial was powered to detect a difference in clinical cure rates of 10%. To better reflect typical emergency department outpatient cellulitis management, patients with most stable comorbidities such as diabetes were not excluded; however, those with conditions that could confound evaluation of response or with anticipated bacterial infection not susceptible to study regimens were excluded. Specific failure criteria were defined based on fever and changes in the measured area of infection. These criteria have not been validated, but there are no validated methods for skin and soft tissue infection evaluation, and the criteria in this trial are easy for clinicians to follow, with demonstrated good interobserver agreement on clinical cure or failure.

Methicillin-resistant *S aureus* was cultured in 41 patients who had treatment failure (10% of the per-protocol population), suggesting that MRSA plays a role in some cases of cellulitis. These cases likely represent small abscesses missed on ultrasound screening or were abscesses in evolution. Clinically, cases diagnosed as cellulitis are occasionally observed in which there is notable induration and sometimes a suggestion of fluctuance with a central pustule, which subsequently progresses to an abscess. Drainage is key to abscess resolution, and MRSA is the predominant cause of these infections. Therefore, because of this phenomenon, a small proportion of cellulitis cases are expected to have antibiotic treatment failure, including with MRSA-active drugs. In this trial,

the proportion was probably minimized because participants were screened with ultrasound to identify occult fluid collections consistent with an abscess and excluded. Empirical treatment with MRSA activity did not achieve superior outcomes overall, and an equal proportion of MRSA was found among clinical failures in each treatment group.

This investigation has limitations. First, the Infectious Diseases Society of America skin infection guidelines recommend antibiotic regimens with activity against MRSA when cellulitis is accompanied by systemic signs of infection, penetrating trauma, evidence of MRSA elsewhere, or history of injection drug use.[8] Although enrollment of individuals with some of these conditions was allowed in the current study, clinicians may have been biased against their participation, thus leaving a selected population that was at relatively lower risk of treatment failure.

Second, even with 500 participants, the power of this trial is limited such that the possibility that regimens with activity against MRSA could improve outcomes in some subgroups cannot be excluded. Third, the most recent data were collected 5 years ago, and it is unknown whether the findings reflect the bacteriology or antimicrobial susceptibility of cellulitis among patients currently treated in emergency departments. However, in a prior study, MRSA prevalence and susceptibility to trimethoprim-sulfamethoxazole did not change over a 4-year interval (2004-2008) at these sites.[14] Fourth, to try to ensure accurate diagnosis of cellulitis without abscess, bedside ultrasound was used to exclude an occult fluid collection. Although most US emergency departments have bedside ultrasound available, this may not be available in some settings; these findings should be cautiously applied to patients in whom abscess is not identified based on physical examination alone.

Fifth, in the per-protocol population, nearly 3 times as many participants randomized to cephalexin plus placebo vs cephalexin plus trimethoprim-sulfamethoxazole were nonadherent, which may suggest insufficient blinding. The imbalance of the proportion evaluable per-protocol between the treatment groups was largely attributable to this difference in adherence. Even with this imbalance, significant outcome differences favoring the latter group were not observed. Another much larger trial comparing trimethoprim-sulfamethoxazole and placebo that used the same masking did not find this difference in adherence.[15] There is no reason to believe that treatment with 2 antibiotics would be better tolerated by patients than treatment with 1 antibiotic. Sixth, although based on reports of poorly described populations in the preantibiotic era, the rate of spontaneous resolution of cellulitis has been reported to be as high as 66%,[16] which could bias these results toward the null hypothesis. It has been suggested that many cases of cellulitis are misdiagnosed and are instead noninfectious conditions, such as stasis dermatitis.[17] It is possible that some participants did not truly have an infection, but these participants likely reflect those treated for cellulitis in typical practice.

Conclusions

Among patients with uncomplicated cellulitis, the use of cephalexin plus trimethoprim/sulfamethoxazole compared with cephalexin alone did not result in higher rates of clinical resolution of cellulitis in the per-protocol analysis. However, because the imprecision around the findings in the mITT analysis included a clinically important difference favoring cephalexin plus trimethoprim-sulfamethoxazole, further research may be needed.

ARTICLE INFORMATION

Accepted for Publication: April 18, 2017.

Author Affiliations: Department of Emergency Medicine, Olive View–UCLA Medical Center, David Geffen School of Medicine at UCLA, Los Angeles, California (Moran, Krishnadasan, Abrahamian, Talan); Division of Infectious Diseases, Department of Medicine, Olive View–UCLA Medical Center, David Geffen School of Medicine at UCLA, Los Angeles, California (Moran, Talan); Department of Emergency Medicine, Ronald Reagan Medical Center, David Geffen School of Medicine at UCLA, Los Angeles, California (Mower); Department of Emergency Medicine, Maricopa Medical Center, University of Arizona and Mayo Graduate School of Medicine, Phoenix (LoVecchio); Department of Emergency Medicine, Truman Medical Center, University of Missouri–Kansas City School of Medicine, Kansas City (Steele); Department of Emergency Medicine, Johns Hopkins Medical Center, Johns Hopkins School of Medicine, Baltimore, Maryland (Rothman); Department of Emergency Medicine, Lewis Katz School of Medicine at Temple University, Philadelphia, Pennsylvania (Karras); Cota Enterprises Inc, McLouth, Kansas (Hoagland); EMMES Corporation, Rockville, Maryland (Pettibone).

Author Contributions: Drs Moran and Krishnadasan had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Moran, Mower, Abrahamian, LoVecchio, Steele, Karras, Talan.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Moran, Krishnadasan, Talan.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Moran, Krishnadasan, Mower, Hoagland.
Obtained funding: Moran, Krishnadasan, Mower, Talan.
Administrative, technical, or material support: Moran, Krishnadasan, Mower, Abrahamian, LoVecchio, Steele, Rothman, Karras, Pettibone, Talan.
Study supervision: Moran, Krishnadasan, Abrahamian, LoVecchio, Steele, Rothman, Karras, Talan.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Moran reports receipt of a grant and consulting fees from Allergan and a grant from Cempra. Dr Mower reports receipt of a grant and consulting fees from Allergan. Dr Abrahamian reports receipt of speakers bureau/consultation fees from Merck, Allergan, the Medicines Company, Cempra, Summit Therapeutics, Tetraphase Pharmaceuticals, Paratek Pharmaceuticals, and Janssen Research and Development and research grants from the Centers for Disease Control and Prevention, Merck, and Cempra. Drs LoVecchio and Steele and Ms Hoagland report receipt of a grant and consulting fees from Allergan. Dr Talan reports receipt of consulting fees from Allergan, Cempra, GlaxoSmithKline, and Merck. No other disclosures were reported.

Funding/Support: This research was supported by grant 1U01 HHSN272200700032C to Drs Moran and Talan from the National Institute of Allergy and Infectious Diseases.

Role of the Funder/Sponsor: The National Institutes of Allergy and Infectious Diseases participated in the design and conduct of the study, management of the data, review of the manuscript, and decision to submit the manuscript for publication but did not have the ability to veto submission.

Additional Contributions: We thank Christine Chiou, MD, Maureen Mehigan, RN, BSN, Hyung Koo, RN, BSN, and Janie Russell, National Institutes of Allergy and Infectious Diseases, who provided general oversight during protocol development and study implementation; the DMID-CROMS Pharmacovigilance Group at the National Institutes of Allergy and Infectious Diseases, who provided regulatory oversight; Richard Pollard, MD, University of California, Davis, School of Medicine, John Powers, MD, Scientific Applications International Corporation, Sheldon Kaplan, MD, Baylor College of Medicine, and Scot Evans, PhD, Harvard University, who served on the data and safety monitoring board; Arthur C. Jeng, MD, and Glenn E. Mathisen, MD, Olive View-UCLA Medical Center, Shmuel Shoham, MD, and Geetika Sood, MD, Johns Hopkins University School of Medicine, Jeffrey L. Foti, MD, and Michael Levine, MD, Maricopa Medical Center, Byungse Suh, MD, PhD, and Lawrence I. Kaplan, Temple University School of Medicine, Laura Fitzmaurice, MD, and Gary Michael Gaddis, MD, PhD, Truman Medical Center/University of Missouri Kansas City, who served as independent safety monitors; Thad Zajdowicz, MD, Nancy Browning, PhD, and Ryan May, Emmes Corporation, who helped develop the protocol and statistical analysis plan, managed data, and conducted interim analyses; the staff at PPD and ICON Clinical Research, who conducted regulatory and data monitoring; Amy Stubbs, MD, Department of Emergency Medicine, Truman Medical Center, University of Missouri School of Medicine, a subinvestigator with Dr Steele; Kavitha Pathmarajah, MPH, Laura Weigand, PT, DPT, MA, Jesus Torres, MD, MPH, Gabina Martin, BSN, RN, Yvette Flores, BS, Maureen Fulgencio, BS, Britany Zeglin, BS, Stephen Peterson, BS, Mary Mulrow, RN, MA, MN, Shelley Fuentes, Laurie Kemble, BHS, CRC, Danielle Beckham, RN, MSN, BSN, Niccole Neal, RN, BSN, CRC, Kathleen Hatala, RN, and Carol Von Hofen, RN, the study coordinators who screened and enrolled study participants, collected data at all study visits, and entered and cleaned data collected at their sites; and the residents and staff at the participating emergency departments for screening potential patients and for assistance with wound assessments. No compensation was provided for these contributions beyond usual salary.

REFERENCES

1. Hersh AL, Chambers HF, Maselli JH, Gonzales R. National trends in ambulatory visits and antibiotic prescribing for skin and soft-tissue infections. *Arch Intern Med*. 2008;168(14):1585-1591.

2. Pallin DJ, Egan DJ, Pelletier AJ, Espinola JA, Hooper DC, Camargo CA Jr. Increased US emergency department visits for skin and soft tissue infections, and changes in antibiotic choices, during the emergence of community-associated methicillin-resistant *Staphylococcus aureus*. *Ann Emerg Med*. 2008;51(3):291-298.

3. Gunderson CG, Martinello RA. A systematic review of bacteremias in cellulitis and erysipelas. *J Infect*. 2012;64(2):148-155.

4. Jeng A, Beheshti M, Li J, Nathan R. The role of beta-hemolytic streptococci in causing diffuse, nonculturable cellulitis: a prospective investigation. *Medicine (Baltimore)*. 2010;89(4):217-226.

5. Chira S, Miller LG. *Staphylococcus aureus* is the most common identified cause of cellulitis: a systematic review. *Epidemiol Infect*. 2010;138(3):313-317.

6. Crisp JG, Takhar SS, Moran GJ, et al; Emergency ID Net Study Group. Inability of polymerase chain reaction, pyrosequencing, and culture of infected and uninfected site skin biopsy specimens to identify the cause of cellulitis. *Clin Infect Dis*. 2015;61(11):1679-1687.

7. Moran GJ, Krishnadasan A, Gorwitz RJ, et al; Emergency ID Net Study Group. Methicillin-resistant *S aureus* infections among patients in the emergency department. *N Engl J Med*. 2006;355(7):666-674.

8. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2014;59(2):147-159.

9. Pallin DJ, Camargo CA Jr, Schuur JD. Skin infections and antibiotic stewardship: analysis of emergency department prescribing practices, 2007-2010. *West J Emerg Med*. 2014;15(3):282-289.

10. US Food and Drug Administration. *Guidance for Industry: Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment*. October 2013. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071185.pdf. Accessed March 17, 2017.

11. Pallin DJ, Binder WD, Allen MB, et al. Clinical trial: comparative effectiveness of cephalexin plus trimethoprim-sulfamethoxazole vs cephalexin alone for treatment of uncomplicated cellulitis: a randomized controlled trial. *Clin Infect Dis*. 2013;56(12):1754-1762.

12. D'Agostino RB Sr, Massaro JM, Sullivan LM. Non-inferiority trials: design concepts and issues—the encounters of academic consultants in statistics. *Stat Med*. 2003;22(2):169-186.

13. Elliott DJ, Zaoutis TE, Troxel AB, Loh A, Keren R. Empiric antimicrobial therapy for pediatric skin and soft-tissue infections in the era of methicillin-resistant *Staphylococcus aureus*. *Pediatrics*. 2009;123(6):e959-e966.

14. Talan DA, Krishnadasan A, Gorwitz RJ, et al; Emergency ID Net Study Group. Comparison of *Staphylococcus aureus* from skin and soft-tissue infections in US emergency department patients, 2004 and 2008. *Clin Infect Dis*. 2011;53(2):144-149.

15. Talan DA, Mower WR, Krishnadasan A, et al. Trimethoprim-sulfamethoxazole vs placebo for uncomplicated skin abscess. *N Engl J Med*. 2016;374(9):823-832.

16. Spellberg B, Talbot GH, Boucher HW, et al; Antimicrobial Availability Task Force of the Infectious Diseases Society of America. Antimicrobial agents for complicated skin and skin-structure infections: justification of noninferiority margins in the absence of placebo-controlled trials. *Clin Infect Dis*. 2009;49(3):383-391.

17. Weng QY, Raff AB, Cohen JM, et al. Costs and consequences associated with misdiagnosed lower extremity cellulitis [published online November 2, 2016]. *JAMA Dermatol*. doi:10.1001/jamadermatol.2016.3816