

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

MARCH 19, 2015

VOL. 372 NO. 12

Clindamycin versus Trimethoprim–Sulfamethoxazole for Uncomplicated Skin Infections

Loren G. Miller, M.D., M.P.H., Robert S. Daum, M.D., C.M., C. Buddy Creech, M.D., M.P.H., David Young, M.D., Michele D. Downing, R.N., M.S.N., Samantha J. Eells, M.P.H., Stephanie Pettibone, B.S., Rebecca J. Hoagland, M.S., and Henry F. Chambers, M.D., for the DMID 07-0051 Team*

ABSTRACT

BACKGROUND

Skin and skin-structure infections are common in ambulatory settings. However, the efficacy of various antibiotic regimens in the era of community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) is unclear.

METHODS

We enrolled outpatients with uncomplicated skin infections who had cellulitis, abscesses larger than 5 cm in diameter (smaller for younger children), or both. Patients were enrolled at four study sites. All abscesses underwent incision and drainage. Patients were randomly assigned in a 1:1 ratio to receive either clindamycin or trimethoprim–sulfamethoxazole (TMP-SMX) for 10 days. Patients and investigators were unaware of the treatment assignments and microbiologic test results. The primary outcome was clinical cure 7 to 10 days after the end of treatment.

RESULTS

A total of 524 patients were enrolled (264 in the clindamycin group and 260 in the TMP-SMX group), including 155 children (29.6%). One hundred sixty patients (30.5%) had an abscess, 280 (53.4%) had cellulitis, and 82 (15.6%) had mixed infection, defined as at least one abscess lesion and one cellulitis lesion. *S. aureus* was isolated from the lesions of 217 patients (41.4%); the isolates in 167 (77.0%) of these patients were MRSA. The proportion of patients cured was similar in the two treatment groups in the intention-to-treat population (80.3% in the clindamycin group and 77.7% in the TMP-SMX group; difference, –2.6 percentage points; 95% confidence interval [CI], –10.2 to 4.9; $P=0.52$) and in the populations of patients who could be evaluated (466 patients; 89.5% in the clindamycin group and 88.2% in the TMP-SMX group; difference, –1.2 percentage points; 95% CI, –7.6 to 5.1; $P=0.77$). Cure rates did not differ significantly between the two treatments in the subgroups of children, adults, and patients with abscess versus cellulitis. The proportion of patients with adverse events was similar in the two groups.

CONCLUSIONS

We found no significant difference between clindamycin and TMP-SMX, with respect to either efficacy or side-effect profile, for the treatment of uncomplicated skin infections, including both cellulitis and abscesses. (Funded by the National Institute of Allergy and Infectious Diseases and the National Center for Advancing Translational Sciences, National Institutes of Health; ClinicalTrials.gov number, NCT00730028.)

From the Los Angeles Biomedical Research Institute (L.G.M., S.J.E.) and Division of Infectious Diseases, Harbor–UCLA (University of California, Los Angeles) Medical Center (L.G.M., S.J.E.), Torrance, David Geffen School of Medicine at UCLA, Los Angeles (L.G.M., S.J.E.), Division of Plastic and Reconstructive Surgery, University of California, San Francisco (UCSF) (D.Y.), and Division of Infectious Diseases, San Francisco General Hospital and UCSF (M.D.D., H.F.C.), San Francisco — all in California; Division of Pediatric Infectious Diseases, University of Chicago, Chicago (R.S.D.); Division of Pediatric Infectious Diseases, Vanderbilt University, Nashville (C.B.C.); the EMMES Corporation, Rockville, MD (S.P.); and Cota Enterprises, Meriden, KS (R.J.H.). Address reprint requests to Dr. Miller at the Division of Infectious Diseases, Harbor–UCLA Medical Center, 1000 W. Carson St., Box 466, Torrance, CA 90509, or at lgmiller@ucla.edu.

*A list of additional members of the Division of Microbiology and Infectious Diseases (DMID) 07-0051 Team is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2015;372:1093-103.

DOI: 10.1056/NEJMoa1403789

Copyright © 2015 Massachusetts Medical Society.

SKIN AND SKIN-STRUCTURE INFECTIONS (hereafter referred to as skin infections) are common conditions among patients seeking medical care in the United States,^{1,2} accounting for approximately 14.2 million outpatient visits in 2005¹ and more than 850,000 hospital admissions.³ Skin infections are associated with considerable complications, including bacteremia, the need for hospitalization and surgical procedures, and death.^{4,5}

Results of cultures of skin-infection lesions in the United States have shown that most of the infections are caused by methicillin-resistant *Staphylococcus aureus* (MRSA),^{6,7} but the efficacy of various antibiotic regimens in areas where community-associated MRSA is endemic has not been defined.^{8,9} Either clindamycin or trimethoprim-sulfamethoxazole (TMP-SMX) is recommended because of the low cost and activity against community-associated MRSA and methicillin-susceptible *S. aureus* (MSSA) strains of each of these drugs,^{2,10-12} yet there are few comparative data on the safety and efficacy of these antibiotic agents for the treatment of skin infections. To address this limitation, we performed a randomized clinical trial comparing clindamycin and TMP-SMX for the treatment of uncomplicated skin infections at four U.S. centers located in areas of community-associated MRSA endemicity.

METHODS

STUDY DESIGN AND POPULATION

We performed a multicenter, prospective, randomized, double-blind clinical trial of clindamycin versus TMP-SMX for the treatment of uncomplicated skin infections. Patients were eligible if they had two or more of the following signs or symptoms for 24 or more hours: erythema, swelling or induration, local warmth, purulent drainage, and tenderness to pain or palpation. Patients were categorized as having cellulitis (defined as inflammation of the skin and associated skin structures without signs of a drainable fluid collection), abscess (defined as a circumscribed, drainable collection of pus), or both (if lesions of both cellulitis and abscess were present). Exclusion criteria were superficial skin infections (e.g., impetigo), skin infection at a body site that requires specialized management (e.g., perirectal, genital, or hand infection), a human or animal bite at the infection site, high fever (oral temperature, $>38.5^{\circ}\text{C}$

[$>38.0^{\circ}\text{C}$ in children 6 to 11 months of age]), receipt of immunosuppressive medications or the presence of an immunocompromising condition such as diabetes or chronic renal failure, morbid obesity (body-mass index [the weight in kilograms divided by the square of the height in meters], >40), surgical-site or prosthetic-device infection, and receipt of antibacterial therapy with antistaphylococcal activity in the previous 14 days. Patients were ineligible if they lived in a long-term care facility, had cancer or an inflammatory disorder that required treatment in the previous 12 months, or had major surgery in the previous 12 months. All the inclusion and exclusion criteria are listed in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org. The full protocol and statistical-analysis plan are also available at NEJM.org.

STUDY POPULATION, STRATIFICATION, AND RANDOMIZATION

From May 2009 through August 2011, patients were recruited at four locations (University of Chicago Medical Center, Chicago; San Francisco General Hospital, San Francisco; Harbor-UCLA [University of California, Los Angeles] Medical Center, Torrance, CA; and Vanderbilt University Medical Center, Nashville) from urgent care clinics, emergency departments, and affiliated clinics. All the patients or their parents or guardians provided written informed consent, and assent was obtained when age-appropriate. The protocol was approved by the institutional review board at each institution.

Patients were stratified into one of two groups on the basis of the characteristics of their infection before randomization: a group that included patients with a larger abscess or cellulitis (larger-abscess-cellulitis group) or a group that included patients with a smaller abscess (limited-abscess group). The protocol and data-analysis plan prespecified that the limited-abscess group and the larger-abscess-cellulitis group be analyzed separately because their treatment assignments differed, in that the limited-abscess stratum included a placebo group. Patients who had a single abscess with a greatest diameter up to 5.0 cm (≤ 3.0 cm in patients 6 to 11 months of age and ≤ 4.0 cm in patients 1 to 8 years of age) were stratified into the limited-abscess group. All other patients, including those with an abscess greater than 5.0 cm in diameter (and proportionally smaller in young

children), patients with two or more sites of skin infection, and patients with cellulitis without abscess (including erysipelas), were stratified into the larger-abscess–cellulitis group. The size of the abscess cavity was measured manually in three dimensions (width, length, and depth) and recorded on a standardized form. All abscesses were treated by means of incision and drainage. In this article, we describe the results for the larger-abscess–cellulitis group only.

STUDY MEDICATION

After abscesses were drained (if present) and the size of the abscesses was determined, patients were randomly assigned in a 1:1 ratio to receive clindamycin or TMP-SMX. Variable-block randomization, with assignments made independently at each site, was performed by an independent contract research organization (EMMES) that developed the randomization code.

Clindamycin was given as two 150-mg tablets three times daily. TMP-SMX was given at doses of 160 mg of trimethoprim and 800 mg of sulfamethoxazole administered as two single-strength tablets twice daily. Patients randomly assigned to receive TMP-SMX were given two placebo pills for the midday dose. Pediatric doses were adjusted according to the body weight of the patient (Table S2 in the Supplementary Appendix); liquid suspensions were available for pediatric dosing. Pills were overencapsulated to prevent identification by study staff and patients, and the taste of the clindamycin liquid preparations was masked with the use of flavoring both to prevent identification and to improve adherence. Patients were unaware of the treatment assignments, as were the study staff members, with the exception of the research pharmacists, who determined the correct dosing. The study medications were purchased by the study sponsor, the National Institute of Allergy and Infectious Diseases of the National Institutes of Health.

MICROBIOLOGIC STUDIES AND DEMOGRAPHIC DATA

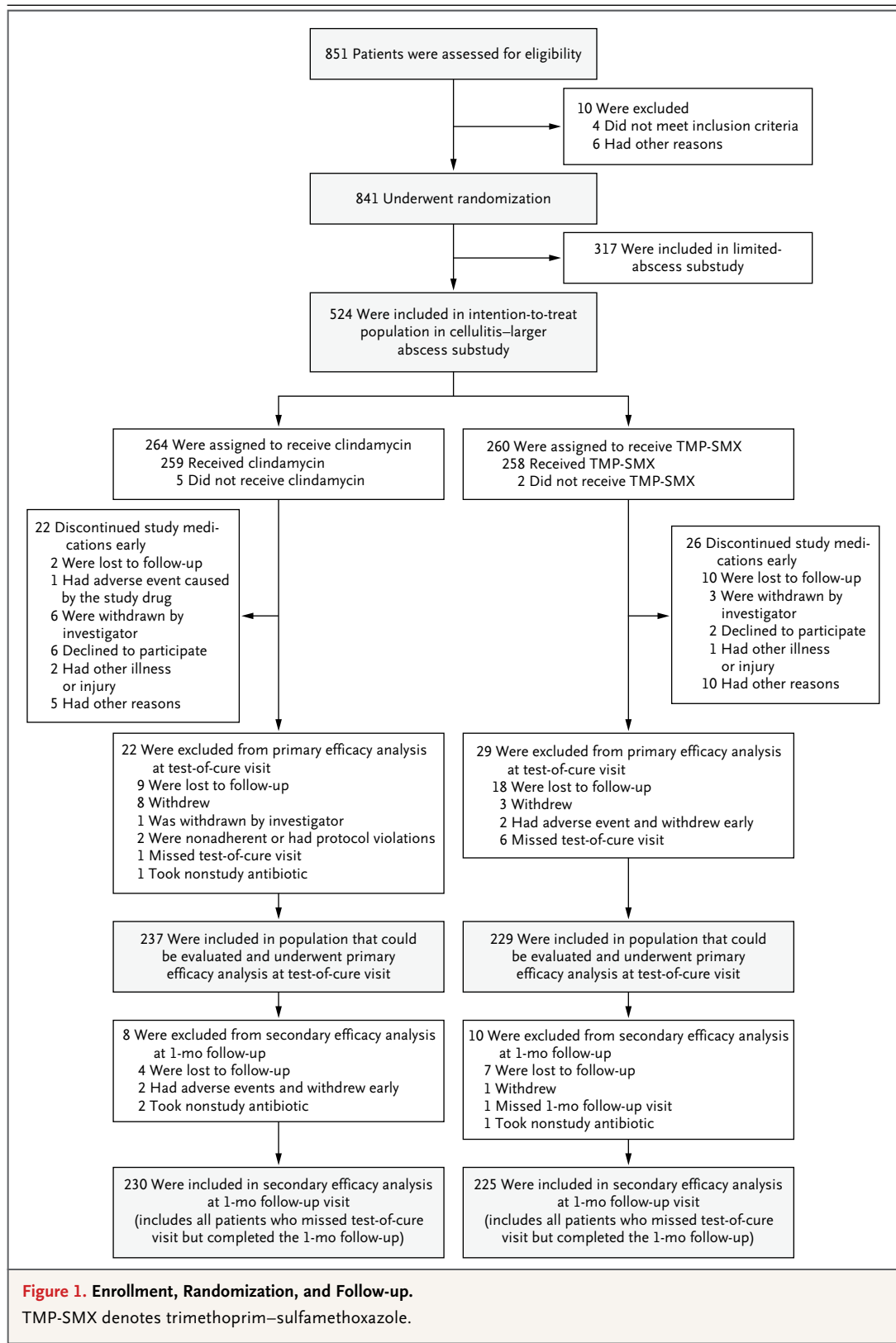
To prevent investigator bias if treatment failures occurred, investigators were unaware of the microbiologic results, although the results could be obtained by an independent safety monitor on request. Swab cultures were obtained if there was a skin break, exudate, blister fluid, or other material that could be cultured. Nonsuppurative lesions were not cultured. Cultures, species identification

of isolates, and susceptibility tests were performed by the clinical microbiology laboratory at each participating institution in accordance with methods approved by the Clinical and Laboratory Standards Institute.¹³ External oversight for study activities was provided by two contract research organizations, Pharmaceutical Product Development (PPD) and the Division of Microbiology and Infectious Diseases Clinical Research Operations and Management Support (DMID-CROMS).

Patients were surveyed about demographic characteristics and coexisting conditions. Patients were seen at the end of treatment (day 12), at the test of cure (7 to 10 days after completion of the prescribed 10-day course of therapy), and at the 1-month follow-up (day 40). Information about clinical response and possible medication side effects was obtained with the use of standardized forms.

STATISTICAL ANALYSIS

The primary study outcome was clinical cure at the test-of-cure visit. Two primary efficacy analyses were performed: one in the intention-to-treat population and the other in the population of patients who could be evaluated (Fig. 1). A lack of clinical cure was defined as a lack of resolution of signs or symptoms of infection, the occurrence of side effects that necessitated discontinuation of treatment with the study medication within the first 48 hours, or any one of the following before the test-of-cure visit: occurrence of a skin infection at a new body site, unplanned surgical treatment of the skin infection, or hospitalization related to the infection. The primary null hypothesis was that clindamycin and TMP-SMX would have equal rates of cure. The study was designed as a superiority trial with 80% power to detect an absolute difference between the two treatment groups of 10 percentage points in cure rates (85% vs. 95%) in the population that could be evaluated, at an alpha level of 0.05. Assuming a 20% attrition rate, we calculated that 524 patients (262 in each group) needed to be enrolled. The prespecified secondary outcomes were cure rates at the end of treatment and at the 1-month follow up visit; cure rates in the adult and pediatric populations; cure rates among patients with cellulitis, abscess, or mixed abscess and cellulitis (defined as separate lesions of abscess and cellulitis) at the test-of-cure visit; and adverse-event rates. Comparisons



between groups were performed with the use of Pearson's chi-square test, Fisher's exact test, or an analysis-of-variance test, as appropriate; all tests were two-sided. Interim analyses for safety were performed by an independent data and safety monitoring committee. Findings from the trial are described in accordance with Consolidated Standards of Reporting Trials (CONSORT) guidelines.¹⁴

RESULTS

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE PATIENTS

A total of 524 patients were enrolled; 264 received clindamycin treatment, and 260 received TMP-SMX treatment (Fig. 1). A total of 52.3% of the patients were male, 53.2% were black, 40.3% were white, and 28.6% were Hispanic. The mean age was 27.1 years. A total of 29.6% of the patients were children (Table 1, and Table S3 in the Supplementary Appendix). There were no significant demographic differences between the groups.

Abscess was present in 160 patients (30.5%), cellulitis in 280 (53.4%), and mixed abscess and cellulitis in 82 (15.6%); the lesions in 2 patients (0.4%) were not characterized. There were no significant differences between the groups with regard to clinical presentation, signs, or symptoms. Incision and drainage were performed in 44.5% of the patients. Detailed clinical information on the patients is provided in Table 1.

Cultures were obtained for 296 patients (56.5%). The most common baseline isolate found in culture was *S. aureus* (217 of 524 patients, 41.4%) (Table 2); 27 of the 217 isolates (12.4%) were clindamycin-resistant, and 1 of 217 isolates (0.5%) was TMP-SMX-resistant. Stratification of culture results according to skin infection type is shown in Table S4 in the Supplementary Appendix.

CLINICAL CURE AT THE TEST-OF-CURE VISIT

The rate of cure in the intention-to-treat population (524 patients) at the test-of-cure visit was 80.3% (95% confidence interval [CI], 75.2 to 85.4) in the clindamycin group and 77.7% (95% CI, 72.3 to 83.1) in the TMP-SMX group (difference, -2.6 percentage points; 95% CI, -10.2 to 4.9; $P=0.52$) (Table 3). In the population that could be evaluated (466 patients), the rate of cure was 89.5% (95% CI, 85.2 to 93.7) in the clindamycin

group and 88.2% (95% CI, 83.7 to 92.7) in the TMP-SMX group (difference, -1.2 percentage points; 95% CI, -7.6 to 5.1; $P=0.77$) (Fig. 2).

There were no significant differences between treatment groups, in either the intention-to-treat population or the population that could be evaluated, in subgroups consisting of children, adults, or patients with cellulitis, abscesses, or mixed abscess and cellulitis lesions (Table 3). In addition, there were no significant between-group differences in subgroups of patients infected with *S. aureus*, MRSA, or MSSA in either the intention-to-treat population or the population that could be evaluated. In the population that could be evaluated, 11 of 15 clindamycin-treated patients with clindamycin-resistant *S. aureus* isolates were cured, as compared with 77 of 84 patients with susceptible isolates (73.3% [95% CI, 47.0 to 99.7] vs. 91.7% [95% CI, 85.0 to 98.3], $P=0.06$).

EFFICACY AT 1 MONTH

Cure rates at the 1-month follow-up visit were similar for the clindamycin and TMP-SMX groups in the intention-to-treat population (193 of 264 patients [73.1%; 95% CI, -67.6 to 78.6] and 176 of 260 patients [67.7%; 95% CI, 61.8 to 73.6], respectively; difference, -5.4 percentage points [95% CI, -13.6 to 2.8]; $P=0.18$) and in the population that could be evaluated (193 of 230 patients [83.9%; 95% CI, 78.9 to 88.9] and 176 of 225 patients [78.2%; 95% CI, 72.6 to 83.8]; difference, -5.7 percentage points [95% CI, -13.3 to 1.9]; $P=0.15$), respectively.

ADVERSE EVENTS

Overall rates of adverse events were similar in the clindamycin and TMP-SMX groups (18.9% and 18.6%, respectively). The most common adverse events in the clindamycin and TMP-SMX groups were diarrhea (9.7% and 10.1%), nausea (2.3% and 2.7%), vomiting (2.3% and 1.6%), pruritis (1.5% and 1.2%), and rash (1.2% and 0.8%) (Table S5 in the Supplementary Appendix). There were no cases of *Clostridium difficile*-associated diarrhea. Most adverse events were mild or moderate and resolved without sequelae. There were no treatment-associated serious adverse events (Table S6). The rates of treatment discontinuation due to adverse events were similar in the two groups (8.3% and 8.8%) (Table S7 in the Supplementary Appendix).

Table 1. Baseline Characteristics of the Patients, According to Treatment Group.*

Characteristic	Clindamycin Group (N=264)	TMP-SMX Group (N=260)	All Patients (N=524)
Female sex — no. (%)	129 (48.9)	121 (46.5)	250 (47.7)
Hispanic ethnic background — no. (%)†			
Non-Hispanic or Non-Latino	188 (71.2)	186 (71.5)	374 (71.4)
Hispanic or Latino	76 (28.8)	74 (28.5)	150 (28.6)
Race or ethnic group — no. (%)‡			
American Indian or Alaskan Native	1 (0.4)	2 (0.8)	3 (0.6)
Asian	5 (1.9)	4 (1.5)	9 (1.7)
Hawaiian or Pacific Islander	4 (1.5)	2 (0.8)	6 (1.1)
Black	141 (53.4)	138 (53.1)	279 (53.2)
White	102 (38.6)	109 (41.9)	211 (40.3)
Multiracial	10 (3.8)	4 (1.5)	14 (2.7)
Other or unknown	1 (0.4)	1 (0.4)	2 (0.4)
Age group — no. (%)			
<1 yr	6 (2.3)	5 (1.9)	11 (2.1)
1–8 yr	45 (17.0)	42 (16.2)	87 (16.6)
9–17 yr	30 (11.4)	27 (10.4)	57 (10.9)
≥18 yr	183 (69.3)	186 (71.5)	369 (70.4)
Temperature — °C	36.61±0.50	36.59±0.52	36.60±0.51
Area of wound — cm ² §	43.84±140.03	35.35±71.13	39.62±111.28
Purulent drainage present — no. (%)	124 (47.0)	113 (43.5)	237 (45.2)
Incision and drainage performed — no. (%)	122 (46.2)	111 (42.7)	233 (44.5)
Type of lesion — no. (%)¶			
Abscess only	80 (30.3)	80 (30.8)	160 (30.5)
Cellulitis only	136 (51.5)	144 (55.4)	280 (53.4)
Mixed abscess and cellulitis	47 (17.8)	35 (13.5)	82 (15.6)

* Complete data on demographics and age, stratified according to treatment group, are provided in Table S3 in the Supplementary Appendix. P values for all comparisons were nonsignificant ($P>0.05$ for all comparisons). The denominator for calculation of percentages is the number of patients in the intention-to-treat population for each treatment group. Plus-minus values are means \pm SD. TMP-SMX denotes trimethoprim-sulfamethoxazole.

† Race and ethnic group and information on Hispanic ethnic background were self-reported.

‡ Data were available for 263 patients in the clindamycin group and 259 in the TMP-SMX group.

§ Areas were calculated with the use of the formula for an ellipse ($[(\text{length} \times \text{width} \times \pi) / 4]$).

¶ The type of lesion was not known for 2 patients.

|| Patients categorized as having mixed abscess and cellulitis lesions were those who had more than one lesion, with at least one abscess lesion that underwent incision and drainage and at least one cellulitis lesion that did not require incision and drainage.

DISCUSSION

We performed a double-blind, multicenter, randomized clinical trial to compare TMP-SMX and clindamycin, each of which is commonly recommended as empirical therapy for uncomplicated skin infections in the outpatient population with only minor or no coexisting conditions.^{6,7,15,16} The cure rates with TMP-SMX and clindamycin did not

differ significantly. The cure rate with TMP-SMX ranged from 5 percentage points higher to 7 to 10 percentage points lower than the cure rate with clindamycin, on the basis of the 95% confidence intervals for rate differences in the intention-to-treat population and the population that could be evaluated. This well-powered superiority trial did not show the superiority of either intervention. Although it is not appropriate to claim that

Table 2. Wound Culture Results at Baseline.*

Culture Result	Clindamycin Group (N = 264)	TMP-SMX Group (N = 260)	All Patients (N = 524)
	no. of patients (%)		
No culture obtained	110 (41.7)	118 (45.4)	228 (43.5)
Culture obtained but no growth	6 (2.3)	6 (2.3)	12 (2.3)
Culture obtained but no results	4 (1.5)	3 (1.2)	7 (1.3)
Positive culture	144 (54.5)	133 (51.2)	277 (52.9)
<i>Staphylococcus aureus</i>	108 (40.9)	109 (41.9)	217 (41.4)
MRSA	84 (31.8)	83 (31.9)	167 (31.9)
Clindamycin-resistant	12 (4.5)	9 (3.5)	21 (4.0)
TMP-SMX-resistant	1 (0.4)	0	1 (0.2)
MSSA	25 (9.5)	27 (10.4)	52 (9.9)
Clindamycin-resistant	3 (1.1)	3 (1.2)	6 (1.1)
TMP-SMX-resistant	0	0	0
<i>Streptococcus pyogenes</i>	3 (1.1)	5 (1.9)	8 (1.5)
Group B streptococcus	1 (0.4)	1 (0.4)	2 (0.4)
Beta-hemolytic group C streptococcus	2 (0.8)	0	2 (0.4)
Beta-hemolytic group F streptococcus	0	1 (0.4)	1 (0.2)
Non-group A and B beta-hemolytic streptococcus	1 (0.4)	0	1 (0.2)
Viridans group streptococcus	9 (3.4)	9 (3.5)	18 (3.4)
Enterobacter species	1 (0.4)	0	1 (0.2)
Enterococcus species	1 (0.4)	1 (0.4)	2 (0.4)
<i>Escherichia coli</i>	2 (0.8)	2 (0.8)	4 (0.8)
Hemophilus species	2 (0.8)	2 (0.8)	4 (0.8)
Klebsiella species	1 (0.4)	2 (0.8)	3 (0.6)
Lactobacillus species	2 (0.8)	0	2 (0.4)
<i>Proteus mirabilis</i>	9 (3.4)	1 (0.4)	10 (1.9)
Bacterial growth not otherwise specified	2 (0.8)	0	2 (0.4)
Coagulase-negative staphylococcus	19 (7.2)	19 (7.3)	38 (7.3)
Diphtheroid bacilli	8 (3.0)	7 (2.7)	15 (2.9)
Other	11 (4.2)	7 (2.7)	18 (3.4)

* The denominator for the calculation of percentages is the number of patients in the intention-to-treat population for each group. Patients are counted once for each species identified. MRSA denotes methicillin-resistant *S. aureus*, and MSSA methicillin-susceptible *S. aureus*.

there are no differences on the basis of the negative result of the superiority test, important differences can reasonably be ruled out with the use of confidence intervals. Adverse-event rates with the two therapies were similar.

Among all the patients, 46% had one or more abscesses larger than 5 cm in diameter (proportionally smaller in young children), all of which underwent incision and drainage. The 5-cm cutoff was based on data from a single-center observa-

tional study involving children, in which abscesses larger than 5 cm were associated with treatment failure.¹⁷ Although incision and drainage alone may be sufficient for treatment in many cases, there are likely to be subgroups in which antibiotic therapy is needed. Outcomes in antibiotic-treated patients with abscesses in our relatively low-risk population could reflect either similar true efficacies or the adequacy of incision and drainage alone. Large placebo-controlled trials

Table 3. Cure Rate at Test-of-Cure Visit in the Overall Population and Relevant Subgroups.*						
Group with Clinical Cure	Clindamycin Group		TMP-SMX Group		Difference	P Value
	<i>no./total no.</i>	<i>% (95% CI)</i>	<i>no./total no.</i>	<i>% (95% CI)</i>	<i>percentage points</i>	
All patients						
Intention-to-treat population	212/264	80.3 (75.2 to 85.4)	202/260	77.7 (72.3 to 83.1)	-2.6 (-10.2 to 4.9)	0.52
Population that could be evaluated	212/237	89.5 (85.2 to 93.7)	202/229	88.2 (83.7 to 92.7)	-1.2 (-7.6 to 5.1)	0.77
Children						
Intention-to-treat population	70/81	86.4 (78.1 to 94.7)	60/74	81.1 (71.2 to 90.9)	-5.3 (-18.6 to 7.9)	0.39
Population that could be evaluated	70/76	92.1 (85.2 to 99.0)	60/67	89.6 (81.3 to 97.8)	-2.6 (-13.7 to 8.6)	0.77
Adults						
Intention-to-treat population	142/183	77.6 (71.1 to 84.1)	142/186	76.3 (69.8 to 82.9)	-1.3 (-10.6 to 8.1)	0.81
Population that could be evaluated	142/161	88.2 (82.8 to 93.6)	142/162	87.7 (82.1 to 93.2)	-0.5 (-8.5 to 7.4)	1.00
Patients with cellulitis without abscess						
Intention-to-treat population	110/136	80.9 (73.7 to 88.0)	110/144	76.4 (68.9 to 83.9)	-4.5 (-15.1 to 6.1)	0.38
Population that could be evaluated	110/121	90.9 (85.2 to 96.6)	110/127	86.6 (80.1 to 93.1)	-4.3 (-13.1 to 4.6)	0.32
Patients with abscess						
Intention-to-treat population	63/80	78.8 (68.9 to 88.6)	64/80	80.0 (70.4 to 89.6)	1.3 (-12.9 to 15.4)	1.00
Population that could be evaluated	63/73	86.3 (77.5 to 95.1)	64/72	88.9 (80.7 to 97.0)	2.6 (-9.8 to 15.0)	0.80
Patients with mixed abscess and cellulitis						
Intention-to-treat population	39/47	83.0 (70.9 to 95.1)	28/35	80.0 (65.0 to 95.0)	-3.0 (-23.0 to 17.0)	0.78
Population that could be evaluated	39/43	90.7 (80.6 to 100)	28/30	93.3 (82.5 to 100)	2.6 (-13.0 to 18.3)	1.00
Patients with a single lesion in the intention-to-treat population	136/170	80.0 (73.5 to 86.5)	141/174	81.0 (74.8 to 87.3)	1.0 (-8.1 to 10.2)	0.89
Patients with >1 lesion in the intention-to-treat population	76/93	81.7 (73.1 to 90.3)	61/85	71.8 (61.3 to 82.2)	-10.0 (-23.8 to 3.9)	0.15

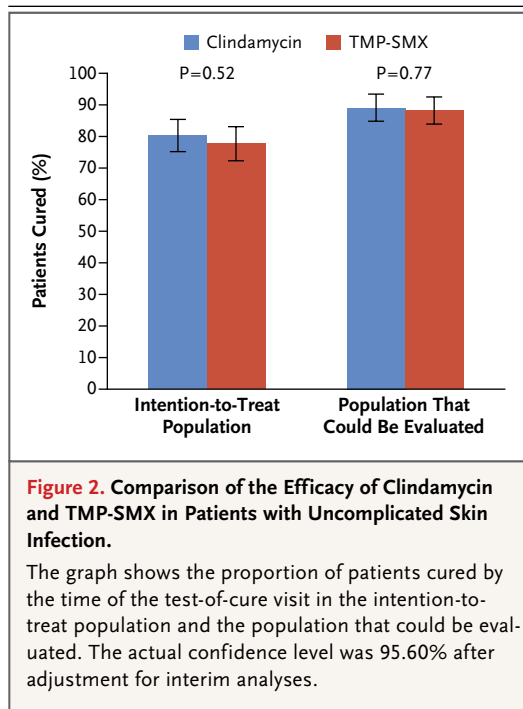
* The actual confidence level was 95.60% after adjustment for interim analyses. P values for comparisons were determined with the use of Fisher's exact test.

are needed to further understand the role of active pharmacologic therapy in the treatment of patients with abscesses.

The cure rates for TMP-SMX and clindamycin were similar among patients who had cellulitis as the sole lesion type. In the prespecified analysis of patients with cellulitis only, the point estimates of the TMP-SMX mean cure rates were 86.6% and 76.4% for the population that could be evaluated and the intention-to-treat population, respectively — rates that are 4.3 percentage points (95% CI, −13.1 to 4.6) to 4.5 percentage points (95% CI, −15.1 to 6.1) lower than the rates with clindamycin. In a post hoc analysis of patients with cellulitis with or without an abscess at another site, the cure rates were 87.9% (138 of 157 patients) with TMP-SMX and 90.9% (149 of 164) with clindamycin in the population that could be evaluated (difference, −3.0 percentage points [95% CI, −10.5 to 4.6]) and 77.1% (138 of 179) and 81.4% (149 of 183), respectively, in the intention-to-treat population (difference, −4.3 percentage points [95% CI, −13.5 to 4.8]). Our study was not powered to determine the superiority of one agent over the other in the subgroup of patients with cellulitis, but the data suggest that if there is a difference in outcome it is probably small. Moreover, in further support of the efficacy of TMP-SMX, the lower boundaries of the confidence intervals are above the 18 to 30% range for the inferiority of placebo to active agents cited for the outcome of cellulitis in the 2013 Food and Drug Administration guidance for acute bacterial skin and skin structure infections.^{18,19}

The cause of cellulitis is incompletely understood, because a causative pathogen is not identified in most cases²⁰; this is consistent with our study, in which 80% of cellulitis lesions could not be cultured because skin was intact. Expert opinion⁸ and empirical data^{21,22} suggest that cellulitis is most commonly caused by *Streptococcus pyogenes*. Our findings are provocative, because TMP-SMX has been considered a poor empirical choice for the treatment of cellulitis. Recent data show that *S. pyogenes* strains may be TMP-SMX-susceptible if low-concentration thymidine agar is used for testing.²³ Our results showing that TMP-SMX and clindamycin have similar efficacy in patients with cellulitis are consistent with these in vitro data.

With respect to adverse events, the rates were similar in the two groups. In particular, the rates



of diarrhea were similar. The absence of *C. difficile*-associated diarrhea may stem from its relatively low incidence in patients with low disease severity and younger age,²⁴⁻²⁶ characteristics that were typical of the patients in this trial. Rash has been a concern with TMP-SMX therapy²⁷; however, dermatologic side-effect rates were similar in the two groups. Overall adverse-event rates were similar in the pediatric and adult subgroups.

Our study has limitations. First, we excluded patients with serious coexisting conditions, and the outcomes of skin infections treated with clindamycin and TMP-SMX in populations with such conditions may differ. However, our investigation involved outpatients, the population in which approximately 95% of skin infections are treated,²⁸ and thus is generalizable to a large population. Second, we examined only two antibiotics, and the comparative efficacy and side-effect profile of other oral medications are unclear. However, the two antibiotics we studied are those typically recommended by experts in areas of MRSA endemicity.^{2,10-12} Third, patients were followed for 1 month after therapy was completed, which is a strength in comparison with studies lacking a documented follow-up visit but is also a limitation. *S. aureus* infections are often recurrent,^{29,30} and 1 month of follow-up may be inad-

equate for assessing the efficacy of a drug in preventing recurrent disease.

Fourth, the dosages of clindamycin and TMP-SMX for skin infections are not well defined. Some have suggested using twice the dose we used (see, e.g., ClinicalTrials.gov number NCT00729937), whereas others have recommended the same dose.⁸ Our data show that the efficacy of TMP-SMX doses of 160 mg and 800 mg does not differ significantly from that of a commonly recommended dose of clindamycin — specifically, 300 mg three times daily.⁸ Finally, the proportions of patients who had an *S. aureus* isolate that was resistant to clindamycin or TMP-SMX (5.2% and 0.2%, respectively) were relatively low. Given the low prevalence of resistance, its contribution to treatment failure is unclear, although there was a trend toward a lower clindamycin cure rate for infections caused by clindamycin-resistant *S. aureus* versus clindamycin-susceptible isolates (73.3% vs. 91.7%, $P=0.06$), which also raises important questions about the spontaneous response rate. The number of patients with inducible clindamycin-resistant isolates was even smaller (three patients in the population that could be evaluated), which precluded making conclusions about its role in treatment failure.

Our study has important strengths. It was a double-blind, randomized clinical trial accompanied by detailed drug accountability (i.e., storage, handling, and dispensing of study drugs, as well as documentation of their administration), detailed

systematic reviews of adverse drug effects, and relatively low rates of attrition (10.5%). We included both adults and children, which is of critical importance given that skin infections are highly prevalent among persons of all ages.^{7,28} Finally, the populations studied were ethnically and geographically diverse. In summary, we found no significant differences between the efficacy of clindamycin and that of TMP-SMX for the treatment of uncomplicated skin infections in children and adults with few or no major coexisting conditions.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Supported by grants from the National Institutes of Allergy and Infectious Diseases (1U01 HHSN272200700031C, to Dr. Chambers) and the National Center for Research Resources (UL1RR033176, now at the National Center for Advancing Translational Sciences, UL1TR000124).

Dr. Miller reports receiving consulting fees from Cubist, Durata, and Pfizer; Dr. Daum, fees for serving on an advisory board from Pfizer; Dr. Creech, grant support from Pfizer and Cubist; Dr. Hoagland, fees for providing statistical analysis and programming services from EMMES; and Dr. Chambers, fees for serving on advisory boards from Theravance and AstraZeneca, consulting fees from Cubist, Pfizer, Trius, and AstraZeneca, and grant support from Cubist; Dr. Chambers also reports that he holds stock in Trius and Merck and that his institution holds a contract for a clinical trial from Cerexa. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Christine Chiou, M.D., Maureen Mehigan, R.N., B.S.N., and Hyung Koo, R.N., B.S.N., at the Division of Microbiology and Infectious Diseases; and Thad Zajdowicz, Nancy Browning, and the staff at EMMES for their support with the conduct of this clinical trial.

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;168:1585-91.
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;51:291-8.
3. Edelsberg J, Taneja C, Zervos M, et al. Trends in US hospital admissions for skin and soft tissue infections. *Emerg Infect Dis* 2009;15:1516-8.
4. Carratalà J, Rosón B, Fernández-Sabé N, et al. Factors associated with complications and mortality in adult patients hospitalized for infectious cellulitis. *Eur J Clin Microbiol Infect Dis* 2003;22:151-7.
5. Lipsky BA, Kollef MH, Miller LG, Sun X, Johannes RS, Tabak YP. Predicting bacteremia among patients hospitalized for skin and skin-structure infections: derivation and validation of a risk score. *Infect Control Hosp Epidemiol* 2010;31:828-37.
6. Moran GJ, Krishnadasan A, Gorwitz RJ, et al. Methicillin-resistant *S. aureus* infections among patients in the emergency department. *N Engl J Med* 2006;355:666-74.
7. Ray GT, Suaya JA, Baxter R. Incidence, microbiology, and patient characteristics of skin and soft-tissue infections in a U.S. population: a retrospective population-based study. *BMC Infect Dis* 2013;13:252.
8. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. *Clin Infect Dis* 2005;41:1373-406.
9. Gorwitz RJ, Jernigan DB, Powers JH, Jernigan JA. Strategies for clinical management of MRSA in the community: summary of an experts' meeting convened by the Centers for Disease Control and Prevention. 2006 (<http://www.cdc.gov/mrsa/pdf/MRSA-Strategies-ExpMtgSummary-2006.pdf>).
10. Hyun DY, Mason EO, Forbes A, Kaplan SL. Trimethoprim-sulfamethoxazole or clindamycin for treatment of community-acquired methicillin-resistant *Staphylococcus aureus* skin and soft tissue infections. *Pediatr Infect Dis J* 2009;28:57-9.
11. Mascitti KB, Gerber JS, Zaoutis TE, Barton TD, Lautenbach E. Preferred treatment and prevention strategies for recurrent community-associated methicillin-resistant *Staphylococcus aureus* skin and soft-tissue infections: a survey of adult and pediatric providers. *Am J Infect Control* 2010;38:324-8.
12. Williams DJ, Cooper WO, Kaltenbach LA, et al. Comparative effectiveness of antibiotic treatment strategies for pediatric

- skin and soft-tissue infections. *Pediatrics* 2011;128(3):e479-e487.
13. Clinical and Laboratory Standards Institute (CLSI). Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard — ninth edition. CLSI document M7-A9. Wayne, PA: CLSI, January 2012 (<http://antimicrobianos.com.ar/ATB/wp-content/uploads/2012/11/03-CLSI-M07-A9-2012.pdf>).
 14. Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Ann Intern Med* 2010;152:726-32.
 15. Chen CJ, Huang YC, Chiu CH, Su LH, Lin TY. Clinical features and genotyping analysis of community-acquired methicillin-resistant *Staphylococcus aureus* infections in Taiwanese children. *Pediatr Infect Dis J* 2005;24:40-5.
 16. David MZ, Daum RS. Community-associated methicillin-resistant *Staphylococcus aureus*: epidemiology and clinical consequences of an emerging epidemic. *Clin Microbiol Rev* 2010;23:616-87.
 17. Lee MC, Rios AM, Aten MF, et al. Management and outcome of children with skin and soft tissue abscesses caused by community-acquired methicillin-resistant *Staphylococcus aureus*. *Pediatr Infect Dis J* 2004;23:123-7.
 18. Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for industry: acute bacterial skin and skin structure infections: developing drugs for treatment. October 2013 (<http://www.fda.gov/downloads/Drugs/Guidances/ucm071185.pdf>).
 19. Itani KM, Shorr AF. FDA guidance for ABSSSI trials: implications for conducting and interpreting clinical trials. *Clin Infect Dis* 2014;58:Suppl 1:S4-S9.
 20. Chira S, Miller LG. *Staphylococcus aureus* is the most common identified cause of cellulitis: a systematic review. *Epidemiol Infect* 2010;138:313-7.
 21. 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;89:217-26.
 22. Eells SJ, Chira S, David CG, Craft N, Miller LG. Non-suppurative cellulitis: risk factors and its association with *Staphylococcus aureus* colonization in an area of endemic community-associated methicillin-resistant *S. aureus* infections. *Epidemiol Infect* 2011;139:606-12.
 23. Bowen AC, Lilliebridge RA, Tong SY, et al. Is *Streptococcus pyogenes* resistant or susceptible to trimethoprim-sulfamethoxazole? *J Clin Microbiol* 2012;50:4067-72.
 24. Loo VG, Bourgault AM, Poirier L, et al. Host and pathogen factors for *Clostridium difficile* infection and colonization. *N Engl J Med* 2011;365:1693-703.
 25. Kyne L, Sougioultzis S, McFarland LV, Kelly CP. Underlying disease severity as a major risk factor for nosocomial *Clostridium difficile* diarrhea. *Infect Control Hosp Epidemiol* 2002;23:653-9.
 26. Pallin DJ, Binder WD, Allen MB, et al. Clinical trial: comparative effectiveness of cephalexin plus trimethoprim-sulfamethoxazole versus cephalexin alone for treatment of uncomplicated cellulitis: a randomized controlled trial. *Clin Infect Dis* 2013;56:1754-62.
 27. Ho JM, Juurlink DN. Considerations when prescribing trimethoprim-sulfamethoxazole. *CMAJ* 2011;183:1851-8.
 28. Miller LG, Eisenberg DE, Chang CL, et al. The burden of skin and soft tissue infections: incidence and costs from a large U.S. population of commercially insured persons aged 0-64 years from 2005 to 2008. Presented at the 51st Annual International Conference on Antimicrobial Agents and Chemotherapy, Chicago, September 17-20, 2011. abstract.
 29. Fritz SA, Hogan PG, Hayek G, et al. Household versus individual approaches to eradication of community-associated *Staphylococcus aureus* in children: a randomized trial. *Clin Infect Dis* 2012;54:743-51.
 30. Miller LG, Tan J, Eells SJ, Benitez E, Radner AB. Prospective investigation of nasal mupirocin, hexachlorophene body wash, and systemic antibiotics for prevention of recurrent community-associated methicillin-resistant *Staphylococcus aureus* infections. *Antimicrob Agents Chemother* 2012;56:1084-6.

Copyright © 2015 Massachusetts Medical Society.

MY NEJM IN THE JOURNAL ONLINE

Individual subscribers can store articles and searches using a feature on the *Journal's* website ([NEJM.org](http://www.nejm.org)) called "My NEJM."

Each article and search result links to this feature. Users can create personal folders and move articles into them for convenient retrieval later.