

ORIGINAL ARTICLE

A Placebo-Controlled Trial of Antibiotics for Smaller Skin Abscesses

Robert S. Daum, M.D., C.M., Loren G. Miller, M.D., M.P.H., Lilly Immergluck, M.D., Stephanie Fritz, M.D., M.S.C.I., C. Buddy Creech, M.D., M.P.H., David Young, M.D., Neha Kumar, M.D., Michele Downing, R.N., M.S.N., Stephanie Pettibone, B.S., Rebecca Hoagland, M.S., Samantha J. Eells, M.P.H., Mary G. Boyle, R.N., M.S.N., Trisha Chan Parker, M.P.H., and Henry F. Chambers, M.D., for the DMID 07-0051 Team*

ABSTRACT

BACKGROUND

Uncomplicated skin abscesses are common, yet the appropriate management of the condition in the era of community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) is unclear.

METHODS

We conducted a multicenter, prospective, double-blind trial involving outpatient adults and children. Patients were stratified according to the presence of a surgically drainable abscess, abscess size, the number of sites of skin infection, and the presence of non-purulent cellulitis. Participants with a skin abscess 5 cm or smaller in diameter were enrolled. After abscess incision and drainage, participants were randomly assigned to receive clindamycin, trimethoprim-sulfamethoxazole (TMP-SMX), or placebo for 10 days. The primary outcome was clinical cure 7 to 10 days after the end of treatment.

RESULTS

We enrolled 786 participants: 505 (64.2%) were adults and 281 (35.8%) were children. A total of 448 (57.0%) of the participants were male. *S. aureus* was isolated from 527 participants (67.0%), and MRSA was isolated from 388 (49.4%). Ten days after therapy in the intention-to-treat population, the cure rate among participants in the clindamycin group was similar to that in the TMP-SMX group (221 of 266 participants [83.1%] and 215 of 263 participants [81.7%], respectively; $P=0.73$), and the cure rate in each active-treatment group was higher than that in the placebo group (177 of 257 participants [68.9%], $P<0.001$ for both comparisons). The results in the population of patients who could be evaluated were similar. This beneficial effect was restricted to participants with *S. aureus* infection. Among the participants who were initially cured, new infections at 1 month of follow-up were less common in the clindamycin group (15 of 221, 6.8%) than in the TMP-SMX group (29 of 215 [13.5%], $P=0.03$) or the placebo group (22 of 177 [12.4%], $P=0.06$). Adverse events were more frequent with clindamycin (58 of 265 [21.9%]) than with TMP-SMX (29 of 261 [11.1%]) or placebo (32 of 255 [12.5%]); all adverse events resolved without sequelae. One participant who received TMP-SMX had a hypersensitivity reaction.

CONCLUSIONS

As compared with incision and drainage alone, clindamycin or TMP-SMX in conjunction with incision and drainage improves short-term outcomes in patients who have a simple abscess. This benefit must be weighed against the known side-effect profile of these antimicrobials. (Funded by the National Institutes of Health; ClinicalTrials.gov number, NCT00730028.)

From the University of Chicago Hospitals, Chicago (R.S.D., N.K.); Harbor-UCLA Medical Center and Los Angeles BioMedical Research Institute at Harbor-UCLA Medical Center, Los Angeles (L.G.M., S.J.E.), and University of California, San Francisco-San Francisco General Hospital, San Francisco (D.Y., M.D., H.F.C.); Morehouse School of Medicine and Emory University-Grady Memorial Hospital and Children's Healthcare of Atlanta, Atlanta (L.I., T.C.P.); Washington University School of Medicine-Barnes-Jewish Hospital and St. Louis Children's Hospital, St. Louis (S.F., M.G.B.); Vanderbilt University School of Medicine and Vanderbilt University Medical Center, Nashville (C.B.C.); EMMES Corporation, Rockville, MD (S.P.); and Cota Enterprises, Meriden, KS (R.H.). Address reprint requests to Dr. Daum at the Dept. of Medicine, University of Maryland School of Medicine, 655 W. Baltimore St., Baltimore, MD 21201, or at rsdaum@gmail.com.

*A list of additional investigators in 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 2017;376:2545-55.

DOI: 10.1056/NEJMoa1607033

Copyright © 2017 Massachusetts Medical Society.

MORE THAN 4 IN 100 PEOPLE SEEK treatment for skin infections annually in the United States.¹ Abscesses are the most common of these infections, and the majority of patients are treated as outpatients.¹ Serious complications, such as bacteremia, occur in rare cases.^{1,2} *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA) strains, causes most skin infections,^{3,4} but the appropriate strategy for the treatment of these infections has not been defined.

Clindamycin and trimethoprim–sulfamethoxazole (TMP-SMX) are recommended for outpatient treatment of abscesses because of their low cost and in vitro activity against community-associated MRSA and methicillin-susceptible strains,⁵ but data on their safety and efficacy are limited. One randomized trial showed that outpatients with skin abscesses treated with incision and drainage and TMP-SMX had a slightly higher cure rate than those treated with incision and drainage and placebo, which supports a role for antibiotic therapy.⁶ We previously evaluated clindamycin and TMP-SMX in a randomized trial involving outpatient adults and children with large (>5 cm) or multiple skin abscesses and cellulitis (either purulent or nonpurulent).⁷ Participants underwent incision and drainage, as appropriate. The cure rates associated with clindamycin were similar to those associated with TMP-SMX. However, the trial did not include the evaluation of a placebo group. Here we report the results of a double-blind, placebo-controlled trial involving children and adults with a single, small abscess. Participants were randomly assigned to receive clindamycin, TMP-SMX, or placebo after incision and drainage.

METHODS

TRIAL DESIGN AND POPULATION

We conducted a multicenter, prospective, randomized, double-blind, placebo-controlled clinical trial involving outpatients. Participants were stratified according to the presence of a surgically drainable abscess, abscess size, the number of sites of skin infection, and the presence of nonpurulent cellulitis. Participants with a single skin abscess 5 cm in diameter or smaller were randomly assigned to receive oral clindamycin, TMP-SMX, or placebo in addition to incision and drainage.

From May 2009 through January 2015, participants were recruited from urgent care clinics, emergency departments, and affiliated clinics at six sites: the University of Chicago Medical Center, Chicago; San Francisco General Hospital, San Francisco; Harbor–University of California, Los Angeles, Medical Center, Torrance; Vanderbilt University Medical Center, Nashville (added in 2011); Washington University, St. Louis (added in 2012); and Morehouse School of Medicine–Emory University, Atlanta (added in 2012). All participants or their parents or guardians provided written informed consent and assent, when age-appropriate. The protocol was approved by the institutional review board at each institution. The authors vouch for the accuracy and completeness of the data and the fidelity of the trial to the protocol, available with the full text of this article at NEJM.org

Participants were eligible for participation if they had a single abscess (defined as a circumscribed, drainable collection of pus) with a greatest diameter of 5.0 cm or less (≤ 3 cm for participants 6 to 11 months of age and ≤ 4 cm for participants 1 to 8 years of age), evidenced by two or more of the following signs or symptoms for at least 24 hours: erythema, swelling or induration, local warmth, purulent drainage, and tenderness to pain or palpation. Abscess size was evaluated manually by measuring the abscess cavity length in three dimensions (width, length, and depth). A standardized incision-and-drainage procedure was implemented by the treating physician, with packing of the abscess as needed.⁸

Exclusion criteria included superficial skin infections (e.g., impetigo), infection at a body site requiring specialized management (e.g., perirectal, genital, or hand infection), human or animal bite, oral temperature higher than 38.5°C (or >38.0°C for children 6 to 11 months of age), presence of systemic inflammatory response syndrome criteria, immunosuppressive therapy or an immunocompromising condition (e.g., diabetes or chronic renal failure), a body-mass index (the weight in kilograms divided by the square of the height in meters) higher than 40, surgical site or prosthetic device infection, or systemic antistaphylococcal antibacterial therapy in the previous 14 days. Participants were ineligible for participation if they required hospitalization, lived in a long-term care facility, had had cancer or an inflammatory disorder treated

in the previous 12 months, or had had major surgery in the previous 12 months. The full list of inclusion and exclusion criteria is provided in Table S3 in the Supplementary Appendix, available at NEJM.org.

RANDOMIZATION AND STUDY AGENTS

After incision and drainage of the abscess and determination of the size of the abscess, participants were randomly assigned in a 1:1:1 ratio to receive placebo, clindamycin, or TMP-SMX. Variable-block randomization was performed by an independent statistics and data-coordinating center (EMMES Corporation).

Clindamycin was given as two 150-mg tablets three times daily. TMP-SMX was given as two tablets (each containing 80 mg of trimethoprim and 400 mg of sulfamethoxazole) twice daily. Participants who were randomly assigned to receive TMP-SMX were given a placebo pill for the midday dose. Pills were over-encapsulated to prevent identification by study staff and participants. Clindamycin, TMP-SMX, and placebo capsules were identical in appearance. Pediatric doses were adjusted according to weight (Table S4 in the Supplementary Appendix), and liquid suspensions were available for pediatric dosing. The suspensions did not differ in appearance or taste and were provided in identical medicine bottles. The study agents were administered for 10 days. Adherence was assessed by self-report and drug accountability for those participants who returned blister packs or suspension bottles.

Participants and all study staff were unaware of the study-group assignments, with the exception of the research pharmacists, who determined the correct dosing. The study medication was purchased by the study sponsor, the National Institute of Allergy and Infectious Diseases of the National Institutes of Health.

MICROBIOLOGIC AND DEMOGRAPHIC DATA

Abscess fluid was submitted for culture, species identification of isolates, and susceptibility testing in accordance with Clinical and Laboratory Standards Institute–approved methods⁹ by the clinical microbiology laboratory at each participating institution. The investigators were unaware of the microbiologic results, although the results could be obtained on request by an independent data and safety monitor in the case of a treatment failure.

Participants were seen at the end of treatment (day 12), at the test-of-cure visit (7 to 10 days after the prescribed 10-day course of therapy), and at the 1-month follow-up (day 40). Information about clinical response and possible side effects of treatment or placebo were obtained with the use of standardized forms.

STATISTICAL ANALYSIS

The primary trial outcome was clinical cure by the time of the test-of-cure visit, stratified according to study group. Two primary efficacy analyses were performed: one in the intention-to-treat population (all participants who underwent randomization) and the other in the population that could be evaluated (participants who received treatment or placebo and completed the end-of-treatment and test-of-cure visits) (Fig. 1). A lack of clinical cure was assessed by the research nurse at each site and was defined as lack of resolution of signs or symptoms of the infection, an inability to continue taking the study agent because of adverse effects within the first 48 hours, or any one of the following: recurrence at the original site of infection or 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, TMP-SMX, and placebo would have equivalent rates of cure at the test-of-cure visit. The trial was designed as a superiority trial with 80% power to detect a 10-percentage-point absolute difference in cure rates (e.g., 85% vs. 95%) among the three study groups in the population that could be evaluated, with an alpha of 0.05. Under the assumption of a 20% attrition rate, 786 participants were required (262 per group). The prespecified exploratory secondary outcomes were the cure rates at the end-of-treatment and 1-month follow-up visits; the cure rates in adults and children; the cure rates for patients infected with methicillin-susceptible *S. aureus*, MRSA, or other strains; and adverse-event rates. Comparisons among the groups were performed with the use of Pearson's chi-square test, Fisher's exact test, an analysis of variance test, or a logistic regression, as appropriate. The statistical analysis plan is available at NEJM.org. Interim analyses for safety and efficacy were performed by an independent data and safety monitoring committee with the use of an O'Brien–Fleming monitor-

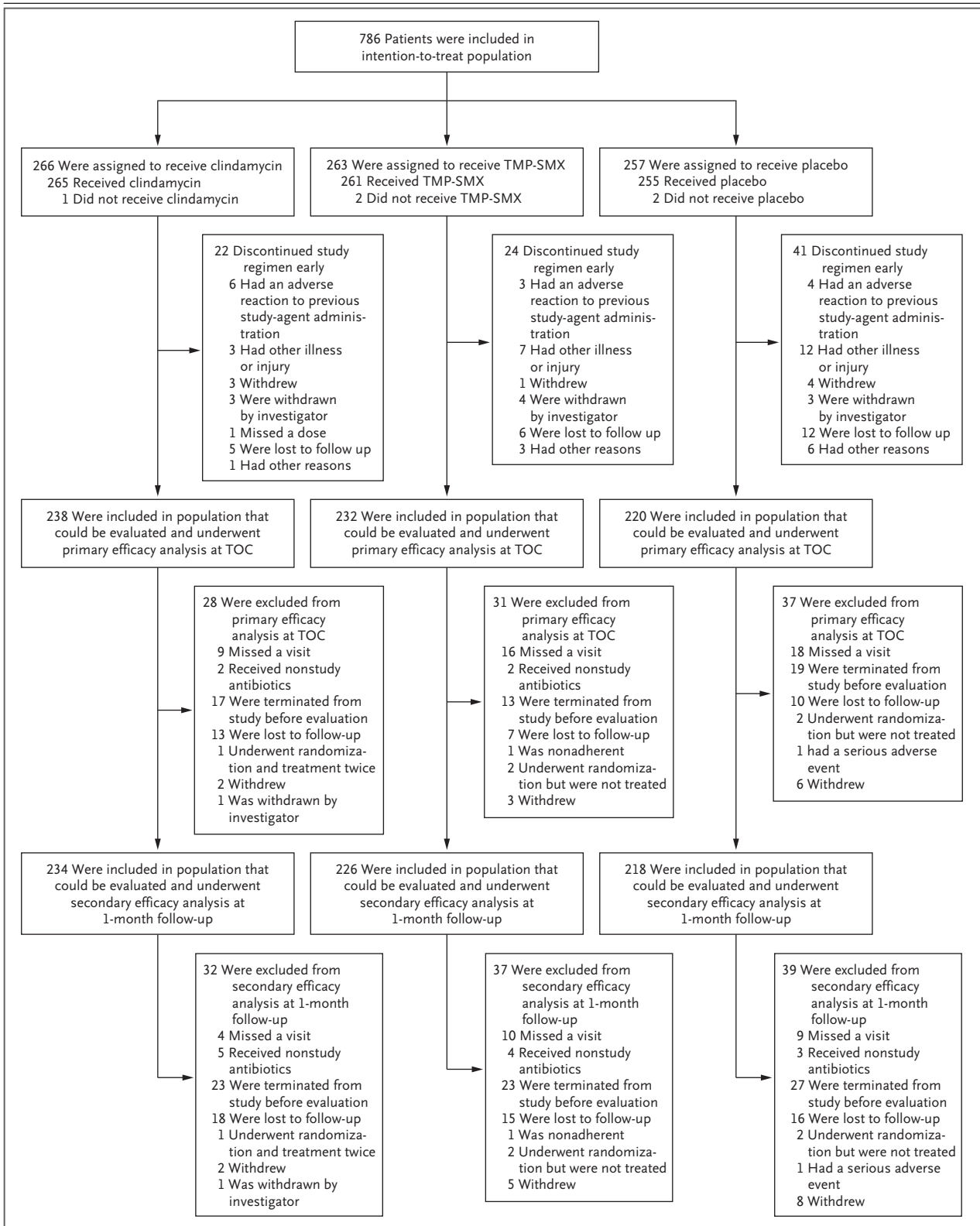


Table 1. Demographic and Clinical Characteristics of the Study Population.*

Characteristic	Clindamycin (N = 266)	TMP-SMX (N = 263)	Placebo (N = 257)	All Groups (N = 786)
Sex — no. (%)				
Male	140 (52.6)	152 (57.8)	156 (60.7)	448 (57.0)
Female	126 (47.4)	111 (42.2)	101 (39.3)	338 (43.0)
Hispanic ethnic background — no. (%)†				
Non-Hispanic and non-Latino	216 (81.2)	208 (79.1)	202 (78.6)	626 (79.6)
Hispanic or Latino	49 (18.4)	55 (20.9)	55 (21.4)	159 (20.2)
Unknown	1 (0.4)	0	0	1 (0.1)
Race or ethnic group — no. (%)‡				
Native American or Alaskan Native	0	2 (0.8)	1 (0.4)	3 (0.4)
Asian	8 (3.0)	4 (1.5)	2 (0.8)	14 (1.8)
Hawaiian or Pacific Islander	2 (0.8)	4 (1.5)	2 (0.8)	8 (1.0)
Black or African American	165 (62.0)	152 (57.8)	167 (65.0)	484 (61.6)
White	80 (30.1)	87 (33.1)	73 (28.4)	240 (30.5)
Multiracial	5 (1.9)	11 (4.2)	8 (3.1)	24 (3.1)
Other or unknown	6 (2.3)	3 (1.1)	4 (1.6)	13 (1.7)
Age — no. (%)				
<1 yr	6 (2.3)	9 (3.4)	2 (0.8)	17 (2.2)
1 to 8 yr	56 (21.1)	51 (19.4)	59 (23.0)	166 (21.1)
9 to 17 yr	39 (14.7)	31 (11.8)	28 (10.9)	98 (12.5)
≥18 yr	165 (62.0)	172 (65.4)	168 (65.4)	505 (64.2)
Body temperature — °C	36.67±0.47	36.63±0.47	36.64±0.46	36.64±0.47
Area of wound — cm ² ‡	3.88±4.90	3.76±3.44	4.04±4.43	3.89±4.30
Area of surrounding erythema — cm ² ‡	26.85±104.34	29.68±93.76	25.76±53.11	27.44±86.82

* Percentages may not total to 100 because of rounding. TMP-SMX denotes trimethoprim–sulfamethoxazole.

† Race and ethnic background were reported by the participants.

‡ Area was calculated with the use of the formula for an ellipse: (length × width × π)/4.

Figure 1 (facing page). Enrollment, Randomization, and Follow-up.

Five participants underwent randomization but were not treated; 2 of these 5 underwent randomization but study agent was not dispensed, 1 recalled having taken a nonstudy drug before enrollment, and 1 received the incorrect study agent. The population that could be evaluated and was included in the secondary efficacy analysis at the 1-month follow-up included participants who missed the test-of-cure visit (TOC) but completed the 1-month follow-up visit. Patients could have been excluded from the efficacy analyses for more than one reason. TMP-SMX denotes trimethoprim–sulfamethoxazole.

ing boundary. In the final analysis, P values of 0.04 or lower were considered to indicate statistical significance. Findings from the trial are described in accordance with CONSORT guidelines.¹⁰

RESULTS

PARTICIPANTS

We enrolled 786 participants: 505 (64.2%) were adults, and 281 (35.8%) were children. The mean age at enrollment was 25.5 years. A total of 448 participants (57.0%) were male (Table 1). Clindamy-

Table 2. Results of Abscess Culture.*

Result	Patients with Result
	(N=786) no. (%)
Culture obtained	781 (99.4)
Culture not obtained	5 (0.6)
Positive culture results	718 (91.3)
Culture obtained but no growth	32 (4.1)
Culture obtained but results not available	31 (3.9)
<i>Staphylococcus aureus</i> isolated	527 (67.0)†
MRSA	388 (49.4)
MSSA	140 (17.8)
Coagulase-negative staphylococcus isolated	104 (13.2)
Streptococcus species isolated	54 (6.9)
Group A streptococcus	7 (0.9)
Group B streptococcus	4 (0.5)
<i>S. anginosus</i>	1 (0.1)
<i>S. agalactiae</i>	1 (0.1)
Beta-hemolytic group C streptococcus	2 (0.3)
Beta-hemolytic group F streptococcus	3 (0.4)
Beta-hemolytic group G streptococcus	1 (0.1)
Non-group A and B beta-hemolytic streptococcus	1 (0.1)
Viridans group streptococcus	36 (4.6)
Other species isolated	118 (15.0)
Acinetobacter species	4 (0.5)
Actinomyces species	3 (0.4)
<i>Citrobacter freundii</i>	1 (0.1)
Corynebacterium species	31 (3.9)
Diphtheroid bacilli	16 (2.0)
<i>Eikenella corrodens</i>	3 (0.4)
Enterobacter species	2 (0.3)
Enterococcus species	7 (0.9)
<i>Escherichia coli</i>	2 (0.3)
Fusobacterium species	1 (0.1)
Haemophilus species	3 (0.4)
Klebsiella species	3 (0.4)
Lactobacillus species	1 (0.1)
Peptostreptococcus species	2 (0.3)
Prevotella species	2 (0.3)
<i>Proteus mirabilis</i>	9 (1.1)
Bacterial growth not otherwise specified	5 (0.6)
Other	42 (5.3)

* Participants whose lesions grew multiple organisms are counted once for each species identified.

† The culture from one participant grew a methicillin-resistant *S. aureus* (MRSA) isolate and a methicillin-susceptible *S. aureus* (MSSA) isolate.

cin was assigned to 266 participants, TMP-SMX to 263 participants, and placebo to 257 participants (Fig. 1). Five participants underwent randomization but were not treated; the study-group assignments and reasons for withdrawal from the trial are summarized in Figure 1. A total of 343 participants were fully adherent to the study regimen (Table S1 in the Supplementary Appendix). The mean abscess depth was 1.64 cm, and the mean abscess area was 3.89 cm² (Table 1). An abscess of 2.0 cm or smaller in diameter was present in 44.6% of participants (Table S2 in the Supplementary Appendix). The results of abscess culture were available for 781 participants (99.4%) (Table 2): *S. aureus* was isolated in 527 participants (67.0%), MRSA in 388 (49.4%), coagulase-negative staphylococci in 104 (13.2%), streptococcus species in 54 (6.9%), and other organisms in 118 (15.0%).

CLINICAL CURE AT THE TEST-OF-CURE VISIT

The rates of clinical cure at the test-of-cure visit in the intention-to-treat population were 83.1% (221 of 266) in the clindamycin group, 81.7% (215 of 263) in the TMP-SMX group, and 68.9% (177 of 257) in the placebo group (Table 3). The cure rate in the placebo group was significantly lower than that in the clindamycin group (rate difference, -14.2 percentage points; 95% confidence interval [CI], -22.0 to -6.4; P<0.001) and that in the TMP-SMX group (rate difference, -12.9 percentage points; 95% CI, -20.8 to -5.0; P<0.001). The difference between the cure rate in the TMP-SMX group and that in the clindamycin group was not significant (-1.3 percentage points; 95% CI, -8.4 to 5.7; P=0.73). The results were similar for the population that could be evaluated (Table 3), with significantly different cure rates for placebo versus either antibiotic but no significant difference between clindamycin and TMP-SMX. A new lesion at a different body site or the use of a rescue medication were more common causes of treatment failure in the placebo group than in the active-treatment groups (Table S8 in the Supplementary Appendix). Treatment failure was rarely due to worsening of the original lesion.

Logistic-regression analysis was performed to determine whether cure rates differed according to age and study group (Table 4). In the population that could be evaluated, children had a significantly higher cure rate with clindamycin

Table 3. Cure Rate at Test-of-Cure Visit in the Overall Population and Relevant Subgroups.*

Group	Clindamycin		TMP-SMX		Placebo	
	No. with Cure/ Total No.	% (95% CI)	No. with Cure/ Total No.	% (95% CI)	No. with Cure/ Total No.	% (95% CI)
All participants						
Intention-to-treat population	221/266	83.1 (78.3–87.9)	215/263	81.7 (76.8–86.7)	177/257	68.9 (62.9–74.9)
Population that could be evaluated	221/238	92.9 (89.3–96.4)	215/232	92.7 (89.0–96.3)	177/220	80.5 (74.8–86.1)
Children						
Intention-to-treat population	90/101	89.1 (82.5–95.7)	75/91	82.4 (74.0–90.8)	61/89	68.5 (58.3–78.7)
Population that could be evaluated	90/92	97.8 (94.3–100.0)	75/81	92.6 (86.3–98.9)	61/74	82.4 (73.1–91.8)
Adults						
Intention-to-treat population	131/165	79.4 (72.9–85.9)	140/172	81.4 (75.3–87.5)	116/168	69.0 (61.8–76.3)
Population that could be evaluated	131/146	89.7 (84.5–95.0)	140/151	92.7 (88.2–97.2)	116/146	79.5 (72.6–86.3)
<i>S. aureus</i> isolated						
Intention-to-treat population	157/188	83.5 (77.9–89.1)	149/179	83.2 (77.5–89.0)	102/160	63.8 (56.0–71.5)
Population that could be evaluated	157/167	94.0 (90.1–97.9)	149/160	93.1 (88.9–97.4)	102/134	76.1 (68.5–83.7)
MRSA isolated						
Intention-to-treat population	116/142	81.7 (75.0–88.4)	110/130	84.6 (78.0–91.2)	73/116	62.9 (53.7–72.2)
Population that could be evaluated	116/126	92.1 (86.9–97.2)	110/117	94.0 (89.3–98.7)	73/96	76.0 (67.0–85.1)
MSSA isolated						
Intention-to-treat population	41/46	89.1 (79.0–99.2)	39/49	79.6 (67.3–91.9)	29/44	65.9 (50.8–81.1)
Population that could be evaluated	41/41	100.0 (98.8–100.0)	39/43	90.7 (80.9–100.0)	29/38	76.3 (61.5–91.1)
No <i>S. aureus</i> isolated						
Intention-to-treat population	57/68	83.8 (74.3–93.3)	59/72	81.9 (72.4–91.5)	69/83	83.1 (74.5–91.8)
Population that could be evaluated	57/63	90.5 (82.4–98.5)	59/65	90.8 (83.0–98.6)	69/76	90.8 (83.6–97.9)

* The actual confidence interval was 95.6% after adjustment for the interim analysis. The intention-to-treat population includes all participants who underwent randomization, and the population that could be evaluated includes participants who received treatment or placebo and completed the required study visits.

Table 4. Logistic-Regression Model of Cure Rates among Children and Adults.

Variable and Population	P Value in the Logistic-Regression Model*		
	TMP-SMX vs. Clindamycin	Placebo vs. Clindamycin	Placebo vs. TMP-SMX
Study group			
Intention-to-treat population	0.37	<0.001	0.003
Population that could be evaluated	0.17	<0.001	<0.001
Age group			
Intention-to-treat population	0.11	0.11	0.98
Population that could be evaluated	0.04	0.03	0.87
Interaction			
Intention-to-treat population	0.17	0.09	0.83
Population that could be evaluated	0.06	0.06	0.74

* The P values refer to the results of a logistic-regression model incorporating study group (clindamycin vs. TMP-SMX) and age group (children vs. adults). After controlling for the effect of age, the differences between placebo and clindamycin and between placebo and TMP-SMX were significant in both the intention-to-treat population and the population that could be evaluated ($P < 0.001$). The cure rates for clindamycin in the population that could be evaluated were significantly higher among children than among adults (among children, $P = 0.04$ for TMP-SMX vs. clindamycin and $P = 0.03$ for placebo vs. clindamycin). None of the interaction terms for the logistic-regression models were significant, indicating that the differences in cure rates between children and adults were not significant in each respective study-group comparison ($P > 0.05$ for the intention-to-treat population and the population that could be evaluated).

than with TMP-SMX or placebo, and this treatment advantage with clindamycin was significantly greater than that seen among adults (for the age-group differences in cure rates, $P = 0.04$ for clindamycin vs. TMP-SMX and $P = 0.03$ for clindamycin vs. placebo); there was no significant difference in cure rates between adults and children in the comparison between the TMP-SMX group and the placebo group ($P = 0.87$). In the intention-to-treat population, there were no significant differences between children and adults in any study-group comparisons (Table 4).

The cure rates among participants in the intention-to-treat population who were culture-positive for *S. aureus* were 83.5% in the clindamycin group and 83.2% in the TMP-SMX group ($P = 0.99$) (Table 3). These rates were significantly higher than the cure rate of 63.8% in the placebo group ($P < 0.001$ for both comparisons). The results were similar for the population that could be evaluated.

Among MRSA-infected participants in the intention-to-treat population, 81.7% of those treated with clindamycin had been cured by the time of the test-of-cure visit, as compared with 84.6% of those treated with TMP-SMX and 62.9% of those who received placebo (Table 3). The cure rates in the clindamycin and TMP-SMX

groups did not differ significantly ($P = 0.63$), whereas the cure rate in the placebo group was significantly lower than that in either the TMP-SMX group ($P = 0.001$) or the clindamycin group ($P < 0.001$). The results were similar for the population that could be evaluated.

Among the participants who were infected with methicillin-susceptible *S. aureus* in the intention-to-treat population, 89.1% of the participants in the clindamycin group were cured, as compared with 79.6% of participants in the TMP-SMX group and 65.9% of participants in the placebo group (Table 3). The cure rate in the placebo group was significantly lower than that in the clindamycin group ($P = 0.01$) but not significantly lower than that in the TMP-SMX group ($P = 0.16$). The difference between the cure rate in the clindamycin group and that in the TMP-SMX group was not significant ($P = 0.26$). Similar results were observed for the population that could be evaluated. The cure rates among participants with an abscess that did not grow *S. aureus* in culture were similar for all treatment groups in the intention-to-treat population and the population that could be evaluated ($P = 0.99$ for all comparisons) (Table 3).

There were 13 participants with *S. aureus* isolates that were resistant to clindamycin — 12

isolates found to be resistant by single-agent testing and 1 found to be resistant by disk-diffusion (D-zone) testing. The cure rate among clindamycin recipients with clindamycin-resistant isolates was significantly lower than that among participants with clindamycin-susceptible *S. aureus* isolates (7 of 13 [53.8%] vs. 145 of 170 [85.3%], $P=0.01$).

CLINICAL CURE AT THE 1-MONTH FOLLOW-UP VISIT

At the 1-month follow-up visit in the intention-to-treat population, 78.6% (209 of 266) of the clindamycin-treated participants, 73.0% (192 of 263) of the TMP-SMX-treated participants, and 62.6% (161 of 257) of the placebo-treated participants remained cured. The difference in cure rates between the TMP-SMX group and the clindamycin group was not significant (-5.6 percentage points; 95% CI, -13.2 to 2.1 ; $P=0.16$). The differences in cure rates between the placebo group and the clindamycin group (-15.9 percentage points; 95% CI, -24.0 to -7.8 ; $P<0.001$) and between the placebo group and the TMP-SMX group (-10.4 percentage points; 95% CI, -18.7 to -2.0 ; $P=0.01$) were significant. The results were similar in the population that could be evaluated.

At the 1-month follow-up visit among participants who had been found to be cured by the time of the test-of-cure visit, new infections at a different body site or a recurrent infection at the original body site had occurred in 6.8% (15 of 221) of clindamycin recipients, 13.5% (29 of 215) of TMP-SMX recipients, and 12.4% (22 of 177) of placebo recipients. The difference in the rates of interval or recurrent infections between the TMP-SMX and clindamycin groups was significant (6.7 percentage points; 95% CI, 0.6 to 12.8; $P=0.03$), but the difference between the placebo and clindamycin groups (5.6 percentage points; 95% CI, -0.8 to 12.0; $P=0.06$) and the difference between the placebo and TMP-SMX groups (-1.1 percentage points; 95% CI, -8.2 to 6.1; $P=0.88$) were not significant. A new lesion at a new location or worsening of the original lesion were among the reasons for failure at the 1-month follow-up visit, although the latter reason was infrequent. There was also a nonsignificant trend toward higher rates of interval or recurrent infections among children who were treated with TMP-SMX; the rate of interval or recurrent infections in this group was 13.3% (10 of 75), as

compared with 4.4% (4 of 90) in the clindamycin group, a difference of 8.9 percentage points (95% CI, 1.1 to 18.9; $P=0.05$).

ADVERSE EVENTS

The rate of treatment-associated adverse events was higher in the clindamycin group (21.9%) than in the TMP-SMX group (11.1%) or the placebo group (12.5%) (Table S5 in the Supplementary Appendix). The most common adverse events were diarrhea (16.2%, 5.4%, and 6.7% respectively) and nausea (2.3%, 4.2%, and 2.4% respectively). Most adverse events were mild or moderate and resolved without sequelae (Table S6 in the Supplementary Appendix). There were no episodes of *Clostridium difficile*-associated diarrhea.

There were nine serious adverse events reported in 8 participants (Table S7 in the Supplementary Appendix). Eight of the events resolved without sequelae and were judged by the investigator not to be related to the study agent; these included a motor-vehicle accident, a case of status asthmaticus, a case of pneumonia, three episodes of worsening cellulitis or abscess, a new perirectal abscess, and a case of emesis. Only one episode, a hypersensitivity reaction with fever, rash, thrombocytopenia, and hepatitis, was thought by the investigator to be related to the study drug (TMP-SMX), and the reaction resolved without sequelae.

DISCUSSION

The cure rates for simple abscesses treated with incision and drainage plus clindamycin or incision and drainage plus TMP-SMX were similar, and both cure rates were significantly higher (by 12 to 13 percentage points) than that among participants who were treated with incision and drainage plus placebo. Our findings show a clinical benefit of antibiotic therapy in addition to incision and drainage that seems limited to patients with *S. aureus* infection. The results complement findings from the trial conducted by Talan et al.,⁶ who found higher cure rates among TMP-SMX-treated participants than among placebo-treated participants in conjunction with abscess drainage (however, this trial did not include children 12 years of age or younger).

Our trial yielded other new findings. First, clindamycin was as effective as TMP-SMX, and the cure rates associated with either agent were

higher than that associated with placebo. Table S8 in the Supplementary Appendix shows that new infections developed more frequently in participants who received placebo than among participants in either antibiotic group. Second, TMP-SMX was effective at half the dose used by Talan et al., although TMP-SMX was administered for 10 days instead of the 7 days used in that trial.⁶ Third, children and adults both benefited from active therapy, although clindamycin may have performed slightly better than TMP-SMX among children. Fourth, clindamycin may be more effective than TMP-SMX in preventing recurrences or new infections after completion of therapy, particularly in children; perhaps a higher dose of TMP-SMX would have been more effective in preventing recurrent or new infections.⁶ Finally, these data underscore the potential clinical relevance of in vitro resistance to clindamycin. Participants infected with a clindamycin-resistant *S. aureus* isolate who were treated with clindamycin had cure rates similar to those who were given placebo. The contribution of resistance to TMP-SMX to treatment failure could not be assessed because there were no resistant isolates in vitro.

The cumulative data from our investigation and that of Talan et al.⁶ call into question the perception — largely based on expert opinion or smaller, underpowered, and lower-quality non-inferiority trials¹¹⁻¹⁴ — that cure rates do not improve with the addition of systemic antibiotic treatment after incision and drainage.¹⁵ These two larger trials show that adjunctive antibiotic therapy improves cure rates for skin abscesses and decreases the recurrence rate.

Antibiotic-related side effects, particularly if frequent or serious, should be taken into account when deciding whether to treat a drained abscess with an antibiotic. In this trial, TMP-SMX was associated with a hypersensitivity reaction, and clindamycin was associated with more adverse events than TMP-SMX. Although no cases of *C. difficile*-associated diarrhea or severe allergic reactions were observed, these and other known side effects must be considered. Our findings suggest that there is a trade-off between more adverse effects and a lower likelihood of infection recurrence when one uses clindamycin rather than TMP-SMX. Such information and the local prevalence of resistance should be used by

treating physicians and policy makers when choosing an antibiotic for adjunctive therapy of cutaneous abscesses.

Our trial has limitations. Two antibiotics that are commonly used and recommended for the treatment of uncomplicated skin infections were studied, but there are others that may be just as effective. For example, doxycycline (which is contraindicated for children younger than 8 years of age and was not studied in this trial) is active against MRSA strains.¹⁶ However, given the higher cure rates that we found, the marginal benefit, if any, would probably be small at best. We followed participants for 1 month; a longer follow-up period may have captured more recurrences.¹⁷ The potential for participants to have treatment failure but be cured of infection subsequently, such as at the 1-month follow-up visit, was not assessed (i.e., if a patient had a treatment failure at the test-of-cure visit, the patient was not evaluated at the 1-month follow-up visit). The exploratory secondary analyses we have discussed provide a potential direction for future analyses.

In conclusion, our results show that short-term outcomes among patients with uncomplicated cutaneous abscesses, particularly those caused by *S. aureus*, are improved by antibiotic treatment with either clindamycin or TMP-SMX in addition to abscess incision and drainage.

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

Supported by a contract from the National Institute of Allergy and Infectious Diseases (NIAID) (HHSN272200700031C to Dr. Chambers) and the National Center for Research Resources (UL1RR033176, now at the National Center for Advancing Translational Sciences, UL1TR000124).

Dr. Daum reports receiving fees for serving on an advisory board from Pfizer and Dynavax and grant support from Theravance and Merck; Dr. Miller, receiving grant support from Gilead Sciences, Achaogen, Merck, Abbott, and Cepheid and consulting fees from Tetraphase; Dr. Creech, receiving grant support from Pfizer, grant support and consulting fees from GlaxoSmithKline, and consulting fees from Theravance; and Dr. Chambers, previously holding stock in Merck and receiving grant support and fees for serving on an advisory board from Genentech and fees for serving on an advisory board from AstraZeneca, Pfizer, Cubist (now Merck), Theravance, Allergan, and Cembra. 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. (all at the Division of Microbiology and Infectious Diseases, NIAID) for assistance and advice.

REFERENCES

1. Miller LG, Eisenberg DF, Liu H, et al. Incidence of skin and soft tissue infections in ambulatory and inpatient settings, 2005-2010. *BMC Infect Dis* 2015;15:362.
2. Lipsky BA, Kolfel 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.
3. 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.
4. 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.
5. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children: executive summary. *Clin Infect Dis* 2011;52:285-92.
6. Talan DA, Mower WR, Krishnadasan A, et al. Trimethoprim-sulfamethoxazole versus placebo for uncomplicated skin abscess. *N Engl J Med* 2016;374:823-32.
7. Miller LG, Daum RS, Creech CB, et al. Clindamycin versus trimethoprim-sulfamethoxazole for uncomplicated skin infections. *N Engl J Med* 2015;372:1093-103.
8. Fitch MT, Manthey DE, McGinnis HD, Nicks BA, Pariyadath M. Abscess incision and drainage. *N Engl J Med* 2007;357(19):e20.
9. Clinical and Laboratory Standards Institute. Methods for dilution antimicrobial susceptibility tests for bacteria which grow aerobically: approved standard. 10th ed. CLSI document M07-A10. Wayne, PA: CLSI, January 2015.
10. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Ann Intern Med* 2010;152:726-32.
11. 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.
12. Schmitz GR, Bruner D, Pitotti R, et al. Randomized controlled trial of trimethoprim-sulfamethoxazole for uncomplicated skin abscesses in patients at risk for community-associated methicillin-resistant *Staphylococcus aureus* infection. *Ann Emerg Med* 2010;56:283-7.
13. Rajendran PM, Young D, Maurer T, et al. Randomized, double-blind, placebo-controlled trial of cephalexin for treatment of uncomplicated skin abscesses in a population at risk for community-acquired methicillin-resistant *Staphylococcus aureus* infection. *Antimicrob Agents Chemother* 2007;51:4044-8.
14. Duong M, Markwell S, Peter J, Barenkamp S. Randomized, controlled trial of antibiotics in the management of community-acquired skin abscesses in the pediatric patient. *Ann Emerg Med* 2010;55:401-7.
15. 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):e10-e52.
16. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis* 2011;52(3):e18-e55.
17. Holmes L, Ma C, Qiao H, et al. Trimethoprim-sulfamethoxazole therapy reduces failure and recurrence in methicillin-resistant *Staphylococcus aureus* skin abscesses after surgical drainage. *J Pediatr* 2016;169:128-34.e1.

Copyright © 2017 Massachusetts Medical Society.