

ORIGINAL ARTICLE

Trimethoprim–Sulfamethoxazole versus Placebo for Uncomplicated Skin Abscess

David A. Talan, M.D., William R. Mower, M.D., Ph.D.,
Anusha Krishnadasan, Ph.D., Fredrick M. Abrahamian, D.O.,
Frank Lovecchio, D.O., M.P.H., David J. Karras, M.D., Mark T. Steele, M.D.,
Richard E. Rothman, M.D., Ph.D., Rebecca Hoagland, M.S.,
and Gregory J. Moran, M.D.

ABSTRACT

BACKGROUND

U.S. emergency department visits for cutaneous abscess have increased with the emergence of methicillin-resistant *Staphylococcus aureus* (MRSA). The role of antibiotics for patients with a drained abscess is unclear.

METHODS

We conducted a randomized trial at five U.S. emergency departments to determine whether trimethoprim–sulfamethoxazole (at doses of 320 mg and 1600 mg, respectively, twice daily, for 7 days) would be superior to placebo in outpatients older than 12 years of age who had an uncomplicated abscess that was being treated with drainage. The primary outcome was clinical cure of the abscess, assessed 7 to 14 days after the end of the treatment period.

RESULTS

The median age of the participants was 35 years (range, 14 to 73); 45.3% of the participants had wound cultures that were positive for MRSA. In the modified intention-to-treat population, clinical cure of the abscess occurred in 507 of 630 participants (80.5%) in the trimethoprim–sulfamethoxazole group versus 454 of 617 participants (73.6%) in the placebo group (difference, 6.9 percentage points; 95% confidence interval [CI], 2.1 to 11.7; $P=0.005$). In the per-protocol population, clinical cure occurred in 487 of 524 participants (92.9%) in the trimethoprim–sulfamethoxazole group versus 457 of 533 participants (85.7%) in the placebo group (difference, 7.2 percentage points; 95% CI, 3.2 to 11.2; $P<0.001$). Trimethoprim–sulfamethoxazole was superior to placebo with respect to most secondary outcomes in the per-protocol population, resulting in lower rates of subsequent surgical drainage procedures (3.4% vs. 8.6%; difference, –5.2 percentage points; 95% CI, –8.2 to –2.2), skin infections at new sites (3.1% vs. 10.3%; difference, –7.2 percentage points; 95% CI, –10.4 to –4.1), and infections in household members (1.7% vs. 4.1%; difference, –2.4 percentage points; 95% CI, –4.6 to –0.2) 7 to 14 days after the treatment period. Trimethoprim–sulfamethoxazole was associated with slightly more gastrointestinal side effects (mostly mild) than placebo. At 7 to 14 days after the treatment period, invasive infections had developed in 2 of 524 participants (0.4%) in the trimethoprim–sulfamethoxazole group and in 2 of 533 participants (0.4%) in the placebo group; at 42 to 56 days after the treatment period, an invasive infection had developed in 1 participant (0.2%) in the trimethoprim–sulfamethoxazole group.

CONCLUSIONS

In settings in which MRSA was prevalent, trimethoprim–sulfamethoxazole treatment resulted in a higher cure rate among patients with a drained cutaneous abscess than placebo. (Funded by the National Institute of Allergy and Infectious Diseases; ClinicalTrials.gov number, NCT00729937.)

From the Departments of Emergency Medicine (D.A.T., A.K., F.M.A., G.J.M.) and Medicine, Division of Infectious Diseases (D.A.T., G.J.M.), Olive View–UCLA Medical Center, and the Department of Emergency Medicine, Ronald Reagan Medical Center (W.R.M.), David Geffen School of Medicine, University of California, Los Angeles, Los Angeles; the Department of Emergency Medicine, Maricopa Medical Center, University of Arizona, and Mayo Graduate School of Medicine — both in Phoenix (F.L.); the Department of Emergency Medicine, Temple University Medical Center, Temple University School of Medicine, Philadelphia (D.J.K.); the Department of Emergency Medicine, Truman Medical Center, University of Missouri School of Medicine, Kansas City (M.T.S.); the Department of Emergency Medicine, Johns Hopkins Medical Center, Johns Hopkins School of Medicine, Baltimore (R.E.R.); and Cota Enterprises, McLouth, KS (R.H.). Address reprint requests to Dr. Talan at Olive View–UCLA Medical Center, 14445 Olive View Dr., North Annex, Sylmar, CA 91342, or at idnet@ucla.edu.

N Engl J Med 2016;374:823–32.

DOI: 10.1056/NEJMoa1507476

Copyright © 2016 Massachusetts Medical Society.

BETWEEN 1993 AND 2005, ANNUAL EMERGENCY department visits for skin and soft-tissue infections in the United States increased from 1.2 million to 3.4 million, primarily because of an increased incidence of abscesses.^{1,2} During this period, community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) emerged as the most common cause of purulent skin and soft-tissue infections in many parts of the world.³ Trimethoprim–sulfamethoxazole, which has retained in vitro activity against community-associated MRSA, is among the most commonly prescribed antibiotics to treat these infections.⁴

The primary treatment of a cutaneous abscess is drainage.⁵ Whether adjunctive antibiotics lead to improved outcomes in patients with uncomplicated abscesses or just more cost and side effects is unclear. Previous investigations, which had small numbers of participants, did not show a benefit of antibiotic treatment.^{6–15} Larger studies are required to show relatively small differences in cure rates, because drainage alone may result in resolution in more than 80% of cases.¹⁶ To determine the efficacy of adjunctive antibiotics, we compared outcomes among 1265 emergency department patients presenting with an uncomplicated cutaneous abscess and treated with drainage who were randomly assigned to receive trimethoprim–sulfamethoxazole or placebo.

METHODS

DESIGN

We conducted a multicenter, double-blind, randomized trial to determine whether trimethoprim–sulfamethoxazole, administered for 7 days, would be superior to placebo in emergency department patients who had a skin abscess receiving drainage and who were treated on an outpatient basis. The full protocol and statistical analysis plan are available with the full text of this article at NEJM.org. The institutional review board at each site approved the trial. Trial sites and conduct are described in the Supplementary Appendix, available at NEJM.org.

TRIAL POPULATION

From April 2009 to April 2013, we enrolled patients older than 12 years of age who had a cutaneous lesion that was suspected to be an abscess on the basis of physical examination and ultrasonography or examination alone and that was

found to have purulent material on surgical exploration. We enrolled only participants who had a lesion that had been present for less than 1 week and that measured at least 2.0 cm in diameter (as measured from the borders of induration, if the lesion was fluctuant, or from the borders of the abscess cavity on ultrasonography, if the lesion was not fluctuant), and for whom their treating clinician intended outpatient treatment. Eligible patients had to agree to return for reevaluation and to provide written informed consent. Exclusion criteria are described in the Supplementary Appendix.

INTERVENTIONS AND BASELINE EVALUATION

Before initiation of the trial, trial personnel underwent standardized training on the general technique¹⁷ and trial-specific procedures for incision and drainage (see the Supplementary Appendix). Using double-blind, Web-based randomization, we assigned participants in a 1:1 ratio to a 7-day course of trimethoprim–sulfamethoxazole (four single-strength pills, each containing 80 mg of trimethoprim and 400 mg of sulfamethoxazole, twice daily) or placebo (four pills containing microcrystalline cellulose, twice daily). The dose of trimethoprim–sulfamethoxazole was based on existing recommendations.¹⁸ We dispensed the active drug or placebo in blister packs; the first dose was taken from the participant's blister pack and administered after drainage of the abscess and before discharge from the emergency department. A participant's study-group assignment could be unblinded before the participant's completion of the trial only if the participant had a treatment failure or adverse event for which an acceptable alternative treatment could not be given and the participant's best care would be threatened if unblinding of the study-group assignment was delayed. An independent contract research organization (EMMES, Rockville, MD) that developed the randomization code performed centralized randomization, with assignments made independently at each site. Details of the randomization and blinding methods are available in the Supplementary Appendix. All medications and placebo were purchased.

We collected baseline clinical information, including the dimensions of the abscess cavity (assessed with the use of both ultrasonography and probe) and the dimensions of erythema and swelling or induration. We sent drainage specimens for standard aerobic bacterial culture and

Table 1. Definitions of Trial Populations and Outcomes among Participants with a Drained Cutaneous Abscess Who Were Assigned to Trimethoprim-Sulfamethoxazole or Placebo.*

Population	Description	Outcome Definition
Modified intention-to-treat 1	Participants who took at least one dose of the active drug or placebo and had an in-person or telephone assessment through 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 at or before the test-of-cure visit. The criteria for clinical failure were as follows: fever (attributable to the infection), an increase in the maximal dimension of erythema by >25% from baseline, or worsening of wound 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 (day 8–10); and fever or more than minimal erythema, swelling, or tenderness by the test-of-cure visit (day 14–21). 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.
Per-protocol	Participants who either took $\geq 75\%$ of the total doses of study drug or placebo during first 5 days and had an in-person test-of-cure visit or were determined to have had clinical failure before the test-of-cure visit and received $\geq 75\%$ of the doses provided during the first 48 hr of the treatment period	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.
FDAGEEP ¹⁹	Participants who received at least one dose of study drug or placebo and completed the follow-up evaluation at 48–72 hr after the start of trial treatment	A clinical response 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 the absence of fever (i.e., temperature $<37.7^{\circ}\text{C}$) on the basis of a trial clinician's assessment.
Safety	Participants who underwent randomization, received the active drug or placebo, and did not return 100% of the doses at the end of the treatment period	Adverse events were coded according to the <i>Medical Dictionary for Regulatory Activities</i> , version 17.0. Investigators categorized adverse events as related or not related to the active drug or placebo.

* All participants who were deemed by a trial clinician to have had clinical failure discontinued the trial regimen and started antibiotic treatment other than trimethoprim-sulfamethoxazole. FDAGEEP denotes Food and Drug Administration guidance early end point.

susceptibility testing at site hospitals. Investigators were not aware of the results of these tests.

OUTCOME MEASURES

We performed evaluations at follow-up visits on day 3 or 4 (during the treatment period), day 8 to 10 (end of the treatment period), day 14 to 21 (test-of-cure assessment), and day 49 to 63 (extended follow-up). We assessed adherence by inspecting blister packs for retained pills. If the participant lost the blister pack, we assessed adherence by means of the record on a memory aid (a booklet that was formatted according to date and time of dose and in which the participant recorded the doses taken) and participant interview.

Descriptions of trial populations, including the modified intention-to-treat 1 (mITT-1) population, the per-protocol population, and the Food and Drug Administration (FDA) guidance early end-point population,¹⁹ and definitions of clinical cure and clinical failure are provided in Table 1

(the definition of and results for the modified intention-to-treat 2 [mITT-2] population are provided in the Supplementary Appendix). The primary outcome was clinical cure of the abscess lesion at the test-of-cure visit (i.e., 7 to 14 days after the end of the treatment period). Participants were classified as having had a clinical cure if they did not meet the criteria for clinical failure at or before the test-of-cure visit. Standardized physical examination criteria for clinical failure were developed by investigator consensus before the initiation of the trial and varied according to the time since the participant started receiving treatment or placebo, as described in detail in Table 1. All participants who met failure criteria discontinued the treatment or placebo and started treatment with an antibiotic other than trimethoprim-sulfamethoxazole, in addition to undergoing any additional surgical drainage that was deemed necessary. For the mITT-1 analysis, participants who were lost to follow-up were considered to have had clinical failure, and

those who did not present for the test-of-cure visit but could be reached by telephone were classified as having had clinical failure if they reported new antibiotic treatment for their skin infection. Outcome-assessment methods and interrater agreement are described in the Supplementary Appendix.

Secondary outcomes were specified before trial initiation and included composite cure (i.e., resolution of all symptoms and signs of infection, or improvement such that no additional antibiotic therapy or surgical drainage procedure was necessary), surgical drainage procedures, changes in erythema size, the presence of swelling or induration and tenderness, invasive infections (i.e., sepsis, bacteremia, endocarditis, osteomyelitis, septic arthritis, necrotizing fasciitis, or pneumonia), skin infections at the same site and at a different site, hospitalizations, similar infections in household contacts, days missed from normal activities, days missed from work or school, and days that analgesics were used.

STATISTICAL ANALYSIS

We designed our trial as a superiority trial. Our primary hypothesis was that the cure rate among participants with a drained cutaneous abscess who received trimethoprim–sulfamethoxazole would be greater than the cure rate among those who received placebo. We estimated that enrollment of 590 participants would provide a power of 90% to detect an absolute between-group difference of 7.5 percentage points, assuming a cure rate of 90% in the trimethoprim–sulfamethoxazole group in the per-protocol population, at a type I error rate of 5%. During a prespecified interim analysis, the sample-size estimate was revised to 1265 participants to reflect the observed cure rate. We designated the primary analysis as the between-group difference in clinical cure rates at the test-of-cure visit in the per-protocol population and also conducted analyses in the modified intention-to-treat and FDA guidance early end-point populations. We chose to conduct the primary outcome analysis in the per-protocol population to most precisely evaluate outcomes among participants who returned for physical evaluation and treatment effects among those with good adherence with a complete treatment course. A determination of

superiority required the lower boundary of the 95% confidence interval for the between-group difference in clinical cure rates to be greater than zero. We analyzed secondary outcomes in the per-protocol population, for which relatively complete data were available, and report 95% confidence intervals of the between-group difference in outcome rates.

RESULTS

CHARACTERISTICS OF THE PATIENTS AND OF THE LESIONS

Of 1265 enrolled patients, 1247 (98.6%) were randomly assigned to trimethoprim–sulfamethoxazole or placebo and received at least one dose; 1057 participants (83.6%) qualified for the per-protocol population (Fig. 1). Of 1247 who took at least one dose, 807 (64.7%) were determined to be 100% adherent (412 in the placebo

Figure 1 (facing page). Enrollment, Randomization, and Follow-Up of Patients with a Drained Uncomplicated Cutaneous Abscess.

Participants received a 7-day course of trial therapy; follow-up visits occurred on day 3 or 4 (during the treatment period), day 8 to 10 (end of the treatment period), day 14 to 21 (test-of-cure assessment), and day 49 to 63 (extended follow-up). The safety population included participants who received the study drug or placebo and did not return 100% of the doses at the end of the treatment period. The modified intention-to-treat 1 (mITT-1) population included participants who took at least one dose of active drug or placebo and had an in-person or telephone assessment through 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. The per-protocol population included participants who either took at least 75% of the doses provided during the first 5 days of the treatment period and had an in-person test-of-cure visit or were determined to have had clinical failure before the test-of-cure visit and took at least 75% of the doses provided during the first 48 hours of the treatment period. Participants who were excluded from the per-protocol population could have more than one reason for exclusion. The Food and Drug Administration guidance early end point (FDAGEEP) population included participants who took at least one dose of trial medication and completed the follow-up evaluation at 48 to 72 hours after the study drug or placebo was initiated. For information on the modified intention to treat 2 (mITT-2) population, see the Supplementary Appendix. TMP/SMX denotes trimethoprim–sulfamethoxazole.

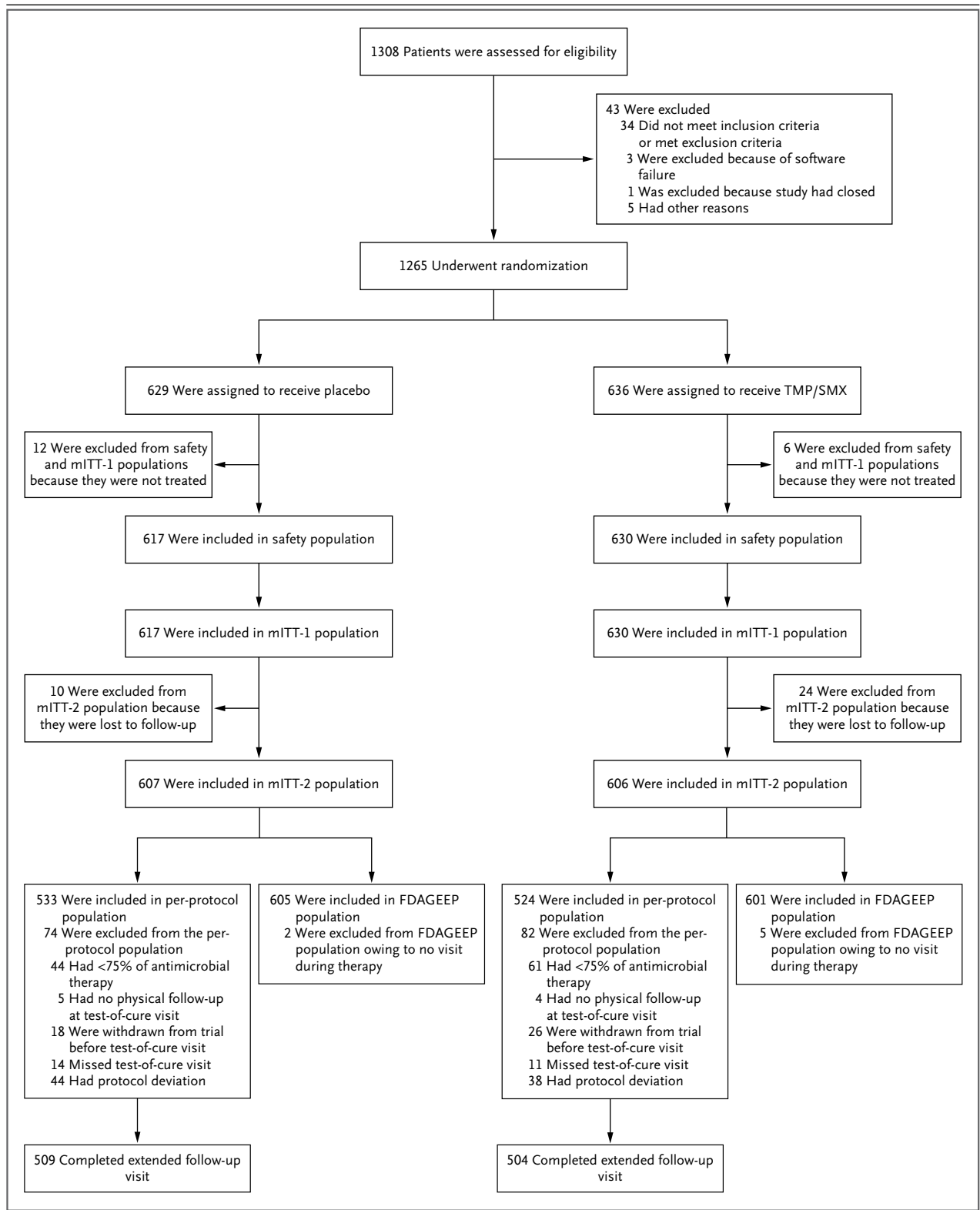


Table 2. Baseline Characteristics in the Modified Intention-to-Treat 1 Population.*

Characteristic	Trimethoprim–Sulfamethoxazole (N=630)	Placebo (N=617)
Age — yr†		
Median (IQR)	35 (26–47)	35 (26–48)
Range	14–69	16–73
Male sex — no. (%)	364 (57.8)	362 (58.7)
Days with symptoms — median (IQR)	4.0 (3.0–5.0)	4.0 (3.0–5.0)
Fever in the week before enrollment — no. (%)	116 (18.4)	113 (18.3)
History of MRSA infection — no. (%)	49 (7.8)	46 (7.5)
Diabetes — no. (%)	69 (11.0)	68 (11.0)
Eczema or other chronic skin infection — no. (%)	28 (4.4)	22 (3.6)
Close household contact with similar infection — no. (%)‡	48 (7.6)	43 (7.0)
Abscess location — no. (%)		
Head or neck	81 (12.9)	89 (14.4)
Trunk, abdomen, or back	130 (20.6)	127 (20.6)
Groin or buttocks	137 (21.7)	119 (19.3)
Arms or hands	150 (23.8)	143 (23.2)
Legs or feet	132 (21.0)	139 (22.5)
Abscess dimension measured by probe — cm		
Length§		
Median (IQR)	2.5 (2.0–3.5)	2.5 (2.0–3.5)
Range	0.5–13.0	0.1–16.0
Width		
Median (IQR)	2.0 (1.5–3.0)	2.0 (1.5–3.0)
Range	0.3–12.0	0.1–10.0
Depth		
Median (IQR)	1.5 (1.0–2.0)	1.5 (1.0–2.0)
Range	0.3–5.5	0.1–5.0
Erythema dimension — cm		
Length		
Median (IQR)	7.0 (4.3–10.0)	6.5 (4.0–10.0)
Range	1.0–42.0	2.0–38.5
Width		
Median (IQR)	5.0 (3.5–8.0)	5.0 (3.0–7.5)
Range	1.0–49.0	1.0–28.5
Area of erythema >75 cm ² — no. (%)¶	129 (20.5)	124 (20.1)
Wound culture results — no. (%)		
MRSA	274 (43.5)	291 (47.2)
Methicillin-susceptible <i>S. aureus</i>	100 (15.9)	102 (16.5)
Coagulase-negative staphylococci	80 (12.7)	61 (9.9)
Streptococcal species	41 (6.5)	22 (3.6)
Other**	104 (16.5)	69 (11.2)

* More information on baseline characteristics in this population is available in Table S1 in the Supplementary Appendix. IQR denotes interquartile range, and MRSA methicillin-resistant *Staphylococcus aureus*.

† Eight participants (0.6%) were younger than 18 years of age.

‡ Shown are participants who had close household contact with someone who had a similar skin infection in the past month.

§ Length was defined as the maximal surface dimension.

¶ Area of erythema was calculated with the use of a formula for an ellipse ($1/4 \times \pi \times \text{length} \times \text{width}$) minus the area of probe measurements of length and width of the abscess area.

|| Streptococcal species include group A streptococcus, group B streptococcus, *S. anginosus*, beta-hemolytic group C streptococcus, beta-hemolytic group F streptococcus, beta-hemolytic group G streptococcus, non-group A and non-group B beta-hemolytic streptococcus, viridans group streptococcus, and alpha-hemolytic streptococcus.

** Other isolates include actinomyces species, bacteroides species, diphtheroid bacilli, *Eikenella corrodens*, enterobacter species, enterococcus species, *Escherichia coli*, fusobacterium species, haemophilus species, klebsiella species, lactobacillus species, peptostreptococcus species, porphyromonas species, prevotella species, *Proteus mirabilis*, and veillonella species.

group and 395 in the trimethoprim-sulfamethoxazole group), and 214 (17.2%) took 76 to 99% of the doses (94 in the placebo group and 120 in the trimethoprim-sulfamethoxazole group).

Baseline characteristics in the mITT-1 population are summarized in Table 2. The median age was 35 years (range, 14 to 73), and 58.2% of the participants were male. A total of 95 participants (7.6%) had a history of MRSA infection. The median length, width, and depth of the abscesses, as measured by probe, were 2.5 cm, 2.0 cm, and 1.5 cm, respectively. The median length and width of erythema were 6.5 cm and 5.0 cm, respectively. MRSA was found in 45.3% of the participants; 97.4% of MRSA isolates were susceptible to trimethoprim-sulfamethoxazole. Of 410 MRSA isolates that were tested, 394 (96.1%) were CC8, Panton-Valentine leukocidin (PVL)-positive, and SCCmec type IV, traits that are strongly associated with pulsed-field gel electrophoresis (PFGE) type USA300.

CLINICAL CURE AND FAILURE

Clinical cure rates are summarized in Table 3 and Figure S1 in the Supplementary Appendix. The abscess cure rate was 80.5% in the trimethoprim-sulfamethoxazole group and 73.6% in the placebo group in the mITT-1 population (difference, 6.9 percentage points; 95% confidence interval [CI], 2.1 to 11.7; $P=0.005$). If we assumed that all participants in the mITT-1 population who were lost to follow-up (58 in the trimethoprim-sulfamethoxazole group and 39 in the placebo group) had a clinical cure rather than clinical failure, the cure rates would be 89.7% and 79.9%, respectively (difference, 9.8 percentage points; 95% CI, 5.7 to 13.9; $P<0.001$). In the per-protocol population, clinical cure occurred in 487 of 524 participants (92.9%) in the trimethoprim-sulfamethoxazole group versus 457 of 533 participants (85.7%) in the placebo group (difference, 7.2 percentage points; 95% CI, 3.2 to 11.2; $P<0.001$). The cure rate was significantly higher in the trimethoprim-sulfamethoxazole group than in the placebo group in the mITT-2 population but not in the FDA guidance early end-point population (i.e., participants in whom response was assessed at 48 to 72 hours). Except for two participants in the placebo group who received a subsequent diagnosis of a local invasive infection at the site of the original abscess lesion, all participants not lost to follow-up who were deemed to have had clinical failure

ultimately had a resolution of their initial skin infection.

SECONDARY OUTCOMES

Secondary outcomes in the per-protocol population are summarized in Table 4. Trimethoprim-sulfamethoxazole was superior to placebo with respect to most secondary outcomes, resulting in lower rates of subsequent surgical drainage procedures (3.4% vs. 8.6%; difference, -5.2 percentage points; 95% CI, -8.2 to -2.2), skin infections at a new site (3.1% vs. 10.3%; difference, -7.2 percentage points; 95% CI, -10.4 to -4.1), and infections among household members (1.7% vs. 4.1%; difference, -2.4 percentage points; 95% CI, -4.6 to -0.2) through the test-of-cure visit. By the test-of-cure visit (7 to 14 days after the end of the treatment period), invasive infections had developed in two participants (0.4%) in the trimethoprim-sulfamethoxazole group (unrelated to their original abscess) and in two participants (0.4%) in the placebo group (a necrotizing infection in the abdominal wall and prepatellar bursitis of the knee at the site of the original abscesses, both due to MRSA); by the extended follow-up visit (42 to 56 days after the end of the treatment period), an invasive infection had developed in one participant (0.2%) in the trimethoprim-sulfamethoxazole group (unrelated to the original abscess).

ADVERSE EVENTS

Adverse events are described in the Supplementary Appendix. Overall rates of adverse events were similar in the trimethoprim-sulfamethoxazole group and the placebo group, and most events were considered to be mild. The most common adverse events involved the gastrointestinal system (42.7% and 36.1%, respectively); no cases of *Clostridium difficile*-associated diarrhea occurred. No treatment-associated serious or life-threatening adverse events occurred. Rates of treatment discontinuation due to adverse events were also similar in the two groups (1.9% and 0.6%, respectively). There were two deaths (one in each group); they were considered to be unrelated to the active drug or placebo.

DISCUSSION

In this trial involving 1265 patients with a drained cutaneous abscess, we found that patients who received trimethoprim-sulfamethoxazole (at doses

Table 3. Cure Rates among Patients with a Drained Cutaneous Abscess in Three Trial Populations.*

Trial Population	Cure of Abscess		Difference (95% CI)	P Value†
	Trimethoprim–Sulfamethoxazole	Placebo		
	no./total no. (%)			
Modified intention-to-treat 1	507/630 (80.5)	454/617 (73.6)	6.9 (2.1 to 11.7)	0.005
Per-protocol‡	487/524 (92.9)	457/533 (85.7)	7.2 (3.2 to 11.2)	<0.001
FDAGEEP	218/601 (36.3)	204/605 (33.7)	2.6 (–3.0 to 8.1)	0.38

* CI denotes confidence interval.

† P values were calculated with a Wald asymptotic test of equality with a continuity correction.

‡ The primary outcome was clinical cure at the test-of-cure visit (7 to 14 days after the end of the 7-day treatment period) in the per-protocol population.

of 320 mg and 1600 mg, respectively, twice daily, for 7 days) had a higher cure rate than those who received placebo. We also found that many secondary outcomes were better in the trimethoprim–sulfamethoxazole group than in the placebo group, including fewer subsequent surgical drainage procedures, new skin infections, and infections among household members through 6 to 8 weeks after the end of the treatment period. Participants who received trimethoprim–sulfamethoxazole had only slightly more gastrointestinal side effects (mostly mild) than those who received placebo and had no serious or life-threatening drug-related adverse reactions.

Previous studies have not shown a benefit of adjunctive antibiotics.⁵⁻¹⁴ We are aware of two randomized, placebo-controlled trials since the emergence of community-associated MRSA that used an antibiotic active against these infections (i.e., trimethoprim–sulfamethoxazole), one involving 161 children and another involving 212 adults.^{14,15} Both studies failed to show a significant between-group difference in the short-term response rate with respect to the primary lesion.

Because cure rates with drainage alone among patients with simple abscesses may exceed 80%, studies with large sample sizes are necessary to test for small differences in response rates. Spellberg and colleagues²⁰ concluded that placebo-controlled studies suggesting an absolute advantage in cure rate with antibiotic treatment of 5 to 10 percentage points were underpowered to confirm this difference statistically. We powered our trial assuming an effect size of 7.5 percentage points and found that trimethoprim–sulfamethoxazole treatment resulted in a significantly higher abscess cure rate than did placebo.

We found that the cure rate with respect to the primary lesion was approximately 7 percent-

age points higher with trimethoprim–sulfamethoxazole than with placebo. Thus, adjunctive oral treatment with trimethoprim–sulfamethoxazole — which is inexpensive, appears to be safe, and is associated with a higher cure rate of the primary lesion than that with placebo — offers the possibility of lower rates of costly subsequent medical visits, surgeries, and hospitalizations and of new infections among patients and their household contacts. On the other hand, drainage alone was associated with a similar rate of response at 48 to 72 hours and a high overall cure rate. Trimethoprim–sulfamethoxazole can cause uncommon but serious complications such as *C. difficile* colitis, renal and electrolyte problems, drug interactions, and rare life-threatening reactions (e.g., Stevens–Johnson syndrome, at an estimated rate of 3 cases per 100,000 exposed persons²¹). Increased antibiotic use may promote bacterial resistance. A similar National Institutes of Health–funded trial (ClinicalTrials.gov number, NCT00730028) may also shed light on the efficacy of adjunctive antibiotics.

Practice guidelines for abscess treatment state that drainage is sufficient for many patients and, primarily on the basis of expert opinion, recommend adjunctive antibiotics for patients who have certain clinical or demographic characteristics, including the systemic inflammatory response syndrome, diabetes, very young or very old age, an infected site with a diameter of more than 5 cm, and surrounding cellulitis.²²⁻²⁴ Participants in this trial had typical skin abscesses, which were generally small (most only 2 to 3 cm). However, most participants had a total lesion size, including associated erythema, of more than 5 cm, and many met other guideline criteria for antibiotic treatment.

This trial has a number of limitations. First,

Table 4. Secondary Outcomes in the Per-Protocol Population.*

Outcome	Trimethoprim-Sulfamethoxazole	Placebo	Difference (95% CI) [†]
Composite clinical cure by test-of-cure visit (%) [‡]	86.5	74.3	12.2 (7.2 to 17.1)
Additional surgical drainage procedure (%)			
By test-of-cure visit	3.4	8.6	-5.2 (-8.2 to -2.2)
By extended follow-up visit	8.0	13.0	-4.9 (-8.8 to -1.1)
Hospitalization by test-of-cure visit (%)	3.6	6.4	-2.8 (-5.6 to 0.1)
Recurrent skin infection at original site (%)			
By test-of-cure visit	2.1	3.0	-0.9 (-3.0 to 1.2)
By extended follow-up visit	5.0	4.3	0.7 (-2.1 to 3.4)
New skin infection at a different site (%)			
By test-of-cure visit	3.1	10.3	-7.2 (-10.4 to -4.1)
By extended follow-up visit	10.9	19.1	-8.3 (-12.7 to -3.8)
Similar infection in household member (%)			
By test-of-cure visit	1.7	4.1	-2.4 (-4.6 to -0.2)
By extended follow-up visit	3.8	6.2	-2.4 (-5.2 to 0.4)
Presence of swelling or induration (%)			
By visit during therapy	50.3	52.7	-2.4 (-8.7 to 3.8)
By end-of-therapy visit	11.4	15.0	-3.6 (-7.9 to 0.7)
Presence of tenderness (%)			
By visit during therapy	49.0	55.9	-7.0 (-13.2 to -0.8)
By end-of-therapy visit	6.0	10.0	-4.1 (-7.5 to -0.6)
Change in mean area of erythema from baseline (cm)			
By visit during therapy	-25.5±88.4	-22.2±82.6	-3.3 (-13.7 to 7.0)
By end-of-therapy visit	-50.8±77.5	-48.7±66.0	-2.1 (-10.8 to 6.7)
Days missed from normal activities [§]	2.0±3.1	2.6±3.8	-0.5
Days missed from work or school [§]	2.2±3.1	2.4±3.4	-0.2
Days that analgesics were used [§]	6.0±4.9	6.4±4.9	-0.4

* Plus-minus values are means ±SD. Participants received a 7-day course of trial therapy; follow-up visits occurred on day 3 or 4 (during the treatment period), day 8 to 10 (end of the treatment period), day 14 to 21 (test-of-cure assessment), and day 49 to 63 (extended follow-up).

[†] Shown is the difference in percentage points or number of days.

[‡] Composite clinical cure was defined as the resolution of all symptoms and signs of infection, or improvement to such an extent that no additional antibiotic therapy or surgical drainage procedure was necessary.

[§] Data are based on participants' reports in the first 14 days.

although patients with common coexisting conditions, such as diabetes, were not excluded, physicians may have been biased against enrolling some patients who were perceived as being at higher risk. Second, although a combination of 160 mg of trimethoprim and 800 mg of sulfamethoxazole twice daily should achieve serum and blister fluid levels above MRSA minimal inhibitory concentrations,²⁵ we chose a dose of 320 mg of trimethoprim and 1600 mg of sulfamethoxazole twice daily to best test efficacy and for consistency with existing recommendations.¹⁸ Third, we had some degree of nonadherence, which would bias against trimethoprim-sulfamethoxazole, but the higher dose may have mitigated against inadequate treatment. Fourth, we provided training for adequate abscess drain-

age; however, to the extent that some abscesses may not have been fully drained, potential cure rates could be higher, particularly in the placebo group. Fifth, the standardized methods we created to determine clinical failure that necessitated a change in the study regimen may not be valid, although we are unaware of any validated method, and ours had good interrater agreement and were associated with a high cure rate among those who could be assessed by this method (i.e., the per-protocol population). Finally, significant differences between treatment groups with respect to secondary outcomes may be due to chance, although these generally favored trimethoprim-sulfamethoxazole, and, in the case of subsequent infections at new sites, were consistent with results of secondary outcome analyses

in previous studies.^{14,15} These outcomes should be further explored in future studies.

Supported by a grant from the National Institute of Allergy and Infectious Diseases (1U01 HHSN272200700032C, to Drs. Talan and Moran).

Dr. Talan reports receiving consulting and lecture fees from Actavis and fees for serving on advisory boards and grant support from Actavis and Cempra. Dr. Abrahamian reports receiving consulting fees from Cempra, Summit Therapeutics, Tetrphase Pharmaceuticals, and Janssen, lecture fees from Merck, Actavis, and the Medicines Company, and grant support from Cempra and Merck. Dr. Rothman reports receiving grant support from Cepheid. Ms. Hoagland reports that her employer performs statistical analysis and manuscript review under subcontract with EMMES. Dr. Moran reports receiving grant support from Cempra and Durata Therapeutics and being a coauthor of a manuscript about a clinical trial of a drug owned by Cubist Pharmaceuticals. 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., Hyung Koo, R.N., B.S.N., and Janie Russell at the National Institute of Allergy and Infectious Diseases; the members of the Division of Microbiology and Infectious Diseases Clinical Research Operations and Management Support (DMID-CROMS) Pharmacovigilance Group; our data and safety monitoring board — Richard Pollard, M.D., John Powers, M.D., Sheldon Kaplan, M.D., and Scott Evans, Ph.D.; Stephanie Pettibone, Thad Zajdowicz, Nancy Browning, and Ryan May at EMMES; the staff at Pharmaceutical Product Development (PPD) and ICON Clinical Research; our trial coordinators — Kavitha Pathmarajah, M.P.H., Britany Zeglin, B.S., Stephen Peterson, B.S., Mary Mulrow, R.N., M.A., M.N., Shelley Fuentes, Laurie Kemble, B.H.S., C.C.R.N., Danielle Beckham, R.N., M.S.N., Nicole Neal, R.N., Kathleen Hatala, R.N., and Carol Von Hofen, R.N.; Amy Stubbs, M.D., at the Department of Emergency Medicine, Truman Medical Center, University of Missouri School of Medicine; Valerie S. Albrecht, M.P.H., and Brandi Limbago, Ph.D., at the Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention; and the residents and staff at the participating emergency departments.

REFERENCES

- 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.
- Qualls ML, Mooney MM, Camargo CA Jr, Zucconi T, Hooper DC, Pallin DJ. Emergency department visit rates for abscess versus other skin infections during the emergence of community-associated methicillin-resistant *Staphylococcus aureus*, 1997-2007. *Clin Infect Dis* 2012;55:103-5.
- 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.
- Talan DA, Krishnadasan A, Gorwitz RJ, et al. Comparison of *Staphylococcus aureus* from skin and soft-tissue infections in US emergency department patients, 2004 and 2008. *Clin Infect Dis* 2011;53:144-9.
- Singer AJ, Talan DA. Management of skin abscesses in the era of methicillin-resistant *Staphylococcus aureus*. *N Engl J Med* 2014;370:1039-47.
- Macfie J, Harvey J. The treatment of acute superficial abscesses: a prospective clinical trial. *Br J Surg* 1977;64:264-6.
- Meislin HW, Lerner SA, Graves MH, et al. Cutaneous abscesses: anaerobic and aerobic bacteriology and outpatient management. *Ann Intern Med* 1977;87:145-9.
- Llera JL, Levy RC, Staneck JL. Cutaneous abscesses: natural history and management in an outpatient facility. *J Emerg Med* 1984;1:489-93.
- Llera JL, Levy RC. Treatment of cutaneous abscess: a double-blind clinical study. *Ann Emerg Med* 1985;14:15-9.
- 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.
- Ruhe JJ, Smith N, Bradsher RW, Menon A. Community-onset methicillin-resistant *Staphylococcus aureus* skin and soft-tissue infections: impact of antimicrobial therapy on outcome. *Clin Infect Dis* 2007;44:777-84.
- Szumowski JD, Cohen DE, Kanaya F, Mayer KH. Treatment and outcomes of infections by methicillin-resistant *Staphylococcus aureus* at an ambulatory clinic. *Antimicrob Agents Chemother* 2007;51:423-8.
- Rajendran PM, Young D, Maurer T, et al. Randomized, double-blind, placebo-controlled trial of cephalixin 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.
- 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.
- 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.
- Talan DA. Lack of antibiotic efficacy for simple abscesses: have matters come to a head? *Ann Emerg Med* 2010;55:412-4.
- Fitch MT, Manthey DE, McGinnis HD, Nicks BA, Pariyadath M. Videos in clinical medicine: abscess incision and drainage. *N Engl J Med* 2007;357(19):e20.
- Gilbert DN, Moellering RC, Eliopoulos GM, Sande MA. The Sanford guide to antimicrobial therapy. 38th ed. Sperryville, VA: Antimicrobial Therapy, 2008.
- Guidance for industry: acute bacterial skin and skin structure infections: developing drugs for treatment. Silver Spring, MD: Food and Drug Administration, Center for Drug Evaluation and Research, 2013 (<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071185.pdf>).
- Spellberg B, Boucher H, Bradley J, Das A, Talbot G. To treat or not to treat: adjunctive antibiotics for uncomplicated abscesses. *Ann Emerg Med* 2011;57:183-5.
- Chan HL, Stern RS, Arndt KA, et al. The incidence of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis: a population-based study with particular reference to reactions caused by drugs among outpatients. *Arch Dermatol* 1990;126:43-7.
- 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):e18-55.
- 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. March 2006 (<http://www.cdc.gov/mrsa/pdf/MRSA-Strategies-ExpMtgSummary-2006.pdf>).
- 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):e10-52.
- Bruun JN, Ostby N, Bredesen JE, Kierulf P, Lunde PKM. Sulfonamide and trimethoprim concentrations in human serum and skin blister fluid. *Antimicrob Agents Chemother* 1981;19:82-5.

Copyright © 2016 Massachusetts Medical Society.