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Subgroup Analysis of Antibiotic Treatment for Skin Abscesses

David A. Talan, M.D., **Gregory J. Moran, M.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.**, and **William R. Mower, M.D., Ph.D.**

Department of Emergency Medicine (D.A.T., A.K., F.M.A., G.J.M.) and Department of Medicine, Division of Infectious Diseases (D.A.T., G.J.M.), Olive View-UCLA Medical Center, David Geffen School of Medicine at UCLA, Los Angeles, CA; Department of Emergency Medicine, Ronald Reagan Medical Center, David Geffen School of Medicine at UCLA, Los Angeles, CA (W.R.M.); Department of Emergency Medicine, Maricopa Medical Center, University of Arizona and Mayo Graduate School of Medicine, Phoenix, AZ (F.L.); Department of Emergency Medicine, Temple University Medical Center, Lewis Katz School of Medicine at Temple University, Philadelphia, PA (D.J.K.); Department of Emergency Medicine, Truman Medical Center, University of Missouri-Kansas City School of Medicine, Kansas City, MO (M.T.S.); Department of Emergency Medicine, Johns Hopkins Medical Center, Johns Hopkins School of Medicine, Baltimore, MD (R.E.R.)

Abstract

Objective—Two large randomized trials recently demonstrated efficacy of MRSA-active antibiotics for drained skin abscesses. We determine whether outcome advantages observed in one trial existed across lesion sizes and among subgroups with and without guideline recommended antibiotic indications.

Corresponding author and contact information: David A. Talan, M.D., Olive View-UCLA Medical Center, 14445 Olive View Drive, North Annex, Sylmar, CA 91342, Phone: 747-210-3107, Fax: 747-210-3268, idnet@ucla.edu.

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Dr. Talan reports personal fees for consultation from Allergan, GlaxoSmithKline, and Paratek Pharmaceuticals and research grants from Allergan, Debiopharm, the Centers for Disease Control and Prevention, and the Patient Centered Outcomes Research Institute.

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Design, Setting, and Participants—We conducted a pre-planned subgroup analysis of a double-blind, randomized trial at 5 U.S. EDs demonstrating superiority of trimethoprim-sulfamethoxazole (320/1600 mg twice daily for 7 days) compared to placebo for patients >12 years of age with a drained skin abscess.

Methods—We determined between-group differences in rates of clinical (no new antibiotics) and composite cure (no new antibiotics or drainage) through 7–14 and 42–56 days after treatment among subgroups with and without abscess cavity or erythema diameter ≥5 cm, history of MRSA, fever, diabetes, and comorbidities. We also evaluated treatment effect by lesion size and culture result.

Results—Among 1057 mostly adult participants, median abscess cavity and erythema diameters were 2.5 cm (range, 0.1–16.0) and 6.5 cm (range, 1.0–38.5), respectively; 44.3% grew MRSA. Overall, for trimethoprim-sulfamethoxazole and placebo groups, clinical cure rate at 7–14 days was 92.9% and 85.7%, and composite cure rate at 7–14 was 86.5% and 74.3% and 82.4% and 70.2% at 42–56 days, respectively. For all outcomes, across lesion sizes and among subgroups with and without guideline antibiotic criteria, trimethoprim-sulfamethoxazole was associated with improved outcomes. Treatment effect was greatest with history of MRSA infection, fever, and MRSA etiology.

Conclusions—Treatment with trimethoprim-sulfamethoxazole was associated with improved outcomes regardless of lesion size or guideline antibiotic criteria.

Keywords

Abscess; small; uncomplicated; subgroup; randomized; antibiotics; trimethoprim-sulfamethoxazole; methicillin-resistant *Staphylococcus aureus*; MRSA

INTRODUCTION

Background

The primary treatment of an abscess is drainage.[1] Past studies of adjunctive antibiotic treatment, conducted before and after the emergence of community-associated methicillin-resistant *Staphylococcus aureus* (MRSA),[2] were small and did not clearly demonstrate benefit.[3–12] Recently, two large U.S. randomized placebo-controlled trials demonstrated that treatment with an antibiotic possessing in vitro activity against MRSA was associated with improved outcomes among patients with a skin abscess that received drainage and who were treated as outpatients.[13,14] The trial by Daum et al.[13] enrolled 786 patients who were assigned 1:1:1 to treatment with clindamycin, trimethoprim-sulfamethoxazole, or placebo, and the trial by Talan et al.[14] enrolled 1,265 patients assigned 1:1 to treatment with trimethoprim-sulfamethoxazole or placebo. Talan et al.[14] found significantly fewer antibiotic-treated participants required a new antibiotic through 7–14 days following treatment as well as lower rates of subsequent surgical drainage procedures and infection at a new skin site through 42–56 days following treatment.

Practice guidelines for abscess treatment issued by the U.S. Centers for Disease Control and the Infectious Diseases Society of America prior to these trials stated that drainage is sufficient for many patients.[15–17] Based primarily on expert opinion, the guidelines

recommended adjunctive antibiotics for patients with specific associated conditions, including an infected site diameter >5 cm, cellulitis, Systemic Inflammatory Response Syndrome (SIRS), diabetes, and recurrent infection. The two recent randomized trials demonstrating antibiotic efficacy included patients with a wide range of abscess cavity and surrounding erythema dimensions as well as various comorbidities, including diabetes.[13,14] The extent to which antibiotics are as efficacious for small and uncomplicated abscesses and the relative magnitude of the treatment effect in various subgroups is unclear.

Importance

Between 1993 and 2005, annual emergency department (ED) visits for skin and soft tissue infections in the U.S. increased from 1.2 to 3.4 million, primarily due to an increased incidence of abscesses.[18,19] Determining optimal treatment for affected patients is crucial to assuring rapid recovery without need for further medical interventions and promoting good antibiotic stewardship.

Goals of this investigation

Our goals were to determine the degree to which outcome advantages observed with adjunctive antibiotics for all participants in the study by Talan et al.[14] existed among subgroups with and without conditions for which antibiotics have been selectively recommended and identify patients who most benefit from treatment. Therefore, we conducted a pre-planned subgroup analysis to determine if, among these subgroups of patients, treatment with a seven-day course of trimethoprim-sulfamethoxazole was associated with higher cure rates than placebo such that no additional antibiotics or drainage procedures were required through 7–14 days and 42–56 days after treatment.

METHODS

Study design and setting

We conducted a pre-planned subgroup analysis among participants of a multicenter, double-blind, randomized trial demonstrating superiority of trimethoprim-sulfamethoxazole to placebo for treatment of patients with a skin abscess receiving incision and drainage and treated as an outpatient. The trial, full protocol, and statistical-analysis plan were previously published.[14] The institutional review board at each site approved the trial.

Selection of Participants

Inclusion criteria—From April 2009 to April 2013, we enrolled patients older than 12 years presenting to any of 5 U.S. EDs with a cutaneous lesion suspected to be an abscess based on physical examination and ultrasound, or examination alone, and found to have purulent material upon surgical exploration. We enrolled only participants with a lesion present for <1 week and measuring ≥2.0 cm in diameter (i.e., from the borders of induration, if fluctuant, or borders of abscess cavity on ultrasound, if not fluctuant), for whom their treating clinician intended outpatient treatment and who agreed to return for reevaluation and provided written consent.

Exclusion criteria—We excluded patients with the following conditions: indwelling device; suspected osteomyelitis or septic arthritis; diabetic foot, decubitus, or ischemic ulcer; mammalian bite; wound with organic foreign body; infection of another organ system or skin site; perirectal, perineal or paronychial location; intravenous drug use within previous month with fever; underlying skin condition; long-term care residence; incarceration; immunodeficiency (e.g., absolute neutrophil count <500/mm^3, immunosuppressive drugs, active chemotherapy, or known AIDS assessed by subject history); creatinine clearance <50 mL/min; cardiac condition with risk of endocarditis; allergy or intolerance to trimethoprim-sulfamethoxazole; taking warfarin, phenytoin, or methotrexate; known G-6-PD or folic acid deficiency; pregnant or lactating; trimethoprim-sulfamethoxazole treatment within 24 hours; concurrent treatment with topical or systemic antibiotic; or enrolled in the study within 12 weeks. The treating clinician decided if any laboratory testing was done.

Interventions

We randomized participants to receive a seven-day course of trimethoprim-sulfamethoxazole (4 single-strength pills, 80 mg/400 mg each, twice daily) or placebo (4 pills twice daily). Clinicians had training in standardized incision and drainage technique.[14]

Methods and Measurements

We collected participant demographic and clinical information, including history of MRSA infection and fever, co-morbidities, measured temperature in the ED, and lesion size (Table 1).

We measured abscess cavity and erythema dimension according to the following methods. After the abscess cavity was opened with a scalpel, the internal cavity was probed with the wooden end of a cotton swab or with an instrument such as a hemostat. This broke up loculations in the abscess and allowed the investigator to estimate the internal dimensions of the abscess cavity by noting how far the probe went to the edge of the abscess cavity from the center. Adding the length of the probe from the center to the edge of the abscess cavity in four directions, allowed the length and width of the abscess cavity to be measured. The depth of the abscess cavity was determined by measuring the depth to which the probe went to the bottom of the abscess cavity from the outer skin level. Some patients enrolled with an abscess estimated to be ≥2 cm were smaller upon surgical exploration.

We took all measurements of erythema while the infected area was in a nondependent position, e.g., if infection was on the leg, the subject was lying down, not sitting or standing. The border of erythema was marked with a pen. Maximal dimensions of erythema, both width and length, were recorded in centimeters. Investigators attempted to find the infection edge that best distinguished erythema from non-erythematous skin. Erythema was measured in the dimension of maximal length. The maximal width was measured perpendicular to the axis of the maximal length. The maximal width measurement did not have to be in the center if the area of erythema was irregular.

We sent purulent material from all abscesses for wound culture and susceptibility testing at local site laboratories.

Outcomes

We defined the primary outcome as the difference in abscess clinical cure rates between patients receiving trimethoprim-sulfamethoxazole and those receiving placebo. We defined clinical cure as resolution of all symptoms and signs of infection, or improvement such that no new antibiotics were prescribed through 7–14 days after the end of treatment. In the original trial, primary outcomes were reported in the modified intention-to-treat (mITT) and per-protocol (PP) populations.[14] In both the mITT and PP populations, the clinical cure rate of the trimethoprim-sulfamethoxazole group was significantly higher than that of the placebo group by about the same magnitude, i.e., 7 percentage points. Thus, for this subgroup analysis, we evaluated outcomes in the PP population, i.e., participants who returned for follow-up and had ≥75% medication adherence, whom could be most accurately assessed for outcomes and treatment effect.

We conducted subgroup analyses for three outcomes; 1 - clinical cure at 7–14 days after the end of treatment, as described above; 2 - composite cure, defined as resolution of all symptoms and signs of infection, or improvement such that no additional antibiotics and/or surgical drainage procedure were prescribed through 7–14 days after the end of treatment, and 3 - composite cure through 42–56 days after the end of treatment.

We evaluated these outcomes among subgroups defined by presence or absence of the following characteristics: abscess cavity maximal dimension ≥5 cm; erythema maximal dimension ≥5 cm; history of MRSA infection at any time in the past defined by patient report; fever defined as history of subjective or measured fever in the preceding week by patient report or measured temperature >38°C (100.4°F) in the ED; diabetes; major co-morbidities, defined as relevant serious medical conditions present in >0.5% of the PP population (i.e., diabetes, eczema or chronic edema, chronic obstructive pulmonary disease, congestive heart failure, human immunodeficiency virus infection, and cancer); and culture positive for MRSA or methicillin-susceptible *S. aureus* (MSSA). Among this population of ED patients who were felt to be stable for outpatient care, measured temperature >38°C (100.4°F) was present in <1%. Also, few patients were elderly. Therefore, we could not evaluate subgroups with SIRS and advanced age.

Analysis

We conducted separate analyses for each characteristic for each of the three outcomes described above. We pre-planned secondary assessment of the association of the presence or absence of certain conditions specified by guidelines to determine use of adjunctive antibiotics. As such, we considered all analyses exploratory and unrelated to any specific hypothesis or formal power assessment. Results are presented as point measures of the individual treatment effects (i.e., difference in cure rate among participants treated with trimethoprim-sulfamethoxazole as compared to that of participants treated with placebo) and the associated 95% confidence interval (CI). The between-group difference in cure rates as a function of maximal abscess and erythema linear dimension are presented. We plotted between-group percentage point differences in cure rates by 1 cm increments of abscess cavity or erythema dimension. For each increment, we calculated cure rates for those that had the same or smaller size lesion. We completed calculations using Microsoft® Excel 2016

(Redmond, WA) and the methods of Fleiss.[20] We excluded participants with missing values from relevant analyses.

RESULTS

Characteristics of study subjects

Of 1,265 enrolled patients 1,247 (98.6%) were randomly assigned to trimethoprim-sulfamethoxazole or placebo and received ≥1 dose, and 1,057 (83.6%) participants qualified for the PP population (Figure 1). Participant characteristics in the PP population are summarized in Table 1. Median age was 35 years, (range: 14–73) and 57.8% were male. Diabetes was present in 115 participants (10.9%) and 180 (17.0%) had a major comorbidity. Eighty-five (8.0%) participants reported a history of MRSA infection and 197 (18.6%) reported a history of fever within the preceding week while 8 (0.8%) had a temperature >38°C in the ED. Median abscess length and width were 2.5 cm (IQR, 2.0–3.5, range: 0.1–16.0) and 2.0 cm (IQR, 1.5–3.0, range: 0.1–11.0), respectively. Median length and width of erythema were 6.5 cm (IQR, 4.2–10.0, range: 1.0–38.5) and 5.0 cm (IQR 3.3–8.0, range: 1.0–40.0), respectively. MRSA was cultured from the abscess of 468 (44.3%) participants and MSSA from 172 (16.3%) participants; 461 (98.5%) MRSA isolates and 166 (96.5%) MSSA isolates demonstrated in vitro susceptibility to trimethoprim-sulfamethoxazole.

Main results

Overall, for the primary outcome, clinical cure (no new antibiotics prescribed) through 7–14 days after the end of treatment occurred in 487 of 524 participants (92.9%) in the trimethoprim-sulfamethoxazole group and 457 of 533 participants (85.7%) in the placebo group (difference, 7.2; 95% CI 3.2–11.2).[14] Composite cure (neither a new antibiotic nor an additional surgical drainage procedure) through 7–14 days occurred in 453 of 524 participants (86.5%) in the trimethoprim-sulfamethoxazole group and in 396 of 533 participants (74.3%) in the placebo group (difference, 12.2; 95% CI 7.2–17.1). Composite cure through 42–56 days occurred in 416 of 505 participants (82.4%) in the trimethoprim-sulfamethoxazole group and in 358 of 510 participants (70.2%) in the placebo group (difference, 12.2; 95%CI 6.8–17.6).

Analysis of subgroup of participants with and without high-risk conditions for which antibiotics have been recommended for rates of clinical and composite cure through 7–14 days and composite cure through 42–56 days in the trimethoprim-sulfamethoxazole and placebo groups are shown in Tables 2a, b, and c, respectively. For all three outcomes, cure rates were higher for participants treated with trimethoprim-sulfamethoxazole than for those treated with placebo in all subgroups, i.e., presence or absence of abscess cavity dimension ≥5 cm, erythema dimension ≥5 cm, past MRSA infection, fever, diabetes, or a major comorbidity. The magnitude of the difference in cure rates between the trimethoprim-sulfamethoxazole and placebo groups for all three outcomes was greater than for the whole population among subgroups with a history of MRSA infection and fever. For example, for composite cure through 42–56 days after treatment, the treatment effect for the whole PP population was 12.2 percentage points whereas it was 22.9 percentage points among participants with a history of MRSA and 16.9 percentage points among those with fever.

Based on culture results, the greatest treatment effect was associated with lesions that grew MRSA, and to a lesser degree, MSSA, as opposed to other organisms or no growth. No outcome advantage was associated with trimethoprim-sulfamethoxazole among participants who grew neither MRSA nor MSSA.

Figures 2 and 3 show the between -group percentage point differences in cure rates among the treatment groups by abscess cavity and erythema maximal dimension, further illustrating that the outcome advantage associated with trimethoprim-sulfamethoxazole existed across all lesion sizes.

LIMITATIONS

This trial has limitations. The original trial was not powered to detect a treatment effect in groups other than in the primary outcome population. A significant treatment effect was generally observed among participants with and without high-risk conditions, however, in a few subgroups, the 95%CI of the difference in cure rates crossed 0, which may be a result of small subgroup sizes. Further, multiple comparisons were conducted, which leads to a greater likelihood of observing positive associations due to chance. Analyses were conducted using the PP population for whom follow-up status was available. Although the participant characteristics and magnitude of the treatment effect in the PP and mITT populations were similar, it is possible that the PP population was affected by post-randomization bias. Only patients with a maximal abscess cavity diameter estimated to be ≥2 cm based on physical examination or ultrasound were enrolled. Therefore, our results do not apply to patients with smaller lesions and other conditions that led to ineligibility.

DISCUSSION

Two recent large randomized trials demonstrated the efficacy of adjunctive antibiotics possessing activity against methicillin-resistant *Staphylococcus aureus* (MRSA) for treatment of patients with a drained skin abscess.[13,14] This subgroup analysis was pre-planned to test the validity of guidelines for use of adjunctive antibiotics for a drained skin abscess among the largest reported trial population, which mostly consisted of adults.[14] Although exploratory, these results support adjunctive antibiotic treatment for the small uncomplicated skin abscesses estimated to be at least 2 cm diameter by physical examination or ultrasound. A consistent treatment effect was associated with trimethoprim-sulfamethoxazole treatment among patients with small abscess and erythema size and lacking any condition for which antibiotics have been selectively recommended,[15–17] including history of MRSA infection, fever, diabetes, and other co-morbidities. The findings of a treatment effect among participants with an abscess size <5 cm and those without diabetes are consistent with the results of the trial by Daum et al.[13], in which pediatric and adult patients with small abscesses of no minimum size were enrolled but those with larger abscesses (i.e., >5 cm for adults and >3–4 cm for children) and diabetes were excluded. The treatment effect was observed across all dimensions of abscess cavity and associated erythema. Together, the two trials suggest that adjunctive antibiotics improve cure rates for a drained uncomplicated skin abscess of any size.

Trimethoprim-sulfamethoxazole is highly active against staphylococci, with 97.4% of study MRSA isolates tested demonstrating *in vitro* susceptibility.[14] The treatment effect was highly associated with culture of MRSA, and to a lesser degree, MSSA. No treatment effect was found with lesions that grew other organisms or had no growth, a result also found in the trial by Daum et al., supporting the role of antibiotics to treat the bacterial tissue infection once the abscess has been drained. Non-*S. aureus* lesions may largely represent inflamed but non-infected cysts, with negative cultures or growth representing skin contamination. Daum et al.[13] also found that the cure rate of participants treated with clindamycin was lower among those for which the staphylococcal isolate demonstrated in vitro resistance as opposed to susceptibility, further supporting this biological model. Specimen Gram stain or more recently available rapid polymerase chain reaction-based assays of drainage material to identify staphylococcal infections potentially could guide treatment decisions.

Among all participants, through 42–56 days after treatment, recurrent infection at a new site occurred in 19.1% of the placebo group compared to 10.9% of the trimethoprim-sulfamethoxazole group.[14] The composite cure outcome through 42–56 days after treatment captured all initial treatment failures and subsequent infections that required either a new antibiotic or drainage procedure. The treatment effect associated with trimethoprim-sulfamethoxazole extended through 42–56 days in all clinical subgroups. Further, history of MRSA infection and abscesses that grew MRSA were associated with a greater magnitude of treatment benefit compared to that of the entire study population. These observations suggest that trimethoprim-sulfamethoxazole may reduce MRSA colonization for several weeks following initial treatment.

The outcome advantage associated with trimethoprim-sulfamethoxazole existed across the range of abscess or erythema dimensions. However, the presence of certain characteristics identified by guidelines[15–17] as criteria for antibiotic treatment, i.e., history of MRSA infection and fever, was associated with the greatest treatment effect. For the entire study population, there was a 12.2 percentage point higher rate of neither requiring a new antibiotic nor drainage procedure through 42–56 days after treatment. This difference was 22.9 percentage points among participants with history of MRSA infection and 16.9 percentage points among those with history of fever in the preceding week or measured elevated temperature in the ED.

Further studies could attempt to validate these subgroup treatment effect associations and further inform shared decisionmaking with patients about benefit, risk, and cost associated with the decision to provide adjunctive antibiotics. However, it may be difficult to accrue a sufficient number of patients in these subgroups. Trimethoprim-sulfamethoxazole is off-patent and, currently, a full course costs about $5 USD. Its use was associated with only slightly more mild gastrointestinal side effects than placebo[14], although, this antibiotic is rarely associated with serious adverse reactions, such as Stephens-Johnson syndrome.[21] The trial had inadequate power to detect either an increased rate of rare antibiotic-related adverse effects or a decreased rate of subsequent invasive infections compared to placebo. The study by Daum et al. demonstrated efficacy of clindamycin 150 mg three times daily and trimethoprim-sulfamethoxazole 160 mg/800 mg twice daily compared to placebo.[13] The

trimethoprim-sulfamethoxazole dose was half that used in our trial, and the Daum et al. treated for 10 days, while we treated for 7 days. This investigation also found that adverse events were approximately twice as frequent with clindamycin compared to trimethoprim-sulfamethoxazole. Neither trial detected any cases of *Clostridium difficile* colitis. The costs and risks associated with adjunctive antibiotic treatment must be weighed against those associated with the care and consequences of treatment failure and recurrence.

CONCLUSIONS

This subgroup analysis of the largest reported trial comparing antibiotics to placebo for patients with a drained skin abscess found that trimethoprim-sulfamethoxazole treatment was associated with improved outcomes regardless of abscess or erythema size or the presence or absence of conditions for which antibiotics have been selectively recommended, including history of MRSA infection, fever, diabetes, and major comorbidities. The magnitude of the treatment effect was greatest among subgroups with a history of MRSA infection or fever, and for those with an abscess due to MRSA.

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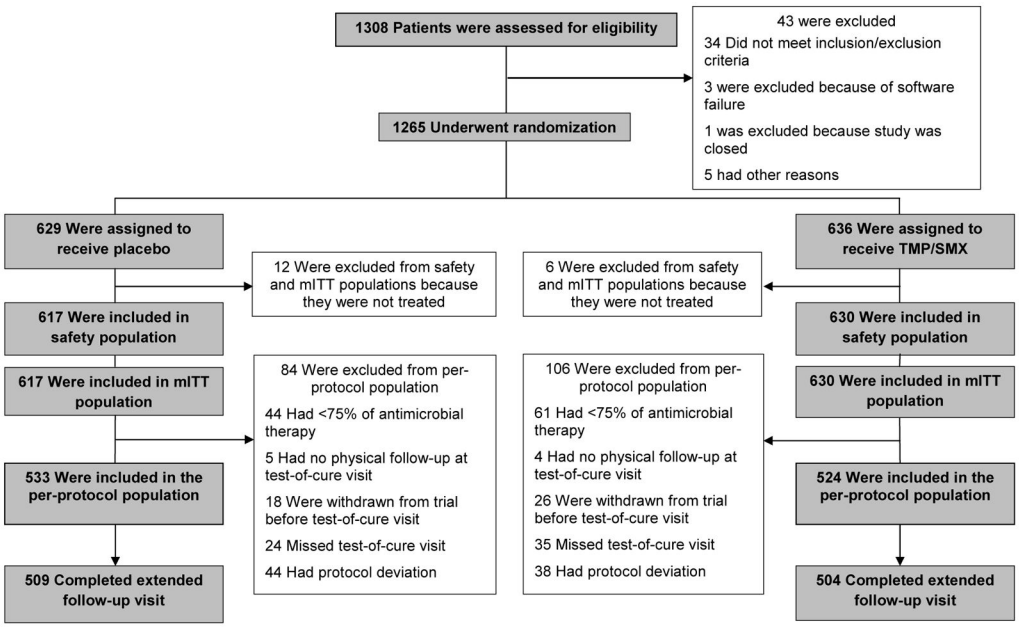

Figure 1.

Enrollment, Randomization, and Follow-Up of Patients with a Drained Skin Abscess Treated with Trimethoprim-Sulfamethoxazole or Placebo.

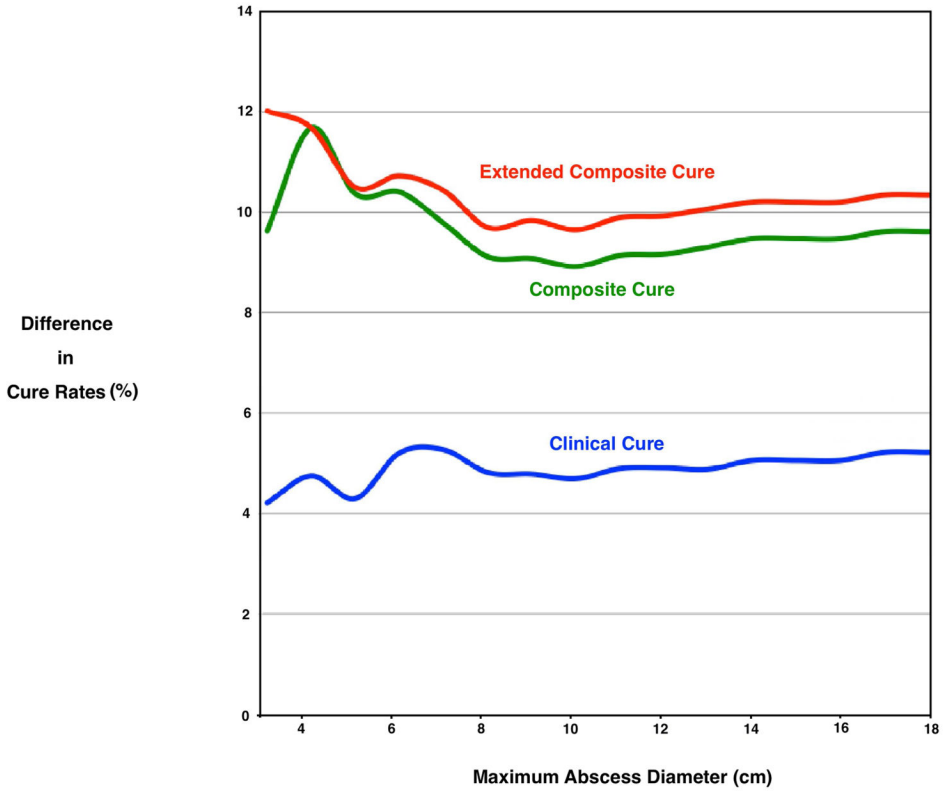

Figure 2.

Difference in Cure Rates* by Abscess Cavity Diameter† Among Participants with a Drained Skin Abscess Treated with Trimethoprim-Sulfamethoxazole Compared to Placebo.

Overall, for trimethoprim-sulfamethoxazole and placebo groups, clinical cure rate at 7–14 days was 92.9% and 85.7% (difference, 7.2; 95% CI 3.2–11.2), composite cure rate at 7–14 was 86.5% and 74.3% (12.2; 95% CI 7.2–17.1) and extended composite cure at 42–56 days was 82.4% and 70.2% (difference, 12.2; 95% CI 6.8–17.6), respectively.

* The between–group percentage point differences in cure rates were plotted by 1 cm increments of abscess cavity or erythema dimension. For each increment, cure rates were calculated for those that had the same or smaller size lesion. Outcomes were defined as follows: clinical cure was defined as resolution of all symptoms and signs of infection, or improvement such that no new antibiotics were prescribed (through 7–14 days after the end of treatment); composite cure was defined as resolution of all symptoms and signs of infection, or improvement such that no additional antibiotics and/or surgical drainage procedure were required (through 7–14 days and 42–56 days after the end of treatment).

†Diameter was defined as the maximal linear dimension (length or width) of the abscess cavity, by probe after incision, and erythema, measured on the skin.

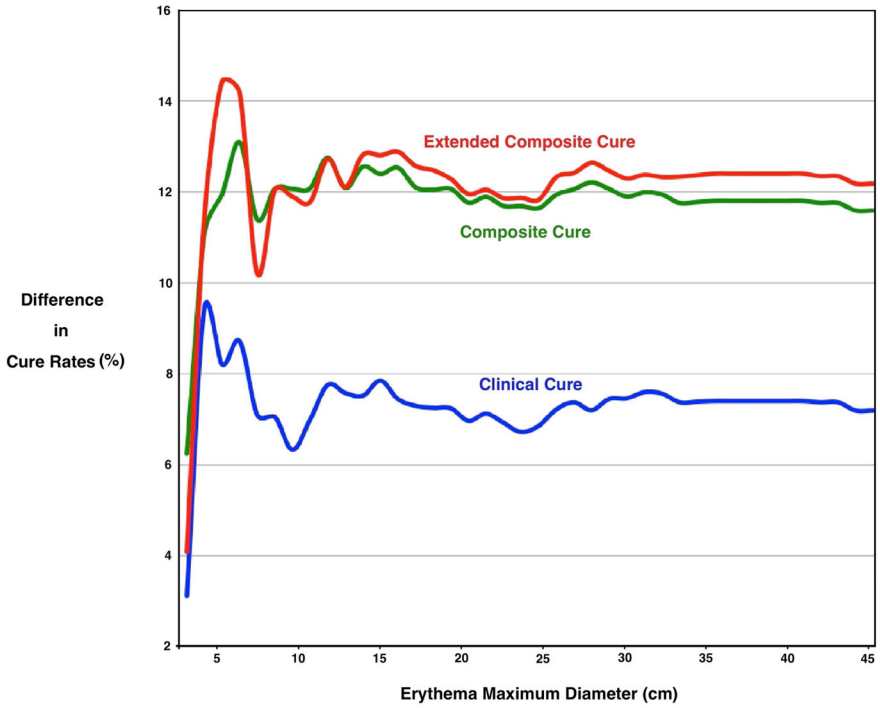

Figure 3.

Difference in Cure Rates* by Erythema Diameter† Among Participants with a Drained Skin Abscess Treated with Trimethoprim-Sulfamethoxazole Compared to Placebo.

Overall, for trimethoprim-sulfamethoxazole and placebo groups, clinical cure rate at 7–14 days was 92.9% and 85.7% (difference, 7.2; 95% CI 3.2–11.2), composite cure rate at 7–14 was 86.5% and 74.3% (12.2; 95% CI 7.2–17.1) and extended composite cure at 42–56 days was 82.4% and 70.2% (difference, 12.2; 95% CI 6.8–17.6), respectively.

* The between-group percentage point differences in cure rates were plotted by 1 cm increments of abscess cavity or erythema dimension. For each increment, cure rates were calculated for those that had the same or smaller size lesion. Outcomes were defined as follows: clinical cure was defined as resolution of all symptoms and signs of infection, or improvement such that no new antibiotics were prescribed (through 7–14 days after the end of treatment); composite cure was defined as resolution of all symptoms and signs of infection, or improvement such that no additional antibiotics and/or surgical drainage procedure were required (through 7–14 days and 42–56 days after the end of treatment).

†Diameter was defined as the maximal linear dimension (length or width) of the abscess cavity, by probe after incision, and erythema, measured on the skin.

Table 1

Baseline Characteristics of Participants with a Drained Skin Abscess Treated with Trimethoprim-Sulfamethoxazole or Placebo in the Per-Protocol Population.

Characteristic	Trimethoprim- sulfamethoxazole (n=524)	Placebo (n=533)
Median age, years (IQR, range) *	35 (26–47.5, 14–69)	35 (26–48, 16–73)
Male Sex – n (%)	303 (57.8)	308 (57.8)
Race – n (%)		
White	244 (46.6)	252 (47.3)
Black	232 (44.3)	233 (43.7)
Asian	5 (1.0)	2 (0.4)
Hawaiian/Pacific Islander	0 (0.0)	1 (0.2)
American Indian/Alaskan Native	3 (0.6)	2 (0.4)
Multi-Racial	22 (4.2)	22 (4.1)
Other/Unknown	18 (3.4)	21 (3.9)
Hispanic Ethnicity - n (%)	178 (34.0)	180 (33.8)
Median (IQR) number of days symptoms	4.0 (3.0–5.0)	4.0 (3.0–5.0)
History of methicillin-resistant *Staphylococcus aureus* (MRSA) infection	45 (8.6)	40 (7.5)
Comorbidities † – n (%)		
Cancer	6 (1.1)	3 (0.6)
CHF	5 (1.0)	4 (0.8)
COPD	6 (1.1)	6 (1.1)
Chronic edema	3 (0.6)	1 (0.2)
Diabetes	58 (11.1)	57 (10.7)
Eczema	22 (4.2)	14 (2.6)
HIV+	7 (1.3)	10 (1.9)
Any of the above	92 (17.6)	88 (16.5)
Abscess related to IV drug use – n (%)	20 (3.8)	13 (2.4)
History of prior antibiotic treatment for skin and soft tissue infection – n (%)	2 (0.4)	4 (0.8)
Close household contact ‡ – n (%)	37/520 (7.1)	39/529 (7.4)
Fever § - n (%)	102/520 (19.6)	98/528 (18.6)
Abscess location – n (%)		
Head/neck	68 (13.0)	78 (14.6)
Trunk/Abdomen/Back	116 (22.1)	108 (20.3)
Groin/Buttocks	113 (21.6)	102 (19.1)

Characteristic	Trimethoprim- sulfamethoxazole (n=524)	Placebo (n=533)
Upper Extremity	117 (22.3)	118 (22.1)
Lower Extremity	110 (21.0)	127 (23.8)
Median abscess dimension by probe of abscess cavity, cm (IQR, range)		
Length[//]	2.5 (2.0–3.5,0.5–13.0)	2.5 (2.0–3.5,0.1–16.0)
Width	2.0 (1.5–3.0,0.3–11.0)	2.0 (1.5–3.0,0.1–10.0)
Depth	1.5 (1.0–2.0,0.3–5.5)	1.5 (1.0–2.0, 0.1–5.0)
Abscess cavity maximal dimension[//] ≥ 5 cm – n (%)	78/523 (14.9)	72/533 (13.5)
Median erythema dimension, cm (IQR, range)		
Length	6.8 (4.5–10.0,1.0–32.0)	6.5 (4.0–10.0,2.0–38.5)
Width	5.0 (3.2–8.0,1.0–40.0)	5.0 (3.4–8.0,1.0–28.5)
Area[//¶]	19.7 (7.0–54.4,0.0–582.8)	21.2 (7.1–55.4,0.0–520.9)
Area[//] of erythema >75 cm^2 – n (%)	107 (20.4)	110 (20.6)
Erythema maximal dimension[//] ≥ 5 cm – n (%)	390 (74.4)	399 (74.9)
Median dimensions of induration/swelling, cm (IQR, range)		
Length	4.5 (3.5–6.5,1.0–19.0)	4.5 (3.2–6.0,0.5–20.0)
Width	4.0 (3.0–5.0,1.0–16.0)	4.0 (3.0–5.0,0.9–29.0)
Area[¶]	7.5 (2.8–18.3,0.0–198.5)	8.2 (2.8–18.1,0.0–396.6)
Baseline wound culture results		
Methicillin-resistant *Staphylococcus aureus*	219 (41.8)	249 (46.7)
Methicillin-susceptible *S. aureus*	86 (16.4)	86 (16.1)
Coagulase-negative staphylococci	68 (13.0)	59 (11.1)
Streptococcal species[**]	36 (6.9)	14 (2.6)
Other[#]	87 (16.6)	63 (11.8)
No growth	80 (15.3)	93 (17.4)
Not done	3 (0.6)	3 (0.6)

Participants with missing data were excluded from relevant analyses.

[*] Eight (0.8%) participants were age 13 to 17 years.

[†] Co-morbidities were those present in >0.5%.

[‡] A close household contact was defined as someone living in the same household with similar skin infection in last month.

[§] Fever was defined as patient report of history of fever in prior week or temperature >38°C in the ED.

[//] Largest measurement of length or width was defined as the maximal dimension.

[¶] Areas of erythema and induration/swelling were calculated using formula for an ellipse (1/4 x πx length x width) minus area of probe measurements of length and width of abscess area.

[**] Streptococcal species included: 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 B beta-hemolytic streptococcus, Viridans group streptococcus, and Alpha-hemolytic streptococcus.

[#] Other isolates included: *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.

Table 2

Table 2a. Subgroup Analysis of Clinical Cure* Rates Through 7–14 days for Participants with a Drained Skin Abscess Treated with Trimethoprim-Sulfamethoxazole or Placebo by Presence or Absence of High-Risk Conditions.

Condition	Cure (n/total no. [%])		Difference (95% CI)
	Trimethoprim- sulfamethoxazole	Placebo	
Abscess cavity ≥5 cm	69/77 (89.6)	54/71 (76.1)	14.7 (1.4 – 28.1)
Abscess cavity <5 cm†	418/446 (93.7)	403/462 (87.2)	6.1 (2.1 – 10.1)
Erythema ≥5 cm	357/390 (91.5)	338/399 (84.7)	6.8 (2.1 – 11.6)
Erythema <5 cm†	130/134 (97.0)	119/134 (88.8)	8.2 (1.4 – 15.0)
History of MRSA infection	43/45 (95.6)	32/40 (80.0)	15.6 (−0.6 – 31.7)
No history of MRSA infection	444/479 (92.7)	425/493 (86.2)	6.5 (2.4 – 10.5)
Fever‡	93/102 (91.2)	78/98 (79.6)	14.3 (3.7 – 24.9)
No fever	391/418 (93.5)	374/430 (87.0)	5.9 (1.7 – 10.1)
Diabetes	50/58 (86.2)	47/57 (82.5)	3.8 (−11.3 – 18.8)
No diabetes	437/466 (93.8)	410/476 (86.1)	7.6 (3.6 – 11.7)
Co-morbidity§	83/92 (90.2)	73/88 (83.0)	8.4 (−2.8 – 19.6)
No co-morbidity	404/432 (93.5)	384/445 (86.3)	7.0 (2.8 – 11.2)
MRSA‖	203/219 (92.7)	202/249 (81.1)	11.6 (5.2 – 18.0)
MSSA	78/86 (90.7)	71/86 (82.6)	8.1 (−3.1 – 19.4)
No MRSA or MSSA	203/216 (94.0)	181/195 (92.8)	1.2 (−4.1 – 6.5)

Table 2b. Subgroup Analysis of Composite Cure* Rates Through 7–14 days Among Participants with a Drained Skin Abscess Treated with Trimethoprim-Sulfamethoxazole or Placebo by Presence or Absence of High-Risk Conditions.

Condition	Cure (n/total no. [%])		Difference (95% CI)
	Trimethoprim- sulfamethoxazole	Placebo	
Abscess cavity ≥5 cm	62/77 (80.5)	51/71 (71.8)	8.5 (−6.3 – 23.4)
Abscess cavity <5 cm†	391/446 (87.7)	345/462 (74.7)	12.2 (7.0 – 17.4)
Erythema ≥5 cm	335/390 (85.9)	295/399 (73.9)	11.5 (5.7 – 17.2)
Erythema <5 cm†	118/134 (88.1)	101/134 (75.4)	11.9 (2.1 – 21.8)
History of MRSA infection	40/45 (88.9)	24/40 (60.0)	28.9 (8.8 – 49.0)
No history of MRSA infection	413/479 (86.2)	372/493 (75.5)	10.2 (5.1 – 15.2)
Fever‡	83/102 (81.4)	64/98 (65.3)	18.4 (5.4 – 31.3)
No fever	368/418 (88.0)	329/430 (76.5)	10.2 (4.9 – 15.5)
Diabetes	44/58 (75.9)	36/57 (63.2)	10.9 (−7.4 – 29.3)
No diabetes	409/466 (87.8)	360/476 (75.6)	11.7 (6.7 – 16.8)
Co-morbidity§	71/92 (77.2)	55/88 (62.5)	13.5 (−0.8 – 27.9)
No co-morbidity	382/432 (88.4)	341/445 (76.6)	11.3 (6.2 – 16.5)
MRSA‖	186/219 (84.9)	163/249 (65.5)	18.3 (10.3 – 26.2)

Table 2b. Subgroup Analysis of Composite Cure* Rates Through 7–14 days Among Participants with a Drained Skin Abscess Treated with Trimethoprim-Sulfamethoxazole or Placebo by Presence or Absence of High-Risk Conditions.

Condition	Cure (n/total no. [%])		Difference (95% CI)
	Trimethoprim- sulfamethoxazole	Placebo	
MSSA	72/86 (83.7)	63/86 (73.3)	10.5 (−2.9 – 23.8)
No MRSA or MSSA	192/216 (88.9)	167/195 (85.6)	3.24 (−3.7 – 10.2)

Table 2c. Subgroup Analysis of Composite Cure* Rates Through 42–56 days Among Participants with a Drained Skin Abscess Treated with Trimethoprim-Sulfamethoxazole or Placebo by Presence or Absence of High-Risk Conditions.

Condition	Cure (n/total no. [%])		Difference (95% CI)
	Trimethoprim-sulfamethoxazole	Placebo	
Abscess cavity ≥5 cm	55/70 (78.6)	47/70 (67.1)	11.4 (−4.61 – 27.5)
Abscess cavity <5 cm†	361/434 (83.2)	311/440 (70.7)	12.5 (6.75 – 18.2)
Erythema >5 cm	307/376 (81.6)	269/383 (70.2)	11.4 (5.13 – 17.7)
Erythema <5 cm†	109/129 (84.5)	89/127 (70.1)	14.4 (3.51 – 25.3)
History of MRSA infection	33/43 (76.7)	21/39 (53.8)	22.9 (0.34 – 45.4)
No history of MRSA infection	383/462 (82.9)	337/471 (71.5)	11.4 (5.81 – 16.9)
Fever‡	76/98 (77.6)	57/94 (60.6)	16.9 (2.99 – 30.8)
No fever	338/403 (83.9)	299/412 (72.6)	11.3 (5.44 – 17.2)
Diabetes	38/56 (67.9)	36/56 (64.3)	3.57 (−15.7 – 22.9)
No diabetes	378/449 (84.2)	322/454 (70.9)	13.3 (7.67 – 18.9)
Co-morbidity§	61/88 (69.3)	54/86 (62.8)	6.53 (−8.7 – 21.7)
No co-morbidity	355/417 (85.1)	304/424 (71.7)	13.4 (7.71 – 19.2)
MRSA‖	166/208 (79.8)	139/235 (59.2)	20.7 (11.9 – 29.4)
MSSA	71/85 (83.5)	57/82 (69.5)	14.0 (0.11 – 27.9)
No MRSA or MSSA	176/209 (84.2)	160/190 (84.2)	0.0 (−7.71 – 7.71)

Abbreviations: MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *S. aureus*

*Overall, for trimethoprim-sulfamethoxazole and placebo groups, clinical cure rate at 7–14 days was 92.9% and 85.7% (difference, 7.2; 95% CI 3.2–11.2), composite cure rate at 7–14 was 86.5% and 74.3% (difference, 12.2; 95% CI 7.2–17.1) and extended composite cure at 42–56 days was 82.4% and 70.2% (difference, 12.2; 95% CI 6.8–17.6), respectively. Outcomes were defined as follows: clinical cure was defined as resolution of all symptoms and signs of infection, or improvement such that no new antibiotics were prescribed (through 7–14 days after the end of treatment); composite cure was defined as resolution of all symptoms and signs of infection, or improvement such that no additional antibiotics and/or surgical drainage procedure were required (through 7–14 days and 42–56 days after the end of treatment).

†Abscess cavity and erythema dimensions were defined as the maximal dimension (length or width).

‡Fever was defined as history of fever within the preceding week or temperature >38°C measured in the ED (0.8%).

§Co-morbidities were defined as those present in >0.5% of study participants: diabetes (10.9%); eczema or other chronic skin condition (3.4%); chronic obstructive pulmonary disease (1.1%); congestive heart failure (0.9%); human immunodeficiency virus infection (1.6%); and cancer (0.9%).

‖Culture results were those based on the organism isolated from primary wound specimen.