Title

A Randomized Trial of Clindamycin Versus Trimethoprim-sulfamethoxazole for Uncomplicated Wound Infection

Journal

Clinical Infectious Diseases, 62(12)

ISSN

1058-4838

Authors

Talan, David A
Lovecchio, Frank
Abrahamian, Fredrick M
et al.

Publication Date

2016-06-15

DOI

10.1093/cid/ciw177

Peer reviewed

Clinical Infectious Diseases

MAJOR ARTICLE

A Randomized Trial of Clindamycin Versus Trimethoprim-sulfamethoxazole for Uncomplicated Wound Infection

David A. Talan,[1,2] Frank Lovecchio,[3] Fredrick M. Abrahamian,[1] David J. Karras,[4] Mark T. Steele,[5] Richard E. Rothman,[6] Anusha Krishnadasan,[1] William R. Mower,[7] Rebecca Hoagland,[8] and Gregory J. Moran[1,2]

[1]Department of Emergency Medicine, and [2]Division of Infectious Diseases, Department of Medicine, Olive View–UCLA Medical Center, David Geffen School of Medicine at UCLA; [3]Department of Emergency Medicine, Maricopa Medical Center, University of Arizona and Mayo Graduate School of Medicine, Phoenix; [4]Department of Emergency Medicine, Temple University Medical Center, Temple University School of Medicine, Philadelphia, Pennsylvania; [5]Department of Emergency Medicine, Truman Medical Center, University of Missouri–Kansas City School of Medicine; [6]Department of Emergency Medicine, Johns Hopkins Medical Center, Johns Hopkins School of Medicine, Baltimore, Maryland; [7]Department of Emergency Medicine, Ronald Reagan Medical Center, David Geffen School of Medicine at UCLA; and [8]Cota Enterprises, Inc, McLouth, Kansas

Background. With the emergence of community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) in the United States, visits for skin infections greatly increased. Staphylococci and streptococci are considered predominant causes of wound infections. Clindamycin and trimethoprim-sulfamethoxazole (TMP-SMX) are commonly prescribed, but the efficacy of TMP-SMX has been questioned.

Methods. We conducted a randomized, double-blind, superiority trial at 5 US emergency departments. Patients >12 years of age with an uncomplicated wound infection received oral clindamycin 300 mg 4 times daily or TMP-SMX 320 mg/1600 mg twice daily, each for 7 days. We compared the primary outcome, wound infection cure at 7–14 days, and secondary outcomes through 6–8 weeks after treatment, in the per-protocol population.

Results. Subjects had a median age of 40 years (range, 14–76 years); 40.1% of wound specimens grew MRSA, 25.7% methicillin-susceptible *S. aureus*, and 5.0% streptococci. The wound infection was cured at 7–14 days in 187 of 203 (92.1%) clindamycin-treated and 182 of 198 (91.9%) TMP-SMX–treated subjects (difference, 0.2%; 95% confidence interval [CI], −5.8% to 6.2%; P = not significant). The clindamycin group had a significantly lower rate of recurrence at 7–14 days (1.5% vs 6.6%; difference, −5.1%; 95% CI, −9.4% to −.8%) and through 6–8 weeks following treatment (2.0% vs 7.1%; difference, −5.1%; 95% CI, −9.7% to −.6%). Other secondary outcomes were statistically similar between groups but tended to favor clindamycin. Adverse event rates were similar.

Conclusions. In settings where MRSA is prevalent, clindamycin and TMP-SMX produce similar cure and adverse event rates among patients with an uncomplicated wound infection. Further study evaluating differential effects of antibiotics on recurrent infection may be warranted.

Clinical Trials Registration. NCT00729937.

Keywords. wound infection; randomized; trimethoprim-sulfamethoxazole; clindamycin; methicillin-resistant *Staphylococcus aureus*.

Between 1993 and 2005, US annual emergency department visits for skin and soft tissue infection (SSTI) increased from 1.2 to 3.4 million, with most patients discharged on oral antibiotics [1]. During this period, community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) emerged as the most common cause of purulent SSTIs in many parts of the world [2].

In 2010, the US Food and Drug Administration (FDA) revised its guidance to industry for the development of drugs to treat SSTI [3]. For the first time, the FDA subdivided SSTI into categories of abscess, cellulitis, and wound infection. Surgical drainage is the primary treatment for an abscess, whereas antimicrobial treatment is paramount for cellulitis and wound infections. For cellulitis, the cause is typically unknown but presumed to be often due to *Streptococcus pyogenes*. For wound infections, a diagnostic culture specimen can usually be obtained. The guidance defined wound infection as "characterized by purulent drainage from a wound with surrounding redness, edema, and/or induration." The guidance was for SSTIs with an area of >75 cm^2, referred to as acute bacterial skin and skin structure infections (ABSSSIs), and has been used to evaluate new parenteral antimicrobials and oral oxazolidinones [4–6].

In the United States, CA-MRSA is frequently isolated from infected wounds with purulent drainage [2, 7]. Clindamycin and trimethoprim-sulfamethoxazole (TMP-SMX) have generally retained in vitro activity against CA-MRSA and are

Received 25 January 2016; accepted 7 March 2016; published online 29 March 2016.

Correspondence: D. A. Talan, Olive View–UCLA Medical Center, 14445 Olive View Drive, North Annex, Sylmar, CA 91342 (idnet@ucla.edu).

Clinical Infectious Diseases® 2016;62(12):1505–13

DOI: 10.1093/cid/ciw177

commonly prescribed off-patent oral antibiotics for SSTI [2, 7]. One large observational trial of patients with SSTI found that the risk of treatment failure with TMP-SMX treatment was more than twice that of clindamycin [8]. It has been observed that TMP-SMX's activity against *S. aureus* is interfered with by tissue factors [9] and that it has inferior in vitro activity against *S. pyogenes* [10].

There are limited comparative effectiveness data evaluating commonly used off-patent oral antibiotics for the treatment of patients with SSTI [11]. Therefore, we compared outcomes among 500 emergency department patients presenting with an uncomplicated wound infection who were randomized to clindamycin or TMP-SMX. We tested the hypothesis that the wound infection cure rate among clindamycin-treated subjects would be greater than that of TMP-SMX–treated subjects.

METHODS

Design

We conducted a multicenter, double-blind, randomized trial to determine whether a 7-day course of clindamycin led to superior outcomes compared to TMP-SMX for treatment of emergency department patients with an uncomplicated wound infection. The full protocol and statistical analysis plan are available in the Supplementary Appendix. Each institutional review board approved the study. Study sites and conduct are described in the Supplementary Appendix.

Participants

From May 2009 to October 2012, we enrolled patients >12 years of age with an uncomplicated infected wound for whom their treating clinician intended outpatient treatment and who agreed to return for reevaluation and provided written consent. Wounds (defined as any break in the skin limited in depth to only involving skin and subcutaneous tissue) had to have erythema, tenderness, and swelling, be ≥2 cm in diameter, with symptoms of <1 week's duration. Sutured cutaneous wounds not potentially involving bowel flora (eg, intra-abdominal surgeries) were included provided sutures were to be removed upon enrollment. All subjects had soft tissue ultrasound; if a fluid collection was detected, drainage was conducted. We excluded patients with the following conditions: infection associated with an indwelling device (eg, intravenous catheter); suspected osteomyelitis or septic arthritis; diabetic foot, decubitus, or ischemic ulcer; mammalian bite; wound with organic foreign body; infection of another organ system/site; perirectal, perineal, or paronychial location; intravenous drug use within previous month and fever; infection involving an area of an underlying skin condition; long-term care residence; incarceration; immunodeficiency (eg, absolute neutrophil count <500 cells/μL, immunosuppressive drugs, active chemotherapy, or known AIDS assessed by subject history); creatinine clearance <50 mL/minute; cardiac condition with risk of endocarditis; history of severe liver disease; allergy or intolerance to clindamycin or TMP-SMX; history of *Clostridium difficile* infection, pseudomembranous colitis, or active diarrhea; taking warfarin, phenytoin, or methotrexate; known glucose-6-phosphate dehydrogenase or folic acid deficiency; pregnant or lactating; treatment with clindamycin or TMP-SMX or another systemic antibiotic in the previous 48 hours unless associated with treatment failure (defined as a patient who has been on prior non–study antibiotics for at least 72 hours and failed); infection for which prior cultures revealed in vitro resistance of a pathogen to clindamycin or TMP-SMX in the previous month; concurrent treatment with topical or systemic antibiotic; or enrollment in the study within 12 weeks. Laboratory testing was done at the discretion of the treating clinician.

Randomization and Blinding

Using double-blind Web-based randomization, we assigned subjects in a 1:1 ratio to a 7-day course of clindamycin (one 300-mg capsule, 4 times daily, with 3 placebo capsules, twice daily for first and third doses) or TMP-SMX (4 single-strength capsules, 80 mg/400 mg, twice daily, with 1 placebo capsule, twice daily for second and fourth doses), to ensure subjects in both arms had the same dosing. These dosages were based on existing recommendations at the study's inception [12]. We dispensed medications in blister packs. The blind could only be broken prior to the subject's completion of the trial if the subject suffered a treatment failure or adverse event for which an acceptable alternative treatment could not be given and the subject's best care would be threatened if knowledge of his or her treatment assignment was delayed. An independent contract research organization (EMMES, Rockville, Maryland) that developed the randomization code performed centralized randomization, with assignments made independently at each site. Details regarding randomization and study medication blinding can be found in the Supplementary Appendix.

Outcome Measures

We performed follow-up visit evaluations on days 3–4 (on therapy), 8–10 (end of therapy), 14–21 (test of cure [TOC]), and 49–63 (extended-follow-up) after initiating therapy. We assessed compliance by inspecting blister packs. If the subject lost the blister pack, then we assessed compliance by the record on a memory aid and subject interview.

Descriptions of study populations, including per-protocol, modified intention-to-treat (mITT-1 and mITT-2), and FDA Guidance early endpoint, and definitions of clinical cure or failure are provided in Table 1. The primary outcome was clinical cure of the wound infection at the TOC visit in the per-protocol population. A subject was classified as a cure if he or she did not meet failure criteria at or before the TOC visit. Standardized physical examination criteria for failure were developed by investigator consensus prior to study initiation and varied by

Table 1. Definitions of Study Populations and Outcomes Among Subjects With an Uncomplicated Wound Infection Treated With Clindamycin or Trimethoprim-Sulfamethoxazole

Population	Description	Outcome Definition
Per-protocol	Subjects who either complied with at least 75% of the first 5 days of treatment doses and had an in-person test-of-cure visit, or who were determined to be a clinical failure before the test-of-cure visit and took at least 75% of the first 48 h of treatment doses.	Clinical cure[a]: Any subject who was not deemed a clinical failure by a study clinician based on the following criteria: On-therapy visit (days 3–4)—fever (attributable to their infection), increase in maximal dimension of erythema >25% from baseline, or worsening of wound swelling and tenderness; end-of-therapy visit (days 8–10)—fever, no improvement in the maximal dimension of erythema from baseline or in swelling and tenderness; test-of cure visit (days 14–21)—fever or more than minimal erythema, swelling, or tenderness. Subjects deemed a clinical failure had treatment with a new antibiotic.
Modified intention-to-treat 1 (mITT-1)	Subjects who took at least 1 dose of study medication and had in-person or telephone assessment through the test-of cure visit. In addition, all subjects who withdrew from the study, were lost to follow-up prior to final classification, or had missing or unassigned outcomes were included.	Clinical cure: Any subject who was not deemed a clinical failure at or before the test-of-cure visit by a study clinician based on no change in antibiotic therapy due to persistence or worsening of infection (see per-protocol definition), the subject's assessment, or assessment by an outside clinician. All subjects who withdrew from the study, were lost to follow-up prior to final classification, or had missing or unassigned outcomes were classified as failures.
Modified intention-to-treat 2 (mITT-2)	Subjects who took at least 1 dose of study medication and had any in-person follow-up evaluation at any time during the study.	Clinical cure: Any subject who was not deemed a clinical failure based on study protocol criteria by a study clinician (see per-protocol definition) prior to or on the last recorded follow-up visit.
Food and Drug Administration Guidance Early Endpoint (FDAGEEP) [3]	Subjects who took at least 1 dose of study medication and completed the follow-up evaluation at 48–72 h after the start of treatment.	Clinical response: Any subject who had a cessation (no change or decrease) in the length, width, and area of erythema from baseline and no worsening seen in swelling/induration and absence of fever (ie, temperature <37.7°C) as assessed by a study clinician.
Safety	Subjects who were randomized, received study product and did not return 100% of doses.	Adverse events were coded according to version 17.0 of the Medical Dictionary for Regulatory Activities. Investigators categorized adverse events as related or not related to the study medication.

[a] These criteria were developed by investigator consensus.

the time since starting treatment as described in detail in Table 1. All subjects meeting failure criteria had their assigned treatment stopped and a new antibiotic treatment started (ie, different than their originally assigned antibiotic), in addition to any surgical drainage that was deemed necessary. For the mITT-1 analysis, those subjects lost to follow-up were considered to have failed treatment, and those who did not present for the TOC visit but could be reached by telephone were classified as a failure if they reported new antibiotic treatment for their skin infection.

Outcome assessment methods and interrater agreement are described in the Supplementary Appendix. We sent drainage specimens for standard aerobic bacterial culture and susceptibility testing at site hospitals. Investigators were blinded to these results.

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

Statistical Analysis

Our primary hypothesis was that the wound infection cure rate among subjects treated with clindamycin would be superior to the cure rate among subjects treated with TMP-SMX. Assuming a 10 percentage point effect size, type I error rate of 5%, power of 90%, expected cure rate with TMP-SMX of 85%, and 85% evaluability, we estimated that we would need to enroll 500 subjects to ensure an adequate sample size. We report our primary outcome as the difference in the proportion of cures between patients receiving clindamycin and those receiving TMP-SMX. We chose to conduct the primary outcome analysis in the per-protocol population to most precisely evaluate outcomes among subjects who returned for physical evaluation and treatment effects among those with good compliance with a complete treatment course, but also conducted analyses in the mITT and FDA Guidance early endpoint populations. Statistical superiority for our primary endpoint required the lower bound of the 95% confidence interval (CI) for the difference in clinical cure rates to be greater than zero, while clinical superiority required the lower bound to exceed 10%. We analyzed secondary outcomes in the per-protocol population and

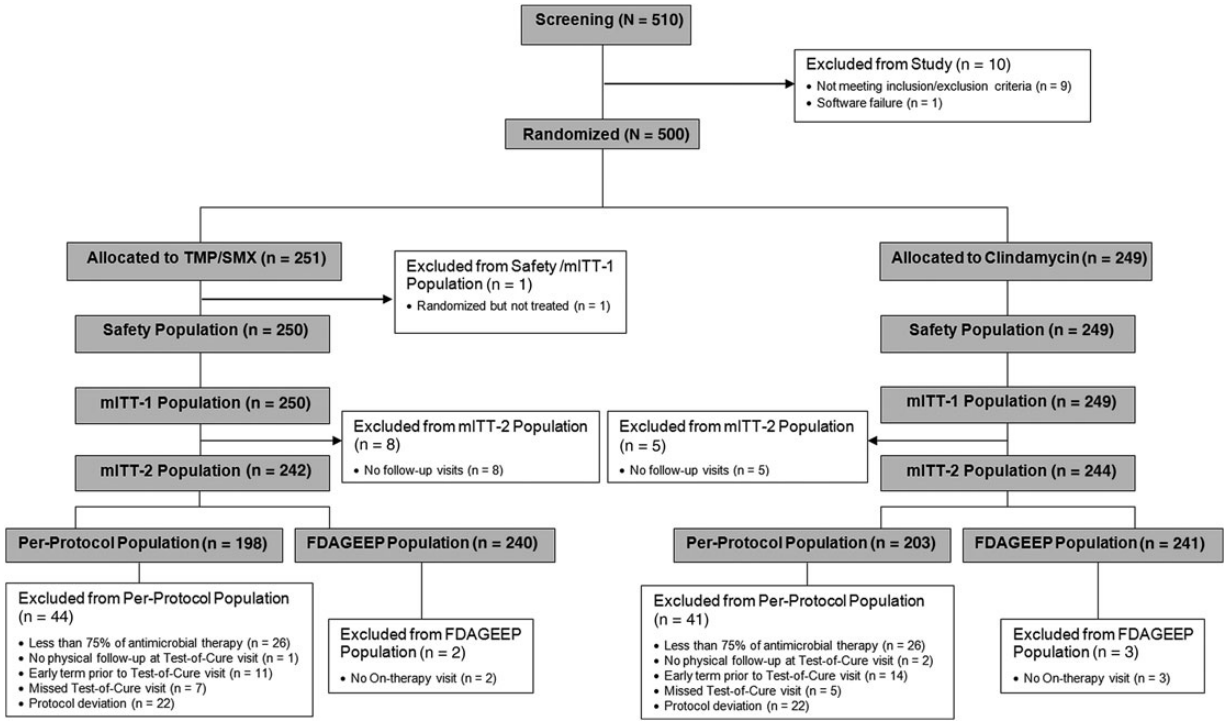

Figure 1. Enrollment, randomization, and follow-up of patients with an uncomplicated wound infection treated with clindamycin or trimethoprim-sulfamethoxazole (TMP/SMX). See Table 1 for a description of the per-protocol, modified intention-to-treat (mITT-1 and mITT-2), and Food and Drug Administration Guidance early endpoint (FDAGEEP) populations and outcome definitions. On-therapy, test-of-cure, and extended follow-up visits occurred on days 3–4, 14–21, and 49–63 after starting treatment, respectively.

report 95% CIs of the difference in outcome rates. We also conducted subgroup analyses of cure rates among subjects with MRSA or methicillin-susceptible *S. aureus* (MSSA) infection, and for those with an infection area ≥75 cm^2 or <75 cm^2 by treatment group.

RESULTS

Of 500 enrolled patients, 249 (49.8%) were randomized to clindamycin and 250 (50.0%) to TMP-SMX and took at least 1 dose; 401 (80.2%) subjects qualified for the per-protocol population (Figure 1). Of 499 who took at least 1 dose, 270 (54.1%) were 100% compliant (136 clindamycin, 134 TMP-SMX) and 132 (26.5%) took 76%–99% of doses (66 clindamycin, 66 TMP-SMX).

Subject characteristics are summarized in Table 2. Median age was 40 years (range, 14–76 years), 63.6% were males. Thirty-two (8.0%) subjects had a history of MRSA infection. Median wound length was 2.0 cm. Median erythema length and width were 7.5 cm and 6.0 cm, respectively. MRSA was found in 40.1% of subjects, MSSA in 25.7%, and streptococci in 5%. The proportion of MRSA isolates susceptible in vitro to clindamycin and TMP-SMX was 95.0% and 97.8%, and that of MSSA isolates was 88.5% and 97.3%, respectively.

Cure rates are summarized in Table 3. The wound infection was cured at 7–14 days after treatment in 187 of 203 (92.1%) clindamycin-treated and 182 of 198 (91.9%) TMP-SMX–treated subjects (91.9%) in the per-protocol population (difference, 0.2%; 95% CI, −5.8% to 6.2%; P = not significant). Cure rates were also similar among the treatment groups in the 2 intention-to-treat populations and the FDA Guidance early endpoint population (ie, response at 48–72 hours).

Secondary outcomes are summarized in Table 4. The clindamycin group had a significantly lower rate of recurrent infection at the original infection site than the TMP-SMX group at 7–14 days after treatment (1.5% vs 6.6%; difference, −5.1%; 95% CI, −9.4% to −.8%) and through 6–8 weeks following treatment (2.0% vs 7.1%; difference, −5.1%; 95% CI, −9.7% to −.6%). Other secondary outcomes were not statistically different but tended to favor clindamycin including lower rates of new site SSTI, surgical drainage procedures, and subsequent hospitalization, as well as less disability time.

Subgroup analyses of cure rates 7–14 days after treatment were conducted in the per-protocol population. Among subjects with MRSA isolated, cure occurred in 70 of 78 (89.7%) of clindamycin-treated and 78 of 83 (94.0%) TMP-SMX–treated subjects (difference, −4.2%; 95% CI, −13.9% to 5.5%). Among subjects with MSSA isolated, cure occurred in 51 of 54 (94.4%) clindamycin-treated and 39 of 48 (81.3%) TMP-SMX–treated subjects (difference, 13.2%; 95% CI, 1.3% to 21.8%). Among subjects with an erythema area <75 cm^2, cure

Table 2. Baseline Characteristics of Subjects With an Uncomplicated Wound Infection Treated With Clindamycin or Trimethoprim-Sulfamethoxazole in the Per-Protocol Population

Characteristic	Clindamycin (n = 203)	Trimethoprim-Sulfamethoxazole (n = 198)
Age, y, median (IQR; range)[a]	38 (26–49; 14–76)	41 (27–51; 14–72)
Male sex	122 (60.1)	133 (67.2)
Race		
White	117 (57.6)	115 (58.1)
Black	73 (36.0)	71 (35.9)
Asian	0 (0.0)	0 (0.0)
Hawaiian/Pacific Islander	0 (0.0)	0 (0.0)
American Indian/Alaska Native	2 (1.0)	0 (0.0)
Multiracial	3 (1.5)	7 (3.5)
Other/unknown	8 (3.9)	5 (2.5)
Hispanic ethnicity	72 (35.5)	63 (31.8)
Days of wound infection symptoms, median (IQR)	3.0 (3.0–5.0)	3.0 (2.0–5.0)
Fever in the week prior to enrollment	34 (16.7)	38 (19.2)
Comorbidities		
History of MRSA infection	14 (6.9)	18 (9.1)
Diabetes	28 (13.8)	19 (9.6)
Eczema or other chronic skin infection	6 (3.0)	5 (2.5)
Chronic edema	2 (1.0)	0 (0.0)
Wound infection related to IV drug use	4 (2.0)	5 (2.5)
History of prior antibiotic treatment for skin infection	5 (2.5)	9 (4.5)
Close household contact with similar infection[b]	15 (7.4)	6 (3.0)
Temperature >38°C	3 (1.5)	2 (1.0)
Pulse >90 beats/min	60 (29.6)	54 (27.3)
Respiration rate >20 breaths/min at baseline	5 (2.5)	3 (1.5)
Wound infection		
Head/neck	21 (10.3)	21 (10.6)
Trunk/abdomen/back	23 (11.3)	20 (10.1)
Groin/buttocks	12 (5.9)	15 (7.6)
Upper extremity	53 (26.1)	46 (23.2)
Lower extremity	94 (46.3)	96 (48.5)
Wound length, cm, median (IQR; range)	2.0 (1.0–3.0; 0.2–18.0)	2.0 (1.0–3.0; 0.1–56.0)
Wound depth		
Limited to skin	158 (77.8)	144 (72.7)
Involves subcutaneous	44 (21.7)	52 (26.3)
Involves deep fascia	1 (0.5)	2 (1.0)
Erythema dimension, cm, median (IQR; range)		
Length[c]	8.0 (4.2–14.0; 1.5–50.0)	7.0 (4.9–13.0; 2.0–56.0)
Width	6.0 (3.0–9.5; 0.5–40.0)	6.0 (3.5–9.0; 1.5–34.0)
Area[d]	37.8 (11.8–94.2; 0.8–1570.8)	39.3 (12.6–94.2; 2.4–827.8)
Area[d] of erythema ≥75 cm^2	60 (29.6)	62 (31.3)
Dimensions of induration/swelling, cm, median (IQR; range)		
Length[c]	5.0 (3.0–7.0; 0.6–37.0)	5.0 (3.0–7.0; 0.4–56.0)
Width	3.5 (2.5–6.0; 0.5–40.0)	4.0 (3.0–6.2; 0.4–22.0)
Area[d]	14.1 (5.5–33.0; 0.2–801.1)	16.1 (7.1–33.9; 0.1–604.8)
Purulent drainage	185 (91.1)	179 (90.4)
Drainage procedure at time of initial treatment	72 (35.5)	67 (33.8)
Baseline wound culture results		
MRSA	78 (38.4)	83 (41.9)
Methicillin-susceptible *S. aureus*	54 (26.6)	49 (24.7)
Coagulase-negative staphylococci	30 (14.8)	27 (13.6)
Streptococcal species[e]	10 (4.9)	10 (5.1)
Other[f]	25 (12.3)	22 (11.1)

Table 2 continued.

Characteristic	Clindamycin (n = 203)	Trimethoprim-Sulfamethoxazole (n = 198)
No growth	30 (14.8)	34 (17.2)
Not done	1 (0.5)	0 (0.0)

Data are presented as No (%) unless otherwise specified.

Abbreviations: IQR, interquartile range; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*.

[a] Four (1.0%) subjects were aged 13–17 years.

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

[c] Length was defined as the maximal dimension.

[d] Area of erythema and induration/swelling was calculated using formula for an ellipse (1/4$x\,\pi \times$ length $\times$ width) minus area of probe measurements of length and width of abscess area.

[e] Streptococcal species include group A *Streptococcus*, group B *Streptococcus*, *Streptococcus anginosus*, β-hemolytic group F *Streptococcus*, β-hemolytic group G *Streptococcus*, and viridans group *Streptococcus*.

[f] Other isolates include *Acinetobacter* species, *Citrobacter freundii*, *Diphtheroid* bacilli, *Eikenella corrodens*, *Enterobacter* species, *Enterococcus* species, *Haemophilus* species, *Klebsiella* species, *Lactobacillus* species, *Morganella morganii*, *Proteus mirabilis*, and *Pseudomonas aeruginosa*.

occurred in 133 of 143 (93.0%) clindamycin-treated and 127 of 136 (93.4%) TMP-SMX–treated subjects, respectively (difference, −0.4%; 95% CI, −6.3% to 5.8%). Among those with an erythema area ≥75 cm^2, cure occurred in 54 of 60 (90.0%) clindamycin-treated and 556 of 62 (88.7%) TMP-SMX–treated subjects, respectively (difference, −0.4%, 95% CI, −6.3% to 5.8%).

Adverse events are described in the Supplementary Appendix. Overall adverse events rates were similar between groups, and most events were mild. The most common drug-associated adverse events involved the gastrointestinal system (clindamycin, 37.3%; TMP-SMX, 32.8%); no cases of *C. difficile*–associated diarrhea occurred. No treatment-associated serious or life-threatening adverse events occurred, including invasive infections. Treatment discontinuation rates due to drug-associated adverse events were also similar (clindamycin, 0.0%; TMP-SMX, 1.2%).

DISCUSSION

Wound infections represent a unique type of SSTI. Unlike abscess, drainage is not the primary treatment and, unlike cellulitis without a wound, a diagnostic specimen is usually available for culture. Accordingly, in 2010 the FDA, in its guidance to industry for the development of new antimicrobials, designated wound infections as distinct from abscess and cellulitis [3]. Subsequent clinical trials have evaluated noninferiority of new parenteral antibiotics and oral oxazolidinones compared to intravenous vancomycin and oral linezolid [4–6]. For the first time that we are aware, among patients with an uncomplicated wound infection, we conducted an adequately powered randomized double-blind trial comparing 2 commonly prescribed off-patent and relatively inexpensive oral antimicrobials, clindamycin and TMP-SMX. We designed this as a superiority trial to test the hypothesis that the wound infection cure rate among clindamycin-treated subjects would be greater than that of TMP-SMX–treated subjects. This hypothesis was based on observational clinical data, experimental findings, and theoretical concerns suggesting inferior efficacy of TMP-SMX [8–10]. We demonstrated that among 500 randomized patients with wound infections caused predominantly by MRSA and MSSA, clindamycin was not superior to TMP-SMX and both treatments produced similar high cure rates at 7–14 days after treatment with similar adverse event rates.

Table 3. Cure Rates Among Subjects With an Uncomplicated Wound Infection Treated With Clindamycin or Trimethoprim-Sulfamethoxazole in the Per-Protocol, Modified Intention-to-Treat, and Food and Drug Administration Guidance Early Endpoint Populations

	Cure by Treatment Group/Total, No. (%)				
Study Population[a]	Clindamycin	Trimethoprim-Sulfamethoxazole	Difference in Cure Rates Between Treatment Groups	95% CI of the Difference in Cure Rates	*P* Value[b]
Per-protocol[c]	187/203 (92.1%)	182/198 (91.9%)	0.2%	−5.8 to 6.2	.91
mITT-1	198/249 (79.5%)	197/250 (78.8%)	0.7%	−6.8 to 8.3	.93
mITT-2	225/244 (92.2%)	223/242 (92.1%)	0.1%	−5.1 to 5.3	.88
FDAGEEP	88/241 (36.5%)	89/240 (37.1%)	−0.6%	−9.6 to 8.5	.97

Abbreviations: CI, confidence interval; FDAGEEP, US Food and Drug Administration Guidance early endpoint; mITT, modified intention-to-treat.

[a] See Table 1 for a description of the per-protocol, mITT-1 and mITT-2, and FDAGEEP (response rate reported) populations and outcome definitions.

[b] *P* values are from a Wald asymptotic test of equality with a continuity correction.

[c] The primary outcome was clinical cure at the test-of-cure visit (7–14 days after the end of a 7-day treatment) in the per-protocol population.

Table 4. Secondary Outcomes Among Subjects With an Uncomplicated Wound Infection Treated With Clindamycin or Trimethoprim-Sulfamethoxazole in the Per-Protocol Population

Outcome	Visit[a]	Response by Treatment Group		Difference in Response Rates Between Treatment Groups	95% CI of the Difference in Response Rates
		Clindamycin	Trimethoprim-Sulfamethoxazole		
Composite clinical cure[b], %	TOC	56.2	57.1	−0.9	−11.1 to 9.3
Surgical drainage procedure, %	TOC	3.0	6.6	−3.6	−8.3 to 1.1
	EFU	3.9	8.6	−4.7	−9.9 to .6
Hospitalization, %	TOC	3.0	6.1	−3.1	−7.7 to 1.5
Recurrent skin infection at original site, %	TOC	1.5	6.6	−5.1	−9.4 to −.8
	EFU	2.0	7.1	−5.1	−9.7 to −.6
New skin infection at a different site, %	TOC	0.5	3.0	−2.5	−5.6 to .5
	EFU	4.4	9.1	−4.7	−10.1 to .8
Similar infection in household member, %	TOC	2.5	0.5	2.0	−.9 to 4.8
	EFU	4.4	3.0	1.4	−2.8 to 5.6
Presence of swelling/induration, %	OT	44.8	45.9	−1.1	−11.4 to 9.2
	EOT	9.5	13.5	−4.0	−10.8 to 2.8
Presence of tenderness, %	OT	45.3	46.4	−1.1	−11.4 to 9.2
	EOT	5.0	9.8	−4.8	−10.5 to .8
Change in mean area of erythema from baseline, cm^2 (SD)	OT	−49.3 (119.7)	−43.1 (98.3)	−6.2	−27.8 to 15.3
	EOT	−86.2 (159.6)	−71.1 (105.1)	−15.1	−41.9 to 11.6
	TOC	−90.0 (165.1)	−75.1 (111.5)	−14.9	−42.7 to 12.8
Days missed from normal activities, mean (SD)	NA	2.1 (3.5)	2.7 (4.1)	−0.6	−1.4 to .1
Days missed from work/school, mean (SD)[c]	NA	1.8 (3.1)	2.7 (4.1)	−1.0	−1.9 to .0
Days analgesics used, mean (SD)[c]	NA	5.6 (5.1)	5.6 (5.3)	0.0	−1.0 to 1.0

Abbreviations: CI, confidence interval; EFU, extended follow-up; EOT, end of therapy; NA, not applicable; OT, on therapy; SD, standard deviation; TOC, test of cure.

[a] Through follow-up visits: OT (3-4 days of treatment); TOC (7–14 days after the end of a 7-day treatment); EFU (42–56 days after the end of a 7-day treatment).

[b] Resolution of all symptoms and signs of infection, or improvement to such an extent that no additional antibiotic therapy and/or surgical procedures were necessary.

[c] Days missed from normal activities and work or school, and days analgesics used were counted based on days reported in the first 14 days.

Williams et al [8] conducted a retrospective review of administrative data for children treated as outpatients for an SSTI. Among children who received drainage procedure, treatment failure over the next year occurred in 107 of 2270 (4.7%) treated with clindamycin compared with 246 of 2206 (11.2%) treated with TMP-SMX. Among children without a drainage procedure, failure occurred in 253 of 5189 (4.9%) treated with clindamycin vs 739 of 8417 (8.8%) treated with TMP-SMX. It has been postulated that *S. aureus*, through its ability to release thymidine from DNA fragments present in high concentrations in pus, may antagonize the antimicrobial effects of TMP-SMX [9]. In addition, TMP-SMX has been found to have poor in vitro activity against *S. pyogenes* [10], although this may be an artifact of thymidine-containing culture media [13]. Despite these concerns, we found that TMP-SMX produced similar outcomes to clindamycin.

The bacteriology of wound infections has not been well described, in part related to a new SSTI classification system introduced by the FDA [3]. We previously used a similar classification scheme in a study of the bacteriology of purulent SSTIs among US emergency department patients that identified the emergence of CA-MRSA as the most frequent cause of these infections [2]. In that study, conducted in 2004, and another similar investigation conducted in 2008 [7], we isolated MRSA from 53% and 42% of wounds, respectively. In the present trial, we enrolled patients with characteristics of an infected wound with any drainage, although in about 90% of cases the drainage was described as purulent. MRSA was isolated from wounds of 40% of subjects and MSSA from 26%. Although these infected wounds were associated with surrounding cellulitis and some lacked purulent drainage, streptococci were isolated in only 5%.

The results of our study are consistent with 1 recent randomized superiority trial that compared oral clindamycin to TMP-SMX in 524 patients with cellulitis, abscess >5 cm, or both and found similar response and adverse events rates among treatment groups [11]. Patients with wounds and, therefore, wound infections were not specifically identified and, unlike our study, patients with common comorbidities, such as diabetes, were excluded. The dose of TMP-SMX was one-half that used in our investigation (ie, 160 mg/800 mg). Although 160 mg/800 mg of TMP-SMX twice daily should achieve serum and blister fluid levels above MRSA minimal inhibitory concentrations [14], we chose a 320 mg/1600 mg dose to best test efficacy and for consistency with existing recommendations at the study's inception [12]. In another randomized trial comparing TMP-SMX and placebo among 1265 patients with an uncomplicated skin abscess receiving drainage, we also used 320 mg/1600 mg

twice daily and found that the abscess cure rate was statistically significantly higher in the TMP-SMX group, with only slightly more mild gastrointestinal side effects compared to the placebo group [15]. Therefore, we think that we have tested an adequate dose of TMP-SMX and found that the 320 mg/1600 mg dose resulted in similar wound infection cure rates compared with clindamycin 300 mg 4 times daily. We do not know if a lower dose of TMP-SMX (eg, 160 mg/800 mg twice daily) would result in lower cure rates or the effect of a different dose of clindamycin. Clinical trials of subjects meeting ABSSSI criteria comparing oritavancin to vancomycin [4], dalbavancin to vancomycin followed by linezolid [5], and tedizolid to linezolid [6] reported similar response rates between the treatment arms among the subgroup of subjects with a wound infection. Only about 30% of subjects in our trial met the ABSSSI criterion of infection area >75 cm^2. Subgroup analysis by erythema area ≥75 cm^2 or <75 cm^2 did not reveal differences in cure rates overall or by treatment group.

Patients with SSTI due to CA-MRSA have been observed to be at increased risk of recurrent infections, so we also examined subsequent infection outcomes and disability [16]. The clindamycin group had a significantly lower rate of recurrent infection at the original infection site than the TMP-SMX group at 7–14 days and 6–8 weeks following treatment (1.5% vs 6.6%, and 2.0% and 7.1%, respectively). Other secondary outcomes were statistically similar but tended to favor clindamycin-treated subjects including lower rates of new-site SSTI, surgical drainage procedures and hospitalizations, and less disability time. Whereas caution must be exercised to not overinterpret secondary outcomes results, notably, Williams et al [8] and Miller et al [17] also reported that the recurrence rate was significantly lower among clindamycin- compared with TMP-SMX–treated subjects. Further study evaluating differential effects of antibiotics on recurrent infection may be warranted.

Subgroup analyses of treatment effect by infecting organism found similar cure rates among those infected with MRSA. Both clindamycin and TMP-SMX demonstrated consistent in vitro activity against MRSA in our study, with ≥95% of isolates susceptible to these agents, despite some reports of communities with high rates of MSRA resistance to clindamycin in the United States [18]. Among those infected with MSSA, we observed a significantly higher cure rate for clindamycin-treated compared with TMP-SMX–treated subjects (94.3% vs 81.3%, respectively). This occurred despite a higher rate of in vitro susceptibility to TMP-SMX (97.3% vs 88.5%, respectively). This result could be due to differences in in vivo killing and toxin inhibition or simply due to chance. In many places in the world, MSSA remains the predominant SSTI pathogen, so this finding may be worth pursuing.

This investigation has limitations. Although patients with common comorbidities, such as diabetes, were not excluded, physicians may have been biased against enrolling some patients perceived as higher-risk. We mainly studied wound infections due to acute trauma but not those associated with chronic wounds and bites, and also excluded patients with severe immunodeficiency, so our findings are not generalizable to these groups. We created standardized methods to determine clinical failure necessitating treatment change that may not be valid, although we are unaware of any validated method, and ours had good interrater agreement and was associated with a high cure rate among those who could be assessed by this method (ie, the per-protocol population). It is possible that some wounds were not infected or may have resolved without antibiotic treatment.

In conclusion, among patients with an uncomplicated wound infection, mostly caused by MRSA and MSSA, 7-day courses of oral clindamycin 300 mg 4 times daily and TMP-SMX 320 mg/1600 mg twice daily have similar efficacy and adverse event rates.

Supplementary Data

Supplementary materials are available at http://cid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

Acknowledgments. We thank the following: Christine Chiou, MD, Maureen Mehigan, RN, BSN, Hyung Koo, RN, BSN, and Janie Russell (National Institute of Allergy and Infectious Diseases [NIAID]); the Division of Microbiology and Infectious Diseases-Clinical Research Operations and Management Support Pharmacovigilance Group; our data safety management board (Richard Pollard, MD, John Powers, MD, Sheldon Kaplan, MD, and Scott Evans, PhD); Stephanie Pettibone, Thad Zajdowicz, Nancy Browning, and Ryan May (EMMES Corporation); the staff at PPD and ICON Clinical Research; our study coordinators (Kavitha Pathmarajah, MPH, Britany Zeglin, BS, Mary Mulrow, RN, Shelley Fuentes, Laurie Kemble, Danielle Beckham, Niccole Neal, Kathleen Hatala, RN, and Carol Von Hofen, RN); Amy Stubbs, MD, at Truman Medical Center; and the residents and staff at the participating emergency departments.

Author contributions. D. A. T. was co–principal investigator, developed study methods, supervised study implementation, and drafted the manuscript; G. J. M. was co–principal investigator, developed study methods, and supervised study implementation; W. R. M. developed study methods and conducted data analysis; A. K. was project director, supervised study implementation, and conducted data analyses; F. M. A. was head site investigator, developed study methods, and supervised site performance; F. L., D. J. K., M. T. S., and R. E. R. were site investigators and supervised site performance; and R. H. conducted data analysis.

Financial support. This research was supported by a contract from the NIAID (grant number 1U01 HHSN272200700032C to D. A. T. and G. J. M.).

Potential conflicts of interest. D. A. T. has served on the speaker's bureau for Actavis, has served on advisory boards for Actavis and Cempra, and has received research support from Actavis and Cempra; F. M. A. has served on speaker's bureaus for Merck, Actavis, and The Medicines Company, and has received research support from Cempra and Merck. R. E. R. has received research support from Cepheid. G. J. M. has received research support from Cempra, Durata, and Cubist. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. 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.
2. 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.
3. US Food and Drug Administration. Guidance for industry. Acute bacterial skin and skin structure infections: developing drugs for treatment. US Food and Drug Administration. August 2010. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071185.pdf. Accessed 30 November 2015.
4. Corey GR, Kabler H, Mehra P, et al. Single-dose oritavancin in the treatment of acute bacterial skin infections. N Engl J Med **2014**; 370:2180–90.
5. Boucher HW, Wilcox M, Talbot GH, et al. Once-weekly dalbavancin versus daily conventional therapy for skin infection. N Engl J Med **2014**; 370:2169–79.
6. Prokocimer P, De Anda C, Fang E, Mehra P, Das A. Tedizolid phosphate vs linezolid for treatment of acute bacterial skin and skin structure infections: the ESTABLISH-1 randomized trial. JAMA **2013**; 309:559–69.
7. Talan DA, Krishnadasan A, Gorwitz RJ, et al. Comparison of *Staphylococcus aureus* from skin and soft tissue infections in U.S. emergency department patients, 2004 and 2008. Clin Infect Dis **2011**; 53:144–9.
8. Williams DJ, Cooper WO, Kaltenbach LA, et al. Comparative effectiveness of antibiotic treatment strategies for pediatric skin and soft-tissue infections. Pediatrics **2011**; 128:e479–87.
9. Proctor RA. Role of folate antagonists in the treatment of methicillin-resistant *Staphylococcus aureus* infection. Clin Infect Dis **2008**; 46:584–93.
10. Kaplan EL, Johnson DR, Del Rosario MC, Horn DL. Susceptibility of group A beta-hemolytic streptococci to thirteen antibiotics: examination of 301 strains isolated in the United States between 1994 and 1997. Pediatr Infect Dis J **1999**; 18:1069–72.
11. Miller LG, Daum RS, Creech CB, et al. Clindamycin versus trimethoprim-sulfamethoxazole for uncomplicated skin infections. N Engl J Med **2015**; 372:1093–103.
12. Gilbert DN, Moellering RC, Eliopoulos GM, Sande MA. The Sanford guide to antimicrobial therapy. 38th ed. Sperryville, VA: Antimicrobial Therapy, **2008**.
13. Bowen AC, Lilliebridge RA, Tong SY, et al. Is *Streptococcus pyogenes* resistant or susceptible to trimethoprim-sulfamethoxazole? J Clin Microbiol **2012**; 50:4067–72.
14. 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.
15. Talan DA, Mower WR, Krishnadasan A, et al. Trimethoprim-sulfamethoxazole versus placebo for uncomplicated skin abscess. N Engl J Med **2016**; 374:823–32.
16. Demos M, McLeod MP, Nouri K. Recurrent furunculosis: a review of the literature. Br J Dermatol **2012**; 167:725–32.
17. Miller L, Daum R, Creech CB, Chambers H. Recurrent infections after treatment of uncomplicated skin and soft tissue infection among patients enrolled in a multicenter randomized double blind controlled trial of clindamycin vs. TMP-SMX for SSTIs [Abstract 625]. In: IDWeek 2013. Available at: https://idsa.confex.com/idsa/2013/webprogram/Paper41725.html. Accessed 2 January 2016.
18. Diep BA, Chambers HF, Graber CJ, et al. Emergence of multidrug-resistant, community associated, methicillin-resistant *Staphylococcus aureus* clone USA300 in men who have sex with men. Ann Intern Med **2008**; 148:249–57.