MAJOR ARTICLE

Clinical Trial: Comparative Effectiveness of Cephalexin Plus Trimethoprim-Sulfamethoxazole Versus Cephalexin Alone for Treatment of Uncomplicated Cellulitis: A Randomized Controlled Trial

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(See the Editorial Commentary by Chambers on pages 1763–4.)

Background. Community-associated methicillin-resistant *S. aureus* (CA-MRSA) is the most common organism isolated from purulent skin infections. Antibiotics are usually not beneficial for skin abscess, and national guidelines do not recommend CA-MRSA coverage for cellulitis, except purulent cellulitis, which is uncommon. Despite this, antibiotics targeting CA-MRSA are prescribed commonly and increasingly for skin infections, perhaps due, in part, to lack of experimental evidence among cellulitis patients. We test the hypothesis that antibiotics targeting CA-MRSA are beneficial in the treatment of cellulitis.

Methods. We performed a randomized, multicenter, double-blind, placebo-controlled trial from 2007 to 2011. We enrolled patients with cellulitis, no abscesses, symptoms for <1 week, and no diabetes, immunosuppression, peripheral vascular disease, or hospitalization (clinicaltrials.gov NCT00676130). All participants received cephalexin. Additionally, each was randomized to trimethoprim-sulfamethoxazole or placebo. We provided 14 days of antibiotics and instructed participants to continue therapy for ≥1 week, then stop 3 days after they felt the infection to be cured. Our main outcome measure was the risk difference for treatment success, determined in person at 2 weeks, with telephone and medical record confirmation at 1 month.

Results. We enrolled 153 participants, and 146 had outcome data for intent-to-treat analysis. Median age was 29, range 3–74. Of intervention participants, 62/73 (85%) were cured versus 60/73 controls (82%), a risk difference of 2.7% (95% confidence interval, −9.3% to 15%; $P = .66$). No covariates predicted treatment response, including nasal MRSA colonization and purulence at enrollment.

Conclusions. Among patients diagnosed with cellulitis without abscess, the addition of trimethoprim-sulfamethoxazole to cephalexin did not improve outcomes overall or by subgroup.

Clinical Trials Registration. NCT00676130.

Keywords. cellulitis; community-associated methicillin-resistant *Staphylococcus aureus*; comparative effectiveness; trimethoprim-sulfamethoxazole; cephalexin.

Community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) is the most common identifiable cause of purulent skin infections, that is, abscess and purulent cellulitis [1, 2]. The frequency of

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Table 1. Inclusion and Exclusion Criteria and Drug Dosing

I. Inclusion Criteria
A. Must have cellulitis as defined here:
1. Definition A (preferred definition): Recent onset of soft tissue erythema, considered by the treating clinician to be bacterial in origin, and associated with signs of infection that include at least 2 of the following: pain, swelling, warmth, fever, lymphangitis, induration, or ulceration.
2. Definition B (*only* for darkly pigmented patients who *cannot* use definition A): Recent onset of soft tissue color change, pain, or swelling, considered by the treating clinician to be bacterial in origin, and at least 1 of the following: warmth, fever, induration, or ulceration
B. Clinical (nonresearch) attending physician agrees with treatment with cephalexin until 3 d after all symptoms gone, using our weight-based dosing
C. Responsible clinical attending physician comfortable with adding trimethoprim-sulfamethoxazole vs placebo to the above
D. Patient understands the study and signs written informed consent
E. Patient agrees to drink at least 1 L of fluid per day
F. Patient will commit to all follow-up appointments
II. Exclusion Criteria
A. Age <12 mo or weight <15 kg
B. Current skin infection has already been treated
C. Allergy to sulfa drugs
D. History of severe allergic reaction to penicillin (defined as anaphylactoid reaction, angioedema, bronchospasm)
E. Current use of any antibiotic (other than topicals)
F. Diabetes mellitus
G. Cellulitis complicated by underlying peripheral vascular disease
H. Renal insufficiency, defined as patient report, clinical suspicion, or creatinine >1.3 or estimated glomerular filtration rate < 60 on the last available set of chemistry results in our computer system
I. Hospital admission required
J. Presence of >1 cc of purulent discharge at any time
K. Cellulitis involving an indwelling vascular, enteric, or urinary catheter
L. Immunocompromise of any etiology
M. Pregnancy
N. Breast feeding
O. Facial cellulitis (infection is above the clavicles)
P. Cellulitis associated with marine or freshwater injury or animal or human bite (insect bites *not* excluded)
Q. History of glucose-6-phosphate dehydrogenase deficiency
R. Taking Coumadin (warfarin), methotrexate, cisapride, phenytoin (Dilantin), digoxin, or dofetilide
S. Known megaloblastic anemia due to folate deficiency.
III. Antibiotic dosing

Weight	Cephalexin	Trimethoprim-sulfamethoxazole (mg trimethoprim)
Children <30 kg:		
15–19 kg:	300 mg 4 times daily	40/200 mg qid
20–24 kg:	400 mg 4 times daily	60/300 mg qid
25–29 kg:	500 mg 4 times daily	72/360 mg qid
Adults and children ≥30 kg:		
<60 kg:	500 mg 4 times daily	80/400 mg qid
60–80 kg:	1000 mg 3 times daily	160/800 mg tid
>80 kg:	1000 mg 4 times daily	160/800 mg qid

skin infections increased with its advent, implying that CA-MRSA caused an epidemic of new disease, rather than merely substituting for methicillin-sensitive *S. aureus* in infections that would have occurred anyway [3].

Multiple studies have found that patients with CA-MRSA abscesses do not benefit from antibiotics; the mainstay of treatment being incision and drainage [4–6]. For most cases of cellulitis, Infectious Diseases Society of America (IDSA) guidelines recommend antibiotics that target streptococci, not CA-MRSA [7]. They do recommend antibiotics that target CA-MRSA for purulent cellulitis, but this accounts for only 8% of purulent skin infections and a smaller proportion of all skin infections [2].

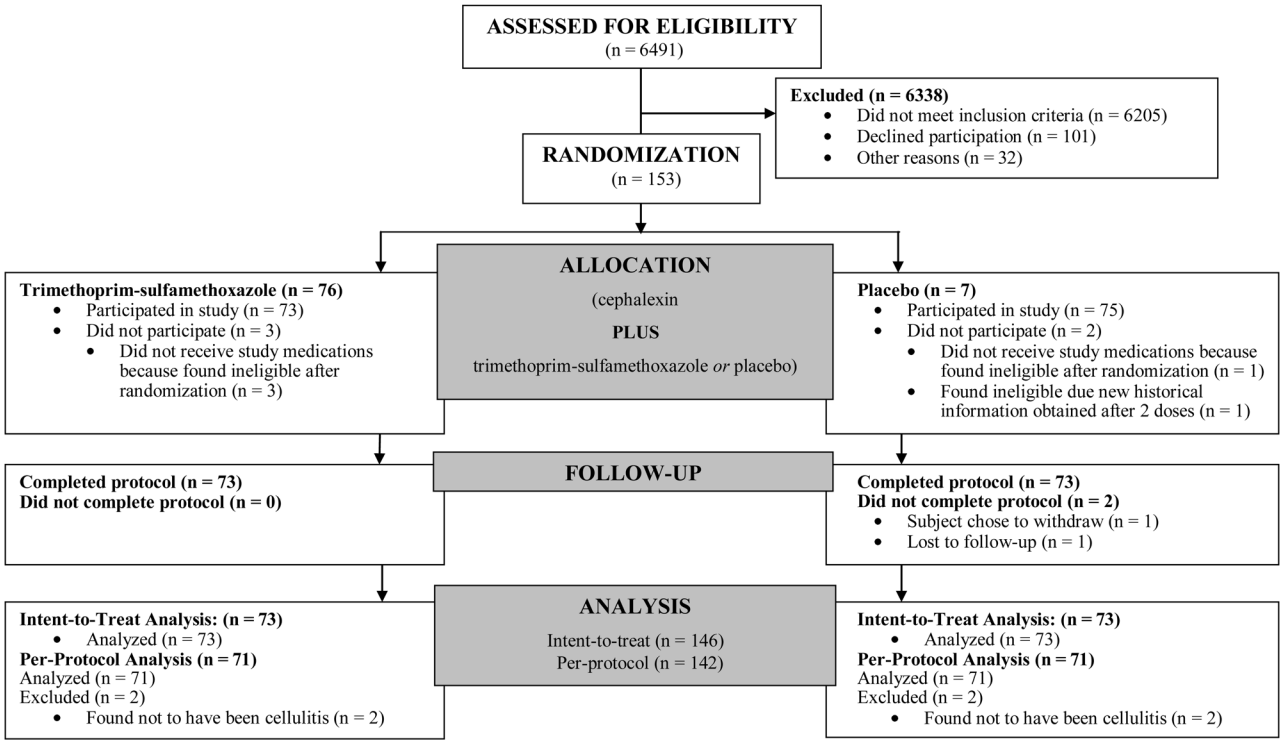

Figure 1. CONSORT Diagram.

In the years preceding publication of the guidelines, antibiotics that target CA-MRSA were prescribed increasingly for skin infections [3, 8, 9]. This may reflect the fact that limited evidence was available—to both practicing clinicians and guideline authors—regarding cellulitis treatment. To date, no experimental trials have been published, and microbiological data relating to cellulitis are usually not obtainable [10]. We conducted a pragmatic comparative effectiveness study, hypothesizing that cephalexin plus trimethoprim-sulfamethoxazole would be more effective than cephalexin alone in the treatment of cellulitis [11].

METHODS

Trial Design

We conducted a double-blind, randomized, placebo-controlled trial from June 2007 through December 2011, with 1:1 parallel group allocation. Potential participants were patients registered for care in 1 of 3 emergency departments located in an area endemic for CA-MRSA [12]. Cellulitis was diagnosed during routine clinical care by attending physicians, board-certified or board-eligible in emergency medicine or pediatric emergency medicine, using explicit criteria (Table 1). Physician coinvestigators enrolled the participants, with trained research coordinators.

Participants

The inclusion and exclusion criteria (Table 1) defined a group of generally-healthy patients with uncomplicated cellulitis and no abscess. Pustules <3 mm in maximal diameter were not considered abscesses. Patients with purulent cellulitis or wound infection could be enrolled if <1 cc of pus was observed or reported by the patient. We collected data on enrolled and non-enrolled patients as specified by CONSORT (Figure 1) [13].

Interventions

We compared cephalexin plus trimethoprim-sulfamethoxazole to cephalexin plus placebo. For adults, guidelines recommend trimethoprim-sulfamethoxazole doses of 160/800 to 320/1600 mg twice daily; cephalexin is commonly prescribed at 500 mg 4 times daily, though twice-daily dosing has been found effective [7, 14]. We used higher, weight-based doses and matched cephalexin and study drug scheduling (Table 1).

Participants were instructed to stop taking the antibiotics 3 days after they believed the infection to be cured, for a minimum of 7 days and a maximum of 14 [15]. We monitored medication adherence via a log filled out by the participants.

Outcomes

The primary outcome was the risk difference for cure in the intent-to-treat group, defined as resolution of symptoms other

Table 2. Baseline Characteristics

Patient Characteristic	All Participants (N = 146)	Trimethoprim-Sulfamethoxazole n (% of total = 73)	Placebo n (% of total = 73)
Age (median [range, interquartile range])	29 (3–74, 23–43)	31 (12–71, 25–47)	27 (3–74, 22–40)
Race (%)			
White	88 (60)	44 (60)	44 (60)
Black	24 (16)	13 (18)	11 (15)
Asian	3 (2)	1 (1.4)	2 (2.7)
Native American	0 (0)	0 (0)	0 (0)
Pacific Islander	0 (0)	0 (0)	0 (0)
Other	1 (0.68)	0 (0)	1 (1.4)
Hispanic	38 (26)	19 (26)	19 (26)
Antibiotics in the past year (%)	57 (39)	24 (33)	33 (45)
Healthcare worker (%)	31 (21)	21 (29)	10 (14)
Past history of skin infection (%)	50 (34)	25 (34)	25 (34)
Physical contact with someone with similar infection (%)	10 (6.9)	4 (5.5)	6 (8.2)
Ever diagnosed with MRSA (%)	3 (2.1)	2 (2.7)	1 (1.4)
Physical contact with someone with MRSA (%)	17 (12)	10 (14)	7 (9.7)
Participated in any of the following sports in the past year: football, hockey, wrestling, rugby, boxing, martial arts, dance (%)	43 (30)	19 (26)	24 (33)
Homeless in the past year (%)	9 (6.2)	3 (4.1)	6 (8.2)
Ever diagnosed with human immunodeficiency virus (%)	0 (0)	0 (0)	0 (0)
Ever used IV drugs (%)	4 (2.7)	0 (0)	4 (5.5)
Physical contact in past year with someone who uses IV drugs (%)	14 (9.6)	5 (6.9)	9 (12)
Ever been in jail (%)	24 (16)	12 (16)	12 (16)
Physical contact in past year with person who has ever been in jail (%)	30 (21)	13 (18)	17 (23)
Stayed overnight in the hospital in the past year (%)	28 (19)	17 (23)	11 (15)
Live in any long-term care facility or care institution (%)	2 (1.4)	1 (1.4)	1 (1.4)
Indwelling line (peripherally inserted central catheter, a Hickman, or a Porta-Cath) (%)	2 (1.4)	1 (1.4)	1 (1.4)
Physical contact in past year with someone with indwelling line (%)	12 (8.2)	8 (11)	4 (5.5)
Adult patient with child in daycare or patient is a child in daycare (%)	16 (11)	8 (11)	8 (11)
Homosexual relations in past year (%)	8 (5.5)	6 (8.2)	2 (2.7)
History of splenectomy (%)	2 (1.4)	2 (2.7)	0 (0)
Ever diagnosed with eczema (%)	9 (6.2)	3 (4.1)	6 (8.2)
Nasal MRSA colonization (data not available at enrollment) (%)	7 (4.9)	4 (5.6)	3 (4.2)
Infection Characteristics at Enrollment (%)			
Purulence	19 (13)	8 (11)	11 (15)
Warmth	136 (94)	69 (96)	67 (92)
Fever	19 (13)	9 (12)	10 (14)
Lymphangitis	16 (12)	8 (13)	8 (12)
Induration	65 (46)	33 (47)	32 (44)
Ulceration	18 (13)	11 (15)	7 (10)
Pain	138 (95)	69 (95)	69 (95)
Edema	106 (74)	58 (81)	48 (68)

Table 2 continued.

Patient Characteristic	All Participants (N = 146)	Trimethoprim-Sulfamethoxazole n (% of total = 73)	Placebo n (% of total = 73)
Portal of entry (any break in the skin preceding the infection)	86 (59)	41 (56)	45 (62)
Reported insect bite	34 (23)	15 (21)	19 (26)
Reported spider bite	8 (5.5)	2 (2.7)	6 (8.2)
Varying Events During the Trial			
Received up to 24 h of intravenous therapy at index visit	40 (27)	18 (25)	22 (30)
Did not attend in-person follow-up visit	19 (13)	7 (9.6)	12 (16)
Telephone plus medical record review follow-up	15 (11)	6 (8)	9 (13)
Medical record review follow-up only	4 (2.7)	1 (1.4)	3 (4.1)

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

than slight residual erythema or edema. This was determined by in-person examination at 12 ± 2 days by any available emergency department physician. We also contacted participants and reviewed medical records at 1 month to be sure that no delayed outcomes were missed. The final determination of cure or failure was made at 1 month and included all available data. Failure was defined as subsequent hospitalization for the same infection, change in antibiotics for any reason, surgical or needle drainage of an abscess, or recurrence of infection within 30 days. For participants who did not attend the in-person determination of cure visit, we used telephone follow-up at 2 weeks and 1 month and medical record review to determine outcome.

The secondary outcome was the association of nasal MRSA colonization at enrollment with treatment response (CHROMagar, Becton Dickinson, Sparks, MD). We examined a number of other possible predictors of response to trimethoprim-sulfamethoxazole (Table 2). These are patient characteristics identified previously as risk factors for CA-MRSA and characteristics of the infection at presentation. These included whether the presence of purulence at enrollment or receipt of initial intravenous therapy could predict treatment response [2]. At the discretion of the treating (nonresearch) physician, some participants received ≤24 hours of intravenous cefazolin or nafcillin. Simultaneously, they received the oral study drug. They commenced oral cephalexin upon stopping intravenous therapy.

We assessed the effect of nonadherence via logistic regression, using treatment assignment and number of nonadherent days to predict outcome. Cellulitis is a clinical diagnosis without proof of a bacterial infection in most cases [10]. Therefore, it was inevitable that some participants would ultimately be found not to have had infectious cellulitis. We determined the final diagnosis using all available information, including subsequent radiographic results, surgical results, and clinical course, and examined this in "per-protocol" analysis.

Sample Size

Prior studies of beta lactams for treatment of cellulitis have found failure rates of 13%–18.7% [16, 17]. Our sample size calculations indicated a requirement of 144 participants to achieve 80% power to detect a response rate difference of at least 13%, with 85% responding in the control group and 98% in the intervention group, with 2-sided alpha 0.05 [16, 17]. No data were analyzed until study completion. The trial was stopped because the sample size was achieved.

Randomization

The research pharmacy generated a randomization sequence with blocks of 4. Medications were put into blinded containers at the time of each enrollment. Pharmacists had no knowledge of clinical characteristics. Clinicians, coordinators, and participants had no access to the randomization sequence and no way to know the contents of each container.

Blinding

We administered cephalexin as 500-mg capsules and study drug as capsules of trimethoprim-sulfamethoxazole 80/400 mg versus placebo encased in larger opaque gelatin capsules. For children unable to swallow capsules, we administered suspensions of cephalexin 50 mg/cc and trimethoprim-sulfamethoxazole 8 mg/cc trimethoprim + 40 mg/cc of sulfamethoxazole. The placebo contained cherry simple syrup, ora-sweet, ora-plus suspension agent, and cellulose powder.

Table 3. Main Results

Total Participants: 146	Trimethoprim-Sulfamethoxazole n (% of total = 73)	Placebo n (% of total = 73)	Risk Difference % (95% CI)	*P* Value
Cure (no failure by final follow-up at 30 d) (%)	62 (85)	60 (82)	2.7 (−9.3% to 15%)	.66
Progression to abscess (%)	5 (6.8)	5 (6.8)	0 (−8.2% to 8.2%)	1.0
Any adverse event (%)	36 (49)	39 (53)	−4.1 (−20% to 12%)	.62
Diarrhea (%)	21 (29)	25 (34)	−5.5 (−21% to 10%)	.48
Nausea (%)	15 (21)	13 (18)	2.7 (−10% to 16%)	.67
Vomiting (%)	5 (6.9)	8 (11)	−4.1 (−13% to 5.1%)	.38
Rash (%)	4 (5.5)	3 (4.1)	1.4 (−5.6% to 8.3%)	.70
Pruritus (%)	5 (6.9)	3 (4.1)	2.7 (−4.6% to 10%)	.47
Candidiasis (%)	1 (1.4)	3 (4.1)	−2.7 (−8.0% to 2.5%)	.31
Clostridium difficile colitis (%)	0 (0)	1 (1.4)	−1.4 (−4.0% to 1.3%)	.32
Other[a] (%)	3 (4.1)	3 (4.1)	0 (−6.4% to 6.4%)	1.0

Abbreviation: CI, confidence interval.

[a] Other adverse events included constipation, flatus, heartburn, bloating, and dysphoria. There were no other reported adverse events.

Statistical Methods

We assessed outcomes according to intent to treat, with the primary outcome being the bivariate risk difference for cure with its 95% confidence interval (CI) and χ^2 testing.

To seek evidence of confounding despite randomization, we performed a secondary analysis, using stepwise logistic regression with liberal "entry" and "stay" criteria of 0.20 and using all predictors shown in Table 2 as candidates. We also sought to identify whether subgroups responded to the intervention differently, that is, whether there was effect modification. For each characteristic, we constructed a logistic regression model with cure as the dependent variable. The independent variables were intervention, characteristic, and the interaction of the two. We deemed interaction *P* values of .05 to be significant—an inclusive criterion, since we tested many possible interactions.

We used SAS 9.2 for all analyses (SAS Institute, Carey, NC). The institutional review boards from the participating hospitals approved the study, and each patient (or parent) provided written informed consent. This trial was registered with Clinicaltrials.gov, record number NCT00676130.

RESULTS

We randomized 153 participants. Four were randomized in error and did not receive the study drug, 1 received 2 doses before it was discovered that he was ineligible, 1 was lost to follow-up, and 1 withdrew voluntarily in the first few days after enrollment, leaving 146 for intent-to-treat analysis. Of these, 15 (11%) did not return for in-person assessment (12 ± 2 days) but were reached by telephone. Four (2.7%) had outcomes determined only by medical record review (Table 2).

Clinical cure was achieved in 62 of 73 (85%) intervention participants versus 60 of 73 (82%) control participants (Table 3), for a nonsignificant risk difference of 2.7% (95% CI, −9.3% to 15%; $P = .66$). Progression to abscess occurred in 5 participants (6.8%) in each group (risk difference 0%; 95% CI, −8.2% to 8.2%; $P = 1.0$).

Of 146 participants, 24 (16%) failed treatment. Each subject could fail treatment for more than 1 reason, and thus reason for failure categories overlap. Reasons for failure included the following: 21 were prescribed additional antibiotics due to clinicians' perception of treatment failure, 6 required incision and drainage, and 3 failed due to drug intolerance (2 controls with allergy, 1 intervention patient with diarrhea). Exclusion of the latter 3 did not change the results (risk difference 1.6%; 95 % CI, −10% to 13%; $P = .79$).

We found no evidence of negative confounding, as the main effect remained null despite our liberal search for confounders (see the Methods section). We also found no evidence of effect modification, as none of the covariates could identify a differential response to the intervention for a subgroup of participants. Nasal colonization data were available for 142 of 146 (97%). Of these, 7 (4.9%) were colonized with MRSA, and this was not associated with response to therapy (interaction $P = .67$). Purulence was present at enrollment in 19 (13%) and did not predict response. The intervention:placebo cure rates were 75%:91% with purulence and 86%:81% without (interaction $P = .26$). Up to 24 hours of initial intravenous therapy with cefazolin or nafcillin was administered to 40 participants (27%; Table 2); they took oral study drug while receiving the intravenous beta lactam. The intervention:placebo cure rates were 72%:82% with intravenous therapy and 89%:82% without

(interaction $P = .24$). Adherence to prescribed antibiotics did not affect the outcome (see the Methods section; adjusted risk difference 1.8%; 95% CI, −14% to 11%; $P = .78$).

Of the 146 intent-to-treat participants, 4 (2.7%) were ultimately found not to have had cellulitis (2 intervention, 2 control). These were included in the intent-to-treat analysis because, in clinical practice, it is difficult to differentiate bacterial cellulitis from other causes of inflammation. Results were unchanged upon per-protocol analysis of the remaining 142, with a nonsignificant risk difference of 4.2% (95% CI, −7.4% to 16%; $P = .45$).

Among the 146 intent-to-treat participants, 75 (51%) had adverse events (Table 3). This was similar in intervention (49%) versus control (53%) groups (risk difference −4.1%; 95% CI, −20% to 12%; $P = .62$). There was 1 serious adverse event—a case of *Clostridium difficile* colitis in the placebo group.

DISCUSSION

We observed no benefit from the addition of trimethoprim-sulfamethoxazole to cephalexin in the outpatient treatment of cellulitis. This supports the guidelines of the IDSA, which recommend against targeting CA-MRSA for nonpurulent cellulitis [7].

Practice in recent years has not corresponded to these guidelines [3, 8, 9]. One study found that 38% of antibiotic regimens for skin infections treated in US emergency departments in 2005 included agents typically active against CA-MRSA [3]. By 2010, according to data from the National Hospital Ambulatory Medical Care Survey, 74% of all antibiotic regimens prescribed at emergency department visits for skin infections included an agent typically active against CA-MRSA (our own unpublished analysis). This nonconcordance of clinical practice and the IDSA guidelines is probably due to the time period when the guidelines were introduced and also the limited evidence base available to inform practice and guideline development regarding cellulitis.

Non-Purulent Cellulitis

The guidelines suggest that cellulitis is usually streptococcal, not staphylococcal. However, this cannot be supported by microbiological arguments, because microbiological data are not obtainable for most cases of cellulitis, with blood cultures positive in only 4%, needle aspiration in 29%, and punch biopsy in 18% [10, 18]. This means that >70% of cellulitis cases are not amenable to microbiological diagnosis. Moreover, among cellulitis cases with cultivable bacteria, *S. aureus* is a common finding [10]. Experimental evidence has also not been available because no trials have been reported, only observational studies [19–23]. These studies have been inconsistent, with 1 retrospective observational study suggesting benefit from antibiotics with activity against CA-MRSA [24]. That study made the nuanced observation that "receipt of an inactive agent . . . before zero time was not associated with later treatment failure." [24] Such subtle caveats emphasize the importance of prospective experimental evidence to justify treatment recommendations.

One line of indirect evidence that supports the guidelines is that epidemiological studies have found that CA-MRSA might be associated with abscesses but not cellulitis [19, 25]. Why CA-MRSA might be associated with abscesses but not cellulitis remains a subject of speculation. CA-MRSA produces exotoxins, including Panton-Valentine leukocidin, that have been found to be modulators of neutrophil chemotaxis, apoptosis, and other properties that might result in purulence and necrosis [26–28]. The observation that abscesses, not cellulitis, increased during the spread of CA-MRSA implies that cellulitis and CA-MRSA are not linked [19]. Once again, this provides indirect evidence to support the guideline's recommendation against CA-MRSA coverage for most cases of cellulitis.

Cellulitis is poorly understood, despite being so common. It remains a condition that is diagnosed purely on clinical grounds, with help from no objective diagnostic test. When discussed in the medical literature, it is described phenomenologically, with reference not to pathology but rather to predisposing conditions and clinical characteristics [10]. Even a major pathology textbook provides no description of the pathology of this common condition [29]. As discussed above, attempts to prove a bacterial etiology usually fail [10, 18]. Thus, when an epidemic of skin infections followed the emergence of CA-MRSA, clinical equipoise resulted, with nationwide practice variation and surging use of agents active against CA-MRSA among patients with skin infections [3, 8, 9].

Purulent Cellulitis

For the uncommon case of purulent cellulitis, the guidelines recommend "empirical therapy for CA-MRSA . . . pending culture results." [7] This recommendation cites a single observational study, which found CA-MRSA to be present in purulent cellulitis. However, that study also found no association of antibiotic susceptibility and outcome [2]. In our study, the presence of purulence at enrollment was not associated with response to trimethoprim-sulfamethoxazole.

Abscess

Considering abscess, the guidelines recommend antibiotics only "for abscesses associated with . . . severe or extensive disease . . . rapid progression in presence of associated cellulitis, signs and symptoms of systemic illness, associated comorbidities or immunosuppression, extremes of age, abscess in an area difficult to drain . . . associated septic phlebitis, and lack of response to incision and drainage alone." The recommendation

that antibiotics be used in such settings was based solely on expert opinion [7].

The present study is typical of pragmatic trials [11]. One feature of comparative effectiveness research is that its pragmatic approach can produce results that contradict what would be logically predictable from biological knowledge. We are in the midst of an epidemic of skin infections caused by CA-MRSA, but antibiotics targeting this organism have not been found helpful in pragmatic studies.

Limitations

The chief limitation of our study is intrinsic to most cases of cellulitis: there is no objective way to make an etiologic diagnosis. Our study was also limited to outpatients, including, for example, no patients with cellulitis complicating lymphedema, for whom blood cultures and intravenous antibiotics are recommended [10]. Our study provides no direct information about the management of such complicated skin infections in hospitalized patients, though it does provide support for the general concept that CA-MRSA is not important in cellulitis. Treatment of patients with life-threatening infections such as necrotizing fasciitis is not informed by this study. In this context, it bears mentioning that we avoided the common term "skin and soft-tissue infections," in favor of simply, "skin infections." "Soft tissue infections," which are not "skin infections," include such syndromes as pyomyositis and fasciitis and are rare. This study does not inform the treatment of such conditions.

We excluded diabetics. We are aware of no evidence that diabetics are at higher risk for CA-MRSA–associated skin infections, and thus our results may be generalizable to them. Most episodes of cellulitis in diabetics are treated as in nondiabetics [7]. While diabetic foot infections do require broader coverage, whether they require coverage for CA-MRSA remains unknown [10]. We assessed MRSA colonization nasally. Only 67% of MRSA-colonized skin infection patients have positive nasal swabs, with other common sites of colonization being the axillae, groin, and perineum [30]. Had we also swabbed the axillae and groin, we might have observed an interaction of colonization and treatment response. While CA-MRSA is almost universally susceptible to trimethoprim-sulfamethoxazole in vitro, it is possible that other agents, such as clindamycin and tetracyclines, might be more effective in vivo. Using diaries, participants indicated whether they took all of their medications each day until self-reported cure, and this is analyzed above. However, we did not record the total duration of therapy (ie, we cannot distinguish stopped therapy from a day of partial adherence). This reflects the study's nature as an effectiveness study, rather than an efficacy study, in that the practicing clinician controls only the prescription, not subsequent adherence. We did not record lesion area, which would have required photography and parsing of each lesion into measurable geometric shapes.

Though it achieved its target, our study was modest in size. This was not an equivalence study, and when we designed the trial, we expected to find a benefit from the intervention. The value of the result is that it is the first evidentiary support for the relevant national guidelines [7]. We know of only 2 other relevant trials: NCT00729937 and NCT00730028. If the IDSA guidelines are correct, those trials and meta-analyses combining their results with ours will narrow the confidence interval. However, those studies have posted no results on ClinicalTrials.gov (as of 30 November 2012), and thus we do not know when they will contribute relevant data from cellulitis patients or how large their samples of cellulitis patients will be.

As clinical trial evidence accumulates, antibiotic prescribing for skin infection patients might even be a reasonable target for antibiotic stewardship interventions, especially given how common skin infections are. Regarding abscesses, the evidence may already be sufficient to consider use of antibiotics for uncomplicated abscesses as a good target for antibiotic stewardship efforts. Regarding cellulitis, we feel that the present trial alone is not sufficient to motivate a stewardship campaign for cellulitis. If the results of the other studies mentioned above echo our own findings, reduction in the use of antibiotics that target CA-MRSA for uncomplicated cellulitis may become a reasonable target.

CONCLUSIONS

In the first study to provide experimental support for IDSA recommendations against antibiotics targeting CA-MRSA for most cases of cellulitis, we found that adding trimethoprim-sulfamethoxazole to cephalexin conferred no benefit relative to therapy with cephalexin alone in the outpatient treatment of cellulitis. Concerns about polypharmacy and antibiotic stewardship may lead us to rely on beta lactams when treating uncomplicated cellulitis.

Notes

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Potential conflicts of interest. All authors: No reported 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. Herold BC, Immergluck LC, Maranan MC, et al. Community-acquired methicillin-resistant *Staphylococcus aureus* in children with no identified predisposing risk. JAMA **1998**; 279:593–8.
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. 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.
4. 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.
5. Rajendran PM, Young D, Maurer T, et al. Randomized, double-blind, placebo-controlled trial of cephalexin for treatment of uncomplicated skin abscesses in a population at risk for community-acquired methicillin-resistant *Staphylococcus aureus* infection. Antimicrob Agents Chemother **2007**; 51:4044–8.
6. 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.
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:e18–55.
8. 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.
9. Herigon JC, Hersh AL, Gerber JS, Zaoutis TE, Newland JG. Antibiotic management of *Staphylococcus aureus* infections in US children's hospitals, 1999–2008. Pediatrics **2010**; 125:e1294–300.
10. Swartz MN. Clinical practice, cellulitis. N Engl J Med **2004**; 350:904–12.
11. Roland M, Torgerson D. What are pragmatic trials? BMJ **1998**; 316:285.
12. 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.
13. Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 statement: Updated guidelines for reporting parallel group randomized trials. Ann Intern Med **2010**; 152:726–32.
14. DiMattia AF, Sexton MJ, Smialowicz CR, Knapp WH Jr. Efficacy of two dosage schedules of cephalexin in dermatologic infections. J Fam Pract **1981**; 12:649–52.
15. Sanford JP, Gilbert DN, Sande MA. The Sanford guide to antimicrobial therapy. Dallas, TX: Antimicrobial Therapy, Inc, **1995**.
16. Dong SL, Kelly KD, Oland RC, Holroyd BR, Rowe BH. ED management of cellulitis: A review of five urban centers. Am J Emerg Med **2001**; 19:535–40.
17. Murray H, Stiell I, Wells G. Treatment failure in emergency department patients with cellulitis. CJEM **2005**; 7:228–34.
18. Duvanel T, Auckenthaler R, Rohner P, Harms M, Saurat JH. Quantitative cultures of biopsy specimens from cutaneous cellulitis. Arch Intern Med **1989**; 149:293–6.
19. 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 CA-MRSA, 1997–2007. Clin Infect Dis **2012**; 55:103–5.
20. Crawford SE, David MZ, Glikman D, King KJ, Boyle-Vavra S, Daum RS. Clinical importance of purulence in methicillin-resistant *Staphylococcus aureus* skin and soft tissue infections. J Am Board Fam Med **2009**; 22:647–54.
21. Eells SJ, Chira S, David CG, Craft N, Miller LG. Non-suppurative cellulitis: Risk factors and its association with *Staphylococcus aureus* colonization in an area of endemic community-associated methicillin-resistant *S. aureus* infections. Epidemiol Infect **2011**; 139:606–12.
22. Jeng A, Beheshti M, Li J, Nathan R. The role of beta-hemolytic streptococci in causing diffuse, nonculturable cellulitis: A prospective investigation. Medicine (Baltimore) **2010**; 89:217–26.
23. Elliott DJ, Zaoutis TE, Troxel AB, Loh A, Keren R. Empiric antimicrobial therapy for pediatric skin and soft-tissue infections in the era of methicillin-resistant *Staphylococcus aureus*. Pediatrics **2009**; 123: e959–66.
24. 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.
25. Karamatsu ML, Thorp AW, Brown L. Changes in community-associated methicillin-resistant *Staphylococcus aureus* skin and soft tissue infections presenting to the pediatric emergency department: Comparing 2003 to 2008. Pediatr Emerg Care **2012**; 28:131–5.
26. Vandenesch F, Naimi T, Enright MC, et al. Community-acquired methicillin-resistant *Staphylococcus aureus* carrying Panton-Valentine leukocidin genes: Worldwide emergence. Emerg Infect Dis **2003**; 9:978–84.
27. Naimi TS, LeDell KH, Como-Sabetti K, et al. Comparison of community- and health care-associated methicillin-resistant *Staphylococcus aureus* infection. JAMA **2003**; 290:2976–84.
28. Genestier AL, Michallet MC, Prevost G, et al. *Staphylococcus aureus* Panton-Valentine leukocidin directly targets mitochondria and induces bax-independent apoptosis of human neutrophils. J Clin Invest **2005**; 115:3117–27.
29. Kumar V, Robbins SL, Abbas AK. Robbins and Cotran pathologic basis of disease. Philadelphia, PA: Saunders/Elsevier, **2010**.
30. Yang ES, Tan J, Eells S, Rieg G, Tagudar G, Miller LG. Body site colonization in patients with community-associated methicillin-resistant *Staphylococcus aureus* and other types of *S. aureus* skin infections. Clin Microbiol Infect **2010**; 16:425–31.