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REVIEW ARTICLE

Sulfamethoxazole-Trimethoprim (Cotrimoxazole) for Skin and Soft Tissue Infections Including Impetigo, Cellulitis, and Abscess

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Skin and soft tissue infections (SSTI) affect millions of people globally, which represents a significant burden on ambulatory care and hospital settings. The role of sulfamethoxazole-trimethoprim (SXT) in SSTI treatment, particularly when group A *Streptococcus* (GAS) is involved, is controversial. We conducted a systematic review of clinical trials and observational studies that address the utility of SXT for SSTI treatment, caused by either GAS or *Staphylococcus aureus*, including methicillin-resistant (MRSA). We identified 196 studies, and 15 underwent full text review by 2 reviewers. Observational studies, which mainly focused on SSTI due to *S aureus*, supported the use of SXT when compared with clindamycin or β-lactams. Of 10 randomized controlled trials, 8 demonstrated the efficacy of SXT for SSTI treatment including conditions involving GAS. These findings support SXT use for treatment of impetigo and purulent cellulitis (without an additional β-lactam agent) and abscess and wound infection. For nonpurulent cellulitis, β-lactams remain the treatment of choice.

Keywords. group A *Streptococcus* (GAS); impetigo; skin and soft tissue infections; *Staphylococcus aureus*; sulfamethoxazole-trimethoprim.

The most common bacterial causes of skin and soft tissue infections (SSTI) are group A *Streptococcus* (GAS) and *Staphylococcus aureus*, the key bacterial agents of impetigo, cellulitis, abscesses, and wound infections [1]. Impetigo is driven by GAS in resource-poor settings [2]; however, in developed settings, impetigo, including bullous impetigo, is more likely to have *S aureus* present [3]. Although it is difficult to culture, cellulitis is commonly a GAS infection [4], whereas *S aureus* is consistently recovered from abscess specimens [5].

More than 162 million children suffer from impetigo at any one time [6]. Impetigo is one of eight dermatologic conditions in the 50 most common causes of the disease in the global burden of disease studies [7], and is the only one of these skin conditions with potentially life-threatening complications. The burden of impetigo is higher in resource-limited settings where poverty, household overcrowding, difficulties with sanitation, humid climate, scabies infestation, and minor trauma contribute to high rates of transmission and infection in childhood [8]. In addition, because the initial lesions rarely require hospitalization, impetigo is predominantly a primary care level consultation in both industrialized and nonindustrialized regions [9, 10], but it has significant sequelae resulting in hospitalization including streptococcal and staphylococcal bacteremia [11–13], skeletal infections [14], acute poststreptococcal glomerulonephritis [15], and possibly acute rheumatic fever [16].

Cellulitis and abscess account for millions of emergency department and primary care visits and are the most common SSTIs requiring hospitalization, which occurs in approximately 5% of cases [4, 17]. An increase in hospitalization for abscess has been described globally [18, 19]. Primary care physicians and healthcare workers in resource-limited settings frequently manage the early stages of these infections. Global morbidity from cellulitis has been estimated to contribute 0.04% of the total global burden of disease and is in the top 10 skin conditions accounting for this [20].

Antimicrobial agents that are able to target both GAS and *S aureus* are valuable to streamline prescription, improve adherence, and minimize adverse events, and β-lactam agents have served this purpose for decades [1]. However, with the global rise of community-associated methicillin-resistant *S aureus* (CA-MRSA) [5, 21], non-β-lactam antimicrobial agents have become increasingly important [2, 22, 23]. One such antibiotic is sulfamethoxazole-trimethoprim (SXT).

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Sulfamethoxazole-trimethoprim is a recommended antibiotic for CA-MRSA SSTI [1, 24], but there is an ongoing belief that SXT is ineffective for GAS SSTI [25], and dual therapy is often recommended when GAS may be present [1]. This belief partly stems from early studies that reported the in vitro resistance of GAS to SXT [26, 27]. However, these studies did not control the thymidine content of test media. Where levels of thymidine may be elevated, thus antagonizing the inhibitory effects of sulfur drugs, the test media require supplementation with lysed horse blood, which releases thymidine phosphorylase to overcome the inhibition [28]. In the current era, the thymidine content of Mueller-Hinton agar (MHA) is standardized at very low levels [29], which no longer makes this a technical problem. With the availability of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints for testing susceptibility of GAS to SXT (www.eucast.org), clinicians can now assess the resistance profile of both *S aureus* and GAS to SXT to inform prescribing decisions. In addition, molecular markers of GAS resistance to trimethoprim (TMP) have recently been reported [30].

In this study, we aimed to (1) determine the clinical efficacy of SXT for SSTI, including SSTI involving GAS, by conducting a systematic review of all published randomized controlled trials (RCTs) and observational studies on the use of SXT for treatment of SSTI and (2) update a previous review of studies assessing the in vitro susceptibility of GAS to SXT and TMP.

METHODS

Search Strategy and Selection Criteria

A systematic literature search (part 1) using the terms ("skin diseases, bacterial"[MeSH Terms]) AND ("trimethoprim, sulfamethoxazole drug combination"[MeSH Terms]) was performed to inform the clinical utility of SXT for the treatment of SSTI caused by either GAS or *S aureus* including MRSA. The systematic review was conducted according to PRISMA guidelines [31]. References were identified through PubMed and Embase for papers published in English between January 1970 and September 2017. Duplicates were removed before titles and abstracts were reviewed for relevance.

A second literature search (part 2) was conducted to address the question of susceptibility of GAS to SXT and TMP as an update to a previous literature review in 2012 [25]. We used the terms ("streptococcus pyogenes"[MeSH Terms] OR "group a streptococcus"[All Fields]) AND (("trimethoprim"[MeSH Terms] AND "sulfamethoxazole"[MeSH Terms] AND ("drug combinations"[MeSH Terms])).

Selection Criteria

We included only RCTs, non-RCTs, and observational studies in part 1. Any literature reporting susceptibility of GAS to SXT or TMP was included in part 2. Full text papers were reviewed by 2 authors (A. C. B. and S. Y. C. T.) for data extraction. Ethics approval was not sought to conduct this systematic review.

Statistical Analysis

The data are synthesized into a narrative summary. A formal meta-analysis was not performed given the heterogeneity of the underlying conditions and interventions.

RESULTS

We identified a total of 196 titles for inclusion in part 1 and assessed 41 titles and abstracts (Figure 1). From these, 15 full text articles met the inclusion criteria. We identified 6 new studies regarding GAS susceptibility to SXT or TMP, only 3 of which

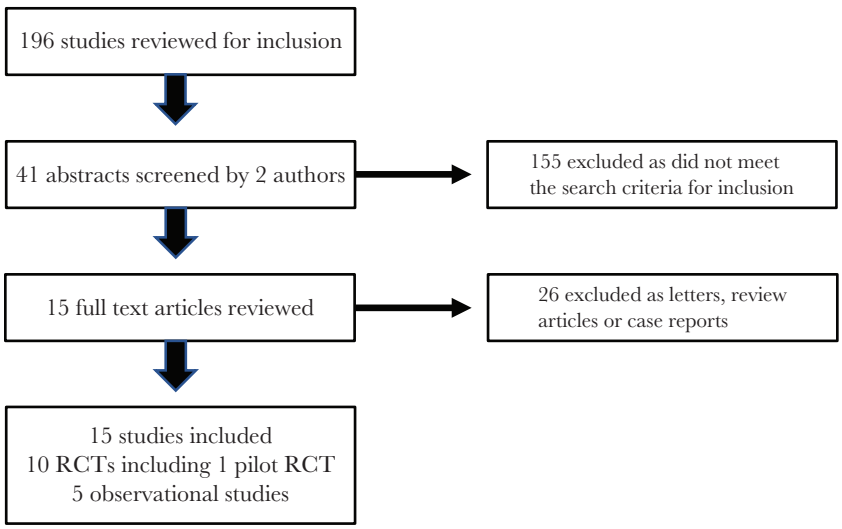

Figure 1. Outline of systematic literature search for clinical trials according to PRISMA methodology. RCT, randomized controlled trial.

contained relevant data. Two more studies were identified from study references (Supplementary Figure).

Clinical Studies

Results from the 15 relevant studies are summarized in Table 1. The 5 observational studies were all retrospective and, as such, may not account for other factors impacting on the outcome: 2 studies showed no difference between SXT and clindamycin for the treatment of SSTI due to CA-MRSA [32, 33], whereas 2 showed increased treatment failures with SXT compared with clindamycin [34] or a β-lactam [35] for SSTI. Large, well conduced RCTs have now surpassed this level of evidence, and the key, recently published RCTs informing this question are further discussed below [2, 22, 36].

Short-course oral SXT (3- or 5-day courses) was shown to be effective for impetigo in one of the largest clinical trials conducted on the treatment of impetigo and only the second that has studied the condition in an endemic, tropical environment where the global burden is the highest [2]. For Australian Indigenous children living in remote areas, 3 days of twice-daily SXT at 20 + 4 mg per kilogram per dose or 5 days of once-daily SXT at 40 + 8 mg per kilogram per dose resulted in successful treatment in 85% of children (as judged by blinded reviews of clinical photographs at day 7 after commencement of treatment) [2]. Unblinded clinical assessments indicated successful treatment in 99% of cases [2]. Participants treated with benzathine penicillin G (BPG) achieved similar rates of successful treatment, but the pain of the injection was reported to be an adverse event for almost one third of the children [2].

Sulfamethoxazole-trimethoprim was compared with clindamycin for the treatment of uncomplicated skin infections including abscess >5 cm (31%), cellulitis (53%), and mixed infections (16%) in 524 patients (30% children) in a multicenter, double-blind RCT in the United States [22]. Antibiotics were prescribed for a 10-day course of treatment. In both the intention-to-treat and evaluable populations, SXT and clindamycin had similar efficacies. Cure was achieved in 80% and 78% at 10–14 days after completion of therapy for SXT and clindamycin, respectively (P = .52) [22]. When the populations were stratified into cellulitis and abscess groups, SXT and clindamycin were comparable in efficacy in both types of infections including cellulitis, a condition considered to be commonly caused by GAS [4]; however, in this trial, there were few GAS isolates detected [22].

Talan et al [36] compared SXT at 320/1600 mg po bid for 7 days with placebo for the treatment of drained abscesses >2 cm. A total of 1247 participants aged >12 years were enrolled in this multicenter, placebo-controlled RCT. Cure of abscess was achieved in 80.5% of participants in the modified intention-to-treat population at test of cure using SXT, whereas only 73.6% were cured in the placebo arm, a difference of 6.9% (95% confidence interval [CI], 2.1%–11.7%, meeting predetermined superiority endpoints). Results from the per-protocol analysis were similar. Although cure rates were high in both arms after abscess drainage, an additional 7% efficacy is both statistically and clinically significant when considering the use of an adjunctive antibiotic with a good safety profile [36]. Secondary outcomes also showed fewer recurrences or serious infections in the SXT arm [36]. This large trial demonstrated that antibiotics can be an important adjunctive treatment for abscess in addition to incision and drainage where other smaller trials have failed to show a benefit [37]. In this study, there were too few patients with GAS cultured (5%) to draw specific conclusions regarding efficacy for abscesses involving GAS.

Treatment of cellulitis alone was evaluated in 926 patients from 3 trials [22, 38, 39]. In 2 trials, SXT in combination with cephalexin was compared with cephalexin alone with no difference found between the 2 regimens [38, 39]. Pooling the results from the intention-to-treat analysis of both studies shows no difference in treatment success between SXT with cephalexin (249 of 321, 77.6%) and cephalexin alone (233 of 321, 72.6%) (P = .14). Among the subgroup of patients enrolled by Miller et al [23] with cellulitis alone (n = 280, 53% of the total study population), there was a nonsignificant difference in treatment success in the intention-to-treat population between clindamycin (110 of 136, 80.9%) and SXT (110 of 144, 76.4%), risk difference –4.5% (95% CI, –15.1 to 6.1). Taken together, these results suggest that coverage of MRSA is not required for uncomplicated, nonpurulent cellulitis. However, it does appear that SXT alone is effective in treating uncomplicated, nonpurulent cellulitis.

Microbiological Susceptibility Data

Since a previous review of GAS susceptibility to SXT in 2012 [25], susceptibility data from 5 more studies have been published (Table 2, including a previously overlooked study published in 2008). While demonstrating the utility of susceptibility testing of GAS to SXT, 3 studies from India found higher rates of resistance ranging from 12% to 78% of tested isolates [30, 40, 41]. The EUCAST group found that 37 (1.4%) of 2592 wild-type *Streptococcus pyogenes* isolates collected from all over Europe tested resistant to cotrimoxazole (available at www.eucast.org).

DISCUSSION

The Infectious Diseases Society of America (IDSA) updated their guidelines for the diagnosis and management of SSTI in 2014 [1]. These guidelines GRADE (Grading of Recommendations Assessment, Development and Evaluation) [42] the available evidence and are widely consulted, including in nonindustrialized settings outside of the United States. The findings of our review highlight 2 key points regarding the use of SXT for SSTI. First, there is now strong, high GRADE evidence that SXT should be recommended for the treatment of impetigo in endemic settings where GAS is the principal

Table 1. Fifteen Included Studies With Available Data on Effectiveness of Sulfamethoxazole-Trimethoprim for Treatment of Skin and Soft Tissue Infections in the Methicillin-Resistant *Staphylococcus aureus* Era

Type of SSTI; Author, Year	Population	Study Design	Interventions	No. of Participants	Primary Outcome	Microbiology
Smaller skin abscesses; Daum, 2017 [49]	Outpatients, children and adults	RCT	Clindamycin vs SXT vs placebo	786	Clinical cure at the time of test-of-cure visit: clindamycin (83.1%), SXT (81.7%), and placebo (68.9%), $P < .001$. Rate difference between clindamycin and SXT –1.3% (95% CI, –8.4% to 5.7%; $P = .73$)	67.0% cultured *S aureus*, 73.6% of which were MRSA. *Staphylococcus pyogenes* 0.9%.
Uncomplicated cellulitis; Moran, 2017 [38]	Outpatients, >12 y.o.	RCT	Cephalexin + SXT vs Cephalexin + placebo	500	Per protocol analysis of clinical cure of cephalexin + SXT 182/218 (83.5%) vs cephalexin + placebo 165/193 (85.5%), $P = .5$. Mean difference –2.0 (95% CI, –9.7 to 5.7) Modified intention to treat analysis of clinical cure of cephalexin + SXT 189/248 (76.2%) vs cephalexin + placebo 171/248 (69.0%), $P = .07$, Mean difference 7.3% (95% CI, –1.0 to 15.5)	Baseline cultures not performed
Uncomplicated skin abscess; Talan, 2016 [36]	Outpatients >12 y.o.	RCT	SXT vs placebo	1247	Clinical cure of SXT (80.5%) vs placebo (73.6%) $P = .005$. Rate difference 6.9% (95% CI, 2.1% to 11.7%)	62% cultured *S aureus*; 5% cultured *S pyogenes*
Skin abscesses, Holmes, 2016 [46]	Children	RCT	SXT for 3 days vs 10 days	249	Clinical cure of SXT 3 days (93%) vs SXT 10 days (97%), $P = .25$	87% cultured *S aureus*; 2% cultured *S pyogenes*
Uncomplicated skin infections including cellulitis; Miller, 2015 [58]	Children and adults	RCT	Clindamycin vs SXT	524	Clinical cure of clindamycin (80.3%) vs SXT (77.7%), $P = .52$. Difference –2.6% (95% CI, –10.2 to 4.9)	Abscess 31%; cellulitis 53%; mixed 16%. 47% no culture/growth, 41% cultured *S aureus*, 2% cultured *S pyogenes*
Impetigo; Bowen, 2014 [2]	Children	RCT	SXT vs benzathine penicillin	508	Treatment success of SXT (85%) vs benzathine penicillin (85%), P = NS. Absolute difference 0.5%; 95% CI, –6.2 to 7.3	90% cultured *S pyogenes*; 81% cultured *S aureus*; 75% cultured both
Uncomplicated cellulitis without abscess; Pallin, 2013 [39]	Children and adults managed as outpatients	RCT	Cephalexin vs cephalexin plus SXT	146	Clinical cure of cephalexin (82%) vs cephalexin plus SXT (85%) $P = .66$. Risk difference 2.7% (95% CI, –9.3 to 15)	No wound cultures performed
MRSA SSTIs; Cadena, 2011 [47]	Adults	Observational cohort	SXT 320/1600 mg twice daily vs SXT 160/800 mg twice daily	291	Clinical resolution with high dose (73%) vs low dose (75%), $P = .79$	100% cultured MRSA (this was the inclusion criteria)
SSTI; Williams, 2011 [35]	Children 0–17 years	Retrospective cohort	Clindamycin vs β-lactam vs SXT	47 501	Drainage procedure (n = 6407): Treatment failure of clindamycin (4.7%) vs SXT (11.2%) vs β -lactam (11.1%) aOR for SXT vs clindamycin 1.92 (95% CI, 1.49 to 2.47). No drainage procedure (41 094): Treatment failure of clindamycin (4.9%), SXT (8.8%) and β-lactam (5.3%) aOR for SXT vs clindamycin 1.67 (95% CI, 1.44 to 1.95)	Drainage: 93% abscess/cellulitis. No drainage: 61.2% abscess/cellulitis, 20.7% impetigo. Microbiology not reported
MRSA SSTI; Frei, 2010 [32]	Adults	Retrospective cohort	Clindamycin vs SXT	149	Treatment failure of clindamycin (32%) vs SXT (39%), $P = .5$	60% incision and drainage. 100% cultured MRSA (this was the inclusion criteria).
Impetigo; Tong, 2010 [59]	Children	Pilot RCT	SXT vs benzathine penicillin	13	Treatment success of SXT (100%) vs benzathine penicillin (83%), P = NS	100% cultured *S aureus*; 31% cultured *S pyogenes*
Uncomplicated abscess; Schmitz, 2010 [48]	Adults	RCT	SXT vs placebo after incision and drainage	212	Treatment failure of SXT 17% vs placebo 26%, $P = .12$. Difference 9% (95% CI, –2% to 21%), 30-day follow up, fewer new lesions: SXT 9% vs placebo 28%, $P = .02$. Difference 19% (95% CI, 4% to 34%)	All had abscess, median size 2.6 cm with surrounding cellulitis. 53% cultured MRSA, 19% MSSA
Non drained, noncultured SSTI; Elliot, 2009 [34]	Children	Retrospective nested case control trial	SXT vs clindamycin vs β-lactam	584	Primary multivariate model, SXT treatment failure OR 2.4 (95% CI, 1.3–4.3) vs clindamycin treatment failure OR 1.4 (95% CI, 0.8–2.6) and β-lactam 1.0 (reference)	26% induration, 8% abscess, 24% impetigo
Skin abscess; Duong, 2010 [37]	Children	RCT	SXT vs placebo	161	Clinical resolution with SXT (96%) vs placebo (95%), P = NS. Difference 1.2% (95% CI, –∞ to 6.8%)	89% cultured *S aureus*; 1% cultured5 *S pyogenes*
SSTI; Hyun, 2009 [33]	Children	Retrospective audit	SXT vs clindamycin after initial IV clindamycin	415	No difference in repeat surgeries. No difference in return to hospital at 30 days: SXT 2.3% vs clindamycin 3.5%, $P = .56$	100% cultured MRSA (this was part of inclusion criteria)

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; IV, intravenous; MRSA, methicillin-resistant S *aureus*; NS, nonsignificant; OR, odds ratio; RCT, randomized controlled trial; SSTI, skin and soft tissue infection; SXT, sulfamethoxazole-trimethoprim; y.o., years old.

Table 2. Recent Studies That Contain Susceptibility Data for Group A *Streptococcus* (GAS) to Sulfamethoxazole-Trimethoprim (SXT) or Trimethoprim (TMP)

Author	Year	Country	Method and Medium	Findings
Imohl et al [60]	2015	Germany	Broth microdilution as per CLSI methods but using EUCAST breakpoints. Agar not specified	11 of 1265 (0.9%) invasive GAS SXT resistant. Increasing SXT nonsusceptibility since 2012
Bowen et al [2, 61]	2014	Australia	MIC determined by Etest on MHF according to EUCAST standards	4 of 455 (0.9%) SXT resistant
Bergmann et al [30]	2014	India	MIC of TMP determined by agar dilution method on MHF	69 of 268 (25.7%) isolates TMP resistant
Devi et al [41]	2011	India	AST determined by disc diffusion on MHS as per CLSI methods	14 of 18 (77.7%) SXT resistant
Jain et al [40]	2008	India	AST determined on MHS by MIC according to CLSI methods	6 of 49 (12.2%) SXT resistant

Abbreviations: AST, antibiotic susceptibility testing; CLSI, Clinical Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; MHF, Mueller Hinton-F agar containing 5% horse blood and 20 mg/L β-NAD; MIC, minimum inhibitory concentration; SXT, sulfamethoxazole-trimethoprim; TMP, trimethoprim.

pathogen. We see no reason why SXT should not also be recommended as an option for staphylococcal impetigo. Second, SXT is also an appropriate single agent for outpatients with other uncomplicated SSTI such as cellulitis and mixed Gram-positive abscesses where GAS may be involved. Advantages of SXT include its ability to be used for short courses, track record of safety, and palatability in children.

Sulfamethoxazole-trimethoprim activity against GAS in vitro [25, 43, 44] provided the supportive laboratory data that SXT could potentially be used to treat uncomplicated SSTI involving GAS. Although most studies of SXT have focused on SSTI where *S aureus* is the main pathogen [32–35, 37, 39, 45–49], the recent trials involving impetigo [2] and cellulitis [22] now clearly demonstrate that the in vitro data can be translated to the clinical setting, at least for uncomplicated SSTI. Notably, Bowen et al [2] observed participants at day 2 and day 7 and demonstrated effective microbiological clearance of GAS from impetigo lesions at rates comparable to intramuscular BPG (reduction from recovery of GAS from impetigo lesions in >85% of participants at baseline to <7% at day 7 with both SXT and BPG).

Concerns have been raised that *S aureus* can acquire free thymidine from deoxyribonucleic acid fragments present in purulent abscess material, thus allowing *S aureus* to bypass the inhibitory effects of SXT on the folate synthesis pathway [50]. Although this is certainly possible, the weight of clinical trial evidence now suggests that with effective incision and drainage of an abscess, such a concern may be mitigated.

In the IDSA guidelines, a 7-day treatment course with an oral antibiotic is recommended for severe or epidemic impetigo [1]. It is recommended that these oral antibiotics should be active against *S aureus* unless cultures yield streptococci alone and include cephalexin, clindamycin, erythromycin, or amoxicillin-clavulanate as treatment options (strong recommendation, high GRADE evidence) [1]. We recommend that SXT should now be added to this list for impetigo (strong recommendation, high GRADE evidence). We agree with the recommendation to use systemic (rather than topical) antibiotics for severe, endemic, or epidemic impetigo [1]. In addition, it may be possible to shorten the treatment course from the current 7-day regimen. Both 3-day and 5-day courses of SXT achieved equivalent cure rates to intramuscular BPG [2].

The treatment of cellulitis and abscess does currently include SXT as one of the treatment options in the IDSA guidelines [1]. However, if GAS is suspected, for example in purulent cellulitis, the addition of a β-lactam active against GAS is recommended [1]. In showing effective treatment of cellulitis, Miller et al [22] in particular demonstrated the clinical efficacy of SXT for the treatment of SSTI where GAS is considered to be an important pathogen. The principles of antimicrobial stewardship support the use of a single agent when cover is effective without the need for the addition of a second agent. Thus, we suggest that SXT as a single agent be added to the recommended list of antimicrobial options for uncomplicated purulent cellulitis (strong recommendation, moderate GRADE evidence).

For nonpurulent cellulitis, the studies finding no benefit in the addition of SXT to cephalexin [38, 39] indicate that MRSA coverage is not usually required, and that β-lactam monotherapy remains the treatment of choice (strong recommendation, moderate GRADE evidence). Although clindamycin or SXT alone have not been directly compared with a β-lactam alone for nonpurulent cellulitis, the high treatment success rates found by Miller et al [22] suggest that both clindamycin and SXT are effective therapies. Thus, where β-lactam therapy is contraindicated (eg, allergy) or poorly tolerated, both clindamycin and SXT are viable options (strong recommendation, moderate GRADE evidence). The twice-daily dosing of SXT may be attractive for children in comparison to clindamycin (3 times per day) or most β-lactams (4 times per day). A clinical trial directly comparing SXT with a β-lactam for nonpurulent cellulitis would address a key remaining question.

Ongoing robust surveillance that links antimicrobial prescription to antimicrobial resistance is needed to continue to understand the impact of widespread use of SXT for SSTI in highly endemic settings. Antibiotic resistance profiles vary globally due to antibiotic selection pressures. Recent studies from Africa demonstrate widespread resistance of *S aureus* to

SXT [51]. Even in this context, the utility of SXT for the treatment of impetigo likely remains strong because it is primarily a GAS-driven infection [2, 52]. In addition, recent data from Africa, where children living with human immunodeficiency virus were randomized to receive SXT prophylaxis or placebo, demonstrated a significant reduction in skin infections in those receiving SXT prophylaxis [53, 54]. The studies from India indicating the presence of GAS strains with resistance to TMP or SXT [40, 41] are of concern and support the need for ongoing monitoring of GAS susceptibility to SXT, especially in regions globally where GAS infections are common and SXT is being increasingly used. As with the broadening of indication for any antibiotic, prospective monitoring for not only resistance rates but also clinical failures associated with such resistance will be critical.

In areas where impetigo is endemic, the option of short-course oral SXT may establish a feasible community-wide strategy that incorporates screening for skin sores and scabies followed by treatment of both. Scabies underlies much of the impetigo in these circumstances, and there has been increasing support for ivermectin mass drug administration in scabies-endemic regions to both control scabies and reduce the high rates of impetigo [55–57]. Future skin programs with ivermectin and short-course oral SXT may painlessly reduce the longstanding burden of both scabies and impetigo in endemic regions.

CONCLUSIONS

In this study, we highlight recent pivotal clinical studies that demonstrate the efficacy of SXT for SSTI, including in cases in which GAS is typically the causative organism. It is time to re-evaluate treatment recommendations and overturn the dogma that SXT is ineffective for GAS SSTI.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Potential conflicts of interest. V. F. served as Chair of V710 Scientific Advisory Committee (Merck) and has received grant support from Cerexa/Actavis, Pfizer, Advanced Liquid Logics, National Institutes of Health (NIH), MedImmune, Cubist/Merck, Karius, Contrafect, and Genentech. NIH Small Business Technology Transfer/Small Business Innovation Research grants pending: Affinergy, Locus, Medical Surface, Inc. V. F. has also been a paid consultant for Achaogen, Astellas, Arsanis, Affinergy, Basilea, Bayer, Cerexa, Contrafect, Cubist, Debiopharm, Durata, Grifols, Genentech, MedImmune, Merck, Medicines Co., Pfizer, Novartis, Novadigm, Theravance, and XBiotech and has received honoraria from Theravance and Green Cross. V. F. has a patent pending in sepsis diagnostics, "Biomarkers for the molecular classification of bacterial infection". Patent application no. US 14/214,853. 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.

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