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

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Title: Sulfamethoxazole-trimethoprim (co-trimoxazole) for skin and soft tissue infections including impetigo, cellulitis and abscess

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Keywords:

Skin and soft tissue infections, impetigo, sulfamethoxazole-trimethoprim, Group A \textit{Streptococcus} (GAS), \textit{Staphylococcus aureus}

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Summary:

We synthesise in this systematic review, the latest evidence for the use of sulfamethoxazole-trimethoprim (SXT) in the treatment of skin infections including impetigo, cellulitis and abscess. SXT is effective for treatment of uncomplicated skin infections caused by *S. aureus* and Group A *Streptococcus*. 
Abstract

Skin and soft tissue infections (SSTI) affect millions globally, representing a significant burden on ambulatory and hospital settings. The role of sulfamethoxazole-trimethoprim (SXT) in SSTI treatment, particularly where Group A Streptococcus (GAS) may be 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, 15 underwent full text review by two reviewers. Observational studies, mainly focused on SSTI due to S. aureus, supported the use of SXT when compared with clindamycin or β-lactams. Of ten randomized controlled trials (RCTs), eight 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 non-purulent cellulitis, β-lactams remain the treatment of choice.
Introduction

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 contexts,[2] although in developed settings impetigo, including bullous impetigo, is more likely to have S. aureus present.[3] Although difficult to culture, cellulitis is commonly a GAS infection[4] while S. aureus is consistently recovered from abscess specimens.[5]

Impetigo is suffered by more than 162 million children at any one time.[6] It is one of eight dermatologic conditions in the 50 most common causes of disease[7] and is the only one of these skin conditions with potentially life-threatening complications. The burden of impetigo falls heavily 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, as the initial lesions rarely require hospitalization, impetigo is predominantly a primary care level consultation in both industrialized and non-industrialized regions.[9][10] but has significant sequelae resulting in hospitalization including streptococcal and staphylococcal bacteremia,[11-13] skeletal infections,[14] acute post streptococcal 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 about 5% of cases.[4, 17] An increase in hospitalization for abscess has been described globally.[18, 19] Primary care physicians and health care workers in resource-limited settings frequently manage the early stages of these infections.
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 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). SXT is a recommended antibiotic for CA-MRSA SSTI[1, 24] but there persists 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 on 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] making this no longer a technical problem. With the availability of 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. In addition, molecular markers of GAS resistance to trimethoprim (TMP) have recently been reported.[30]

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 sulfamethoxazole-trimethoprim (SXT) for the treatment of SSTI caused by either GAS or S. aureus including methicillin-resistant S. aureus (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 randomized controlled trials (RCT), non-randomized clinical trials, 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 two authors (AB, ST) 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 six new studies regarding GAS susceptibility to SXT or TMP, of which only three 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 five observational studies were all retrospective, and as such may not account for other factors impacting on the outcome: two studies showed no difference between SXT and clindamycin for the treatment of SSTI due to CA-MRSA [32, 33] whilst two showed increased treatment failures with SXT compared to clindamycin[34] or a B-lactam[35] for SSTI. Large, well conducted 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]

Involving remote living Australian Indigenous children, 3-days of twice daily SXT at 20+4mg/kg/dose or 5-days of once daily SXT at 40+8mg/kg/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 a reported adverse event for almost one-third of the children.[2]

SXT was compared with clindamycin for the treatment of uncomplicated skin infections including abscess > 5cm (31%), cellulitis (53%) and mixed infections (16%) in 524 patients (30% children) in a multi-centre, double blind RCT in the USA.[22] Antibiotics were prescribed for 10 days duration and in both the intention to treat and evaluable population, 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=0.52.[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] although in this trial there were few GAS isolates detected.[22]

Talan et al compared SXT at 320/1600mg po BD for 7 days with placebo for the treatment of drained abscesses > 2cm.[36] 1247 participants aged > 12 years were enrolled in this multi-centre, 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, difference 6.9% (95% CI 2.1 to 11.7%, meeting pre-determined superiority endpoints). Results from
the per-protocol analysis were similar. While cure rates were high in both arms following 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 three trials.[22, 38, 39] In two trials,
SXT in combination with cephalexin was compared with cephalexin alone with no difference found
between the two 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 (249/321, 77.6%)
and cephalexin alone (233/321, 72.6%), p=0.14. 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 non-significant
difference in treatment success in the intention to treat population between clindamycin (110/136,
80.9%) and SXT (110/144, 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, non-purulent cellulitis.
However, it does appear that SXT alone is effective in treating uncomplicated, non-purulent cellulitis.

Microbiological Susceptibility Data

Since a previous review of GAS susceptibility to SXT in 2012[25], susceptibility data from five 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, three studies from India found
higher rates of resistance ranging from 12 - 78% of tested isolates.[30, 40, 41] The EUCAST group, found that 37 (1.4%) of 2592 wild type \textit{S. pyogenes} isolates collected from all over Europe tested resistant to cotrimoxazole (www.eucast.org, accessed 27 September 2017).

Discussion

The Infectious Diseases Society of America (IDSA) updated their guidelines for the diagnosis and management of SSTI in 2014.[1] These guidelines GRADE[42] the available evidence and are widely consulted, including in non-industrialized settings outside of the USA. The findings of our review highlight two 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 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 out-patients 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.

SXT activity against GAS \textit{in vitro}[25, 43, 44] provided the supportive laboratory data that SXT could potentially be used to treat uncomplicated SSTI involving GAS. While most studies of SXT have focused on SSTI where \textit{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 \textit{in vitro} data can be translated to the clinical setting, at least for uncomplicated SSTI. Notably, Bowen \textit{et. al.} followed 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).[2]
Concerns have been raised that *S. aureus* can acquire free thymidine from DNA fragments present in purulent abscess material, thus allowing *S. aureus* to bypass the inhibitory effects of SXT on the folate synthesis pathway.[50] While 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 cephalaxin, 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] Additionally, 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. in particular demonstrated the clinical efficacy of SXT for the treatment of SSTI where GAS is considered to be an important pathogen.[22] The principles of antimicrobial stewardship would 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 non-purulent 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 B-lactam mono-therapy remains the 
treatment of choice (strong recommendation, moderate GRADE evidence). While clindamycin or SXT 
alone have not been directly compared to a β-lactam alone for non-purulent 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 (e.g., 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 (3x / day) or 
most β-lactams (4x / day). A clinical trial directly comparing SXT with a β-lactam for non-purulent 
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 as it is primarily a GAS driven 
infection.[2, 52] In addition, recent data from Africa, where children living with HIV were randomised 
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.

Where impetigo is endemic, the option of short course oral SXT may make feasible community-wide strategies incorporating 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:

Here we highlight recent pivotal clinical studies that demonstrate the efficacy of SXT for SSTI, including where GAS is typically the causative organism. It is time to re-evaluate treatment recommendations and over-turn the dogma that SXT is ineffective for GAS SSTI.

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Conflicts of interest:

AB, ST, BC, HC and JC have no conflicts of interest to declare.

VGF served as Chair of V710 Scientific Advisory Committee (Merck); has received grant support from Cerexa/Actavis, Pfizer, Advanced Liquid Logics, NIH, MedImmune, Cubist/Merck, Karius, Contrafect, and Genentech. NIH STTR/SBIR grants pending: Affinergy, Locus, Medical Surface, Inc.; has 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, xBiotech, and has received honoraria from Theravance, Green Cross. VGF has a patent pending in sepsis diagnostics, "Biomarkers for the molecular classification of bacterial infection". Patent application # US 14/214,853.

References

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<td>SSTI; Hyun, 2009[33]</td>
<td>Children</td>
<td>Retrospective audit</td>
<td>SXT vs clindamycin following initial IV clindamycin</td>
<td>No difference in repeat surgeries; No difference in return to hospital at 30 days: SXT 2.3% v clindamycin 3.5%, p=0.56 100% cultured MRSA (this was part of inclusion criteria)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: SSTI – skin and soft tissue infection; RCT – randomized controlled trial; SXT – sulfamethoxazole-trimethoprim; MRSA – methicillin-resistant S. aureus; NS – non significant; OR – odds ratio; aOR – adjusted Odds Ratio; 95%CI – confidence interval.

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

Note: CLSI - Clinical Laboratory Standards Institute; EUCAST - European Committee on Antimicrobial susceptibility testing; AST - Antibiotic Susceptibility Testing; MIC - Minimum Inhibitory Concentration; MHF - Mueller Hinton agar containing 5% horse blood and 20mg/l beta-NAD; MHS - Mueller Hinton agar containing sheep blood.

**Table 2:** Recent studies that contain susceptibility data for Group A *Streptococcus* (GAS) to sulfamethoxazole-trimethoprim (SXT) or trimethoprim (TMP).
Figure 1: Outline of systematic literature search for clinical trials according to PRISMA methodology.

- 196 studies reviewed for inclusion
- 41 abstracts screened by 2 authors
- 15 full text articles reviewed
- 15 studies included
  - 10 RCTs including 1 pilot RCT
  - 5 observational studies
- 155 excluded as did not meet the search criteria for inclusion
- 26 excluded as letters, review articles or case reports