Is Trimethoprim-Sulfamethoxazole a Valid Alternative in the Management of Infections in Children in the Era of Community-Acquired Methicillin-Resistant *Staphylococcus aureus*? A Comprehensive Systematic Review

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María Teresa Rosanova, MD, PhD¹, Leticia Cuellar Pompa, MD²,
Guadalupe Perez, MD¹, Norma Sberna, PharmD¹, Pedro Serrano-Aguilar, MD, PhD³,
and Roberto Lede, MD, PhD⁴

Abstract

Objective. To evaluate the use of TMP-SMX compared with other options available for the treatment of children with community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infections. **Data Sources.** The following databases were searched: Medline and PreMedline (OvidSP interface); Excerpta Medica Database (EMBASE; Elsevier interface); Cumulative Index to the Nursing and Allied Health Literature (CINAHL; EbscoHost interface); Sciences Citation Index Expanded (SCI-EXPANDED; Web of Science interface); Cochrane Library (Wiley interface); Scopus (Elsevier interface), and DARE, HTA (CRD interface). The search strategy was the one developed by SIGN to identify randomized clinical trials and systematic reviews. Also, we conducted a hand review of all reference lists of included studies. No language or data limits were added. The last search was done on October 1, 2015. Main key words were trimethoprim or trimethoprim-sulfamethoxazole combination and *Staphylococcus aureus*. **Study Selection.** Only randomized controlled trials comparing TMP-SMX versus any other antibiotic as the first-line treatment in CA-MRSA infections in children were included. Articles were reviewed by 2 reviewers, and in case of discrepancy, the final decision was made by the study coordinator. **Data Extraction.** Only 27 out of 364 articles identified were randomized controlled trials and only 4 fulfilled the eligibility criteria (Jadad score >3). **Data Synthesis.** Evidence found only referred to use of TMP-SMX in soft tissue infections. Heterogeneity among studies precluded meta-analysis. **Conclusions.** Available evidence is not conclusive to promote or refuse TMP-SMX as first-line treatment in CA-MRSA infections in children. Additional well-designed studies are required to further elucidate this issue.

Keywords

antibiotic resistance, clinical pharmacy, clinical practice, infectious disease, medical education

Introduction

Antibiotic resistance has long been a problem associated with *Staphylococcus aureus*, of which the most common is methicillin-resistant *S aureus*. Previously, the treatment for *S aureus* infections was cefazolin or cephalothin as most of the isolated strains were susceptible to β -lactam antibiotics. In recent years, there has been a marked increase in the incidence of invasive community-acquired methicillin-resistant *S aureus* (CA-MRSA) among children worldwide.¹ Some authors have suggested that a change in empirical antibiotic therapy covering CA-MRSA is warranted since the prevalence of CA-MRSA infection exceeds 10% to 15%, although there are no specific data to support this figure.¹⁻⁵

Staphylococcus aureus infections occur at all ages. Even though most of them are mild to moderate, such as skin and soft tissue infections, some, particularly CA-MRSA infections, may be severe and life threatening.²

¹Hospital de Pediatría JP Garrahan, Buenos Aires, Argentina

²Fundación Canaria de Investigación Sanitaria, Tenerife, Spain

³Red de investigación de servicios de salud en enfermedades crónicas, Tenerife, Spain (REDISSEC)

⁴Universidad Abierta Interamericana, Buenos Aires, Argentina

Corresponding Author:

María Teresa Rosanova, MD, PhD, Servicio de Control Epidemiológico e Infectología, Hospital de Pediatría J. P. Garrahan, Buenos Aires, 1408 Argentina.

Email: margris2@yahoo.com.ar

The global epidemiology of CA-MRSA is very heterogeneous, with important geographical differences in the predominant clones and the overall frequency at which these clones are isolated.² In the 1990s, CA-MRSA was described as an emerging pathogen in individuals without known risk factors in different parts of the world; however, in Argentina, CA-MRSA was first reported in 2003, and since then a variety of infections have been reported complicating conventional management because of their particular resistance to antibiotics.²⁻⁵

Empirical treatment of certain infections should be based on the possibility of isolation of CA-MRSA and the antibiotic chosen will depend on the severity and the type and location of the infection. However, optimal treatment of these infections in children has not been extensively studied.⁶⁻¹¹

Although clindamycin is a treatment option for mild or moderate infections, the occurrence of inducible resistance required the availability of alternative antibiotics.⁶ Vancomycin is currently used only in severe infections, given its nephrotoxicity and difficulties to achieve therapeutic levels in all tissues. Linezolid and ceftaroline are treatment options but less generally accessible because of their high costs. Trimethoprim-sulfamethoxazole (TMP-SMX) has in vitro bactericidal activity against CA-MRSA and has excellent oral bioavailability and tolerance, good taste, and low cost. TMP-SMX also achieves good concentrations in bones, lungs, and the central nervous system.¹¹

These conditions make TMP-SMX a potentially useful alternative to treat CA-MRSA. Based on the aforementioned reasons, we decided to conduct a comprehensive review to evaluate if the available evidence supports TMP-SMX as a treatment option for CA-MRSA infections, in spite of the suspected paucity of the literature on the clinical effectiveness of TMP-SMX.⁷⁻¹¹

Materials and Methods

We performed a systematic review of the international literature focused on the use of TMP-SMX for the treatment of infections with suspected or documented CA-MRSA in children.

An electronic search strategy was initially developed in Medline, which we combined with the Systematic Reviews (Ovid limit) and Randomized Controlled Trials search filter developed by the information team at SIGN. We did not add any date or language limits to the search. Once the search strategy was defined, it was adapted for each of the other databases searched. These databases were Medline and PreMedline (OvidSP interface) 1966 to October 1, 2015; Excerpta Medica Database (EMBASE; Elsevier interface) 1974 to October 1, 2015; Cumulative Index to the Nursing and Allied Health Literature (CINAHL; EbscoHost interface) 1982 to October 1, 2015; Sciences Citation Index

Expanded (SCI-EXPANDED; Web of Science interface) 1990 to October 1, 2015; Cochrane Library (Wiley interface) 1989 to October 1, 2015; Scopus (Elsevier interface) 1960 to October 1, 2015; and DARE, HTA (CRD interface) 1960 to October 1, 2015. In addition, to complete the systematic search we conducted a hand review of all reference lists of included studies and of all relevant studies that were not picked up by the electronic search.

We downloaded the results of the search and imported them into Reference Manager, version 10 (Thomson Reuters). We scanned for exact article duplicates, author/title duplicates, and title duplicates using the duplication check feature in Reference Manager. Duplicate records were removed and the remaining records were uploaded to an Excel document for subsequent selection of references relevant to the study.

We included only randomized controlled trials comparing the use of TMP-SMX versus any other antibiotic and/or placebo in confirmed or suspected CA-MRSA infections in children. The quality of the studies included was assessed using the Jadad scale (Jadad score ≥ 3).¹² Other studies, such as quasi-randomized studies, studies using different combinations of antibiotics including TMP-SMX associated with other antibiotics, studies recruiting immunocompromised participants or participants older than 18 years, and studies with rates of participant loss higher than 20% were excluded.

CA-MRSA infections were defined according to the criteria proposed by the Centers for Disease Control and Prevention.⁵

The primary outcome measures considered were clinical and/or microbiological cure in the first 30 days of treatment, and no infection recurrence or adverse effects of the drug were considered as secondary outcomes.

Articles were reviewed by 2 reviewers (MTR and GP). In case of discrepancy, the final decision was made by the study coordinator (RL).

Results

Overall 365 references were found. Only 27 studies were properly designed randomized controlled trials. Initially, we selected the 5 articles performed in children; however, one was subsequently excluded because of it being conducted in adults and children without separately reporting the results in children.^{7-10,13} Pallin et al included only 8 children, but the article does not explain to which treatment arm they were allocated.¹³ Our query about this topic was never answered by the contacted author and therefore this article was finally excluded. Eight studies were excluded because of being conducted in adults only, 13 other studies because TMP-SMX was evaluated as prophylaxis, and 3 others because only adverse events of the drug were considered.

Table 1. Total Search Results.

Database	Platform Access	Date Access	References
Medline y PreMedline	OvidSP	February 24, 2015	46
EMBASE	Elsevier	February 24, 2015	14
Cochrane Library	Wiley	February 24, 2015	49
SCI-EXPANDED	Web of Science	February 24, 2015	114
Scopus	Elsevier	February 24, 2015	166
DARE, HTA	CRD	February 24, 2015	4
CINAHL	EbscoHost	February 24, 2015	17
Total			410
Duplicates			46
Total nonduplicates			364

Table 2. Description of Included Studies.

Study	Design	Patients	Intervention	Main Outcome	Jadad ¹² Score
Duong et al ⁷	Randomized controlled trial	161 children	<i>Experimental group:</i> 10 days of TMP-SMX after incision and drainage <i>Control group:</i> 10 days of placebo after incision and drainage	Treatment failure at the 10-day follow-up	5
Tong et al ⁸	Multicenter, randomized controlled, nonblinded trial	13 children	<i>Experimental group:</i> TMP-SMX (4 mg/kg trimethoprim) orally twice daily for 5 days <i>Control group:</i> single dose of benzylpenicillin (45 mg/kg up to 900 mg)	Successful treatment of impetigo at day 7	4
Bowen et al ⁹	Randomized controlled, open, noninferiority trial	156 children	<i>Experimental group:</i> Cotrimoxazole for 3 days (4 mg/kg trimethoprim) or once-daily cotrimoxazole for 5 days (8 mg/kg trimethoprim) <i>Control group:</i> Benzathine benzylpenicillin (weight-based injection), twice-daily	Treatment success at day 7 in a modified intention-to-treat analysis; patients lost not evaluated	3
Miller et al ¹⁰	Randomized controlled, double-blind trial	524 (155 children)	<i>Experimental group:</i> TMP-SMX for 10 days <i>Control group:</i> Clindamycin for 10 days	Clinical cure 7 to 10 days after the end of treatment	5

Abbreviation: TMP-SMX, trimethoprim-sulfamethoxazole.

Results are summarized in Tables 1 to 4 and Figure 1. Regardless of our aim, it is remarkable that all the studies included were about soft tissue infections.

Studies Included

At an emergency department in Saint Louis, the benefits of antibiotics in surgically managed pediatric skin abscesses were assessed by Duong et al⁷ in a noninferiority trial

(threshold: −7%). The study compared 10 days of TMP-SMX 10 to 12 mg/kg/day administered orally divided into 2 doses versus placebo after incision and drainage of the skin abscess in children aged 3 months to 18 years, who had a skin abscess and a nontoxic status. The primary outcome was treatment failure at the 10-day follow-up, and the secondary outcome was the presence of new lesion development at the 10- and 90-day follow-up. In the study, 161 children were enrolled and divided into 2 homogeneous

Table 3. Quantitative Analysis: Failure Rate^a.

Study	Experimental		Control		OR	95% CI
	Yes	No	Yes	No		
Bowen et al ⁹ (successful treatment)	283	51	133	23	Absolute difference 0% to 5%	6.2 to 7.3
Duong et al ⁷ (treatment failure at 10-day follow-up)	3	70	4	72	Difference 1.2%	Infinity to 6.8%
Miller et al ¹⁰ (children only) (cure rates)	60	7	70	6	-2.6	(-13.7 to 8.6)
Tong et al ⁸ (successful treatment at day 7)	7	0	3	6	1.2	0.83 to 1.72

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval (DerSimonian-Laird):

^aHeterogeneity: I^2 . Tolerance Rosenthal Index: -2.

Table 4. Quantitative Analysis: Adverse events.

Study	Adverse Events, n (%)		Conclusion
	TMP-SMX	Control	
Duong et al ⁷	73 (49) ^a	76 (51) ^a	No difference
Bowen et al ⁹	5 (2) ^b	49 (31) ^c	Not available
Miller et al ¹⁰	48 (18.6) ^d	49 (18.9) ^d	No difference
Tong et al ⁸	No adverse events reported		

Abbreviation: TMP-SMX, trimethoprim-sulfamethoxazole.

^aRash, diarrhea, vomiting, bad taste.

^bInability to tolerate large volumes of syrup, vomiting, rash.

^cInjection-site pain at 48 hours; required analgesia, fever post-BPG.

^dThe most common adverse events in the clindamycin and TMP-SMX groups were diarrhea (9.7% and 10.1%), nausea (2.3% and 2.7%), vomiting (2.3% and 1.6%), pruritus (1.5% and 1.2%), and rash (1.2% and 0.8%).

Figure 1. Articles selected (one more reference [r] was added after data search).

groups through random allocation. This is a high-quality study with a Jadad score of 5/5. CA-MRSA was isolated in 80% of the patients. The failure rates were 5.3% ($n = 4/76$) and 4.1% ($n = 3/73$) in the placebo and antibiotic groups, respectively (difference of 1.2%, with a 1-sided 95% confidence interval [CI] [-infinity to 6.8%]). At the 10-day follow-up new lesions were found in 19 patients on placebo (26.4%) and in 9 patients on antibiotics (12.9%) (yielding a difference of 13.5%, 95% 1-sided CI [-infinity to 24.3%]). At the 3-month follow-up new lesions were found in 15 of 52 (28.8%) in the placebo group and in 13 patients of 46 (28.3%) in the TMP-SMX group (difference 0.5%, 95% 1-sided CI [-infinity to 15.6%]).

Tong Y et al⁸ performed a preliminary comparison of the efficacy of TMP-SMX with intramuscular benzathine penicillin G (IM BPG) in children belonging to an Australian aboriginal community aged between 2 months and 16 years, presenting with purulent or crusted impetigo.⁸ CA-MRSA was isolated by nasal swab cultures in only 3 patients of 13 included. Patients were randomized to receive a single dose of IM BPG (45 mg/kg up to 900 mg) or TMP-SMX (4 + 20 mg/kg up to 160 + 800 mg) orally twice daily for 5 days. This is a moderate- to high-quality study with a Jadad score of 4/5. There was no difference in age, gender, or severity of sores between the 2 groups. The primary outcome was successful treatment of impetigo lesions at day 7. Treatment was successful after 4 days in 6 out of 7 patients treated with TMP-SMX and in 3 out of 6 with IM BPG (relative risk [RR] 1.7; $P = .27$; 95% CI [0.73, 4.03]). Microbiological clearance was obtained by day 4 in 5 out of 7 patients treated with TMP-SMX and in 2 out of 6 with IM BPG (RR 2.1; $P = .28$; 95% CI [0.63, 7.30]); and by day 7, in all 7 treated with TMP-SMX and in 3 out of 6 with IM BPG (RR 2.0; $P = .07$; 95% CI [0.90, 4.45]). Both IM BPG and TMP-SMX were efficacious in healing impetigo in this study.

Bowen et al⁹ conducted a study to determine the benefits of antibiotics in surgically managed pediatric skin abscesses in a noninferiority trial.⁹ Indigenous Australian children

aged 3 months to 13 years with purulent or crusted nonbulbous impetigo were randomly assigned (1:1:1) to receive benzathine-benzylpenicillin, twice-daily cotrimoxazole for 3 days (4 mg/kg plus 20 mg/kg per dose), or once-daily TMP-SMX for 5 days (8 mg/kg plus 40 mg/kg per dose). This is a low- to moderate-quality study with a Jadad score of 3/5. The primary outcome was treatment success at day 7 in a modified intention-to-treat analysis. *S aureus*, *S pyogenes*, or both were recovered from swabs of all but 4 participants. One hundred sixty-five patients (156 were analyzed) were randomized to the arm of twice-daily TMP-SMX for 3 days, 175 (173 analyzed) to the arm of once-daily TMP-SMX for 5 days, and 168 (161 analyzed) to the arm of benzathine-benzylpenicillin. Baseline characteristics of all participants in the trial at the first visit according to study group were comparable. Treatment was successful in 133 (85%) children who received benzathine-benzylpenicillin and in 283 (85%) who received pooled TMP-SMX (absolute difference 0.5%; 95% CI [-6.2 to 7.3]), showing noninferiority of TMP-SMX (10% margin). Results for twice-daily TMP-SMX for 3 days and once-daily TMP-SMX for 5 days were similar. Adverse events occurred in 54 participants, 49 (90%) of whom received benzathine-benzylpenicillin. Before treatment, *S aureus* was identified in 412 (81%) of 508 children, *S pyogenes* in 455 (90%), and both *S aureus* and *S pyogenes* in 377 (74%). Both TMP-SMX and benzathine-benzylpenicillin reduced the proportion of participants with *S pyogenes* positive sores from more than 85% at day 0 to less than 7% at day 7. Rates of *S aureus* fell from 83% at day 0 to 20% at day 7 with TMP-SMX, and from 81% to 52% with benzathine-benzylpenicillin ($P < .0001$) for a comparison of recovery rates at day 7. CA-MRSA recovery fell from 19% on day 0 to 11% at day 7 with benzathine-benzylpenicillin and from 13% on day 0 to 2% at day 7 with TMP-SMX. In the modified intention-to-treat analysis, the authors concluded that there is noninferiority of TMP-SMX compared with benzathine-benzylpenicillin.

Miller et al¹⁰ carried out a randomized double-blind multicenter study in California at 4 US centers located in areas of community associated MRSA endemicity and comparing clindamycin and TMP-SMX for the treatment of uncomplicated skin infections. They enrolled outpatients with uncomplicated skin infections who had cellulitis, abscesses larger than 5 cm in diameter (smaller for younger children), or both.¹⁰ All children with abscesses underwent incision and drainage. Patients were randomly assigned in a 1:1 ratio to receive either clindamycin or TMP-SMX for 10 days. Patients were stratified into 1 of 2 groups on the basis of the characteristics of their infection before randomization. The randomization procedure is not described in the article. This is a high-quality study with a Jadad score of 5/5. A total of 524 patients were enrolled (264 in the clindamycin group and 260 in the TMP-SMX group), including 155 children (29.6%): 81 in the clindamycin group and 74 in the

TMP-SMX group. The demographic characteristics of the children are not specified separately. *S aureus* was isolated from the lesions of 217 patients (41.4%). MRSA was isolated in 167 (77.0%) of those patients. Clindamycin was given as two 150-mg tablets 3 times daily; TMP-SMX was given at doses of 160 mg of trimethoprim and 800 mg of sulfamethoxazole administered as 2 single-strength tablets twice daily. Patients randomly assigned to receive TMP-SMX were given 2 placebo pills for the midday dose. Pediatric doses were adjusted according to the body weight of the patient. Cure rates did not differ significantly between the 2 treatments either in the subgroups of children and adults, or in patients with abscesses versus patients with cellulitis. Results in children were separately reported and in this review only these results are considered. Cure rate was evaluated in 67 children in the TMP-SMX group and in 76 children in the clindamycin group and 60/67 (89.5%) versus 70/76 (92%) were cured. The authors concluded that they did not find significant difference between clindamycin and TMP-SMX, with respect to either efficacy or side-effect profile, for the treatment of uncomplicated skin infections, including both cellulitis and abscesses.

Discussion

We performed this systematic review to evaluate the use of TMP-SMX compared with other options available for the treatment of CA-MRSA infections. We decided not to perform a meta-analysis given the heterogeneity of patients, compared interventions, and main end-points used among the studies included. Regardless of this heterogeneity, most included studies were of high quality (Table 2).

Although we did not exclude studies according to the location and severity of infections, no studies on invasive infections treated with TMP-SMX that met the inclusion criteria were found. Consequently, regardless of our aim, all the studies included were focused on skin and soft tissue infections, the most common being CA-MRSA-related infections.

Antibiotic treatment of skin and soft tissue infections is controversial. Frei et al support the belief that incision and drainage are critical for the management of CA-MRSA skin infections in adults.¹⁴ They conclude that patients who receive TMP-SMX or clindamycin for CA-MRSA-related skin infections experience treatment failure rates that are similar to those of drainage. This statement agrees with the findings by Duong et al, who demonstrated no statistically significant difference in treatment failure rates of the primary skin lesions with or without antibiotics against CA-MRSA.⁷ No difference in treatment failure rates was found between the placebo and antibiotic groups in a subanalysis of data from skin abscesses caused by CA-MRSA. In these patients, antibiotics decreased new lesion development at day 10 of follow-up, but there was no significant difference between the 2 groups regarding new lesion development at the 3-month follow-up. In the short

term, antibiotics may be useful in preventing recurrent skin abscesses but provided no long-term benefits in terms of new lesion development.

Tong et al studied 13 children who had *S aureus* recovered from skin sore swabs. CA-MRSA was only isolated in 3 of them.⁸ The authors stated that both benzathine-benzylpenicillin and TMP-SMX were efficacious in healing impetigo; however, the number of patients was too low to draw any sound conclusions.

Bowen et al showed noninferior efficacy of oral TMP-SMX compared with standard treatment of impetigo using intramuscular benzathine-benzylpenicillin, based on both modified intention-to-treat and per-protocol analyses.⁹ However, long-standing concerns surround the efficacy of TMP-SMX for *S pyogenes* infections as Infectious Diseases Society of America guidelines suggest that for nonpurulent cellulitis TMP-SMX could be combined with amoxicillin to provide coverage for both MRSA and *S pyogenes*.³

Bowen et al concluded that TMP-SMX is an effective antibiotic against *S pyogenes* in vitro and in vivo, and it may be considered alongside benzathine-benzylpenicillin for impetigo treatment.⁹ Clearance of *S aureus* and MRSA were better, providing a 75% reduction in staphylococci detected using TMP-SMX.

Miller et al did not show difference in the efficacy of either intervention (TMP-SMX or clindamycin) for uncomplicated skin infections, and adverse events rates were similar. After the incision and drainage of uncomplicated abscesses, treatment with TMP-SMX did not reduce treatment failure but may have decreased the formation of subsequent lesions.^{10,15}

Elliot et al point out that empiric CA-MRSA coverage is not associated with improved outcomes in the outpatient management of nondrained, noncultured skin and soft tissue infections. Indeed, monotherapy with TMP-SMX may increase the risk of treatment failure in this setting if *S pyogenes* is involved.¹⁶

Williams et al, in a retrospective cohort of children, compared the effectiveness of clindamycin, TMP-SMX, and β -lactams for the treatment of skin and soft tissue infections among 6407 children who underwent drainage. The authors concluded that compared with clindamycin, the use of TMP-SMX or β -lactams was associated with increased risks of treatment failure and recurrence. Associations were stronger for those with a drainage procedure.¹⁷ However, as a retrospective study, this one is too exposed to bias undermining its conclusions.

Clindamycin was demonstrated to be superior to both TMP-SMX and β -lactams for the acute treatment and prevention of skin and soft tissue infection recurrence.¹⁶

These findings, from an observational study of more than 50 000 children with incident skin and soft tissue infections, question the use of TMP-SMX for the treatment of purulent skin and soft tissue infections in CA-MRSA-prevalent regions in which clindamycin resistance remains low.

In other infections the role of TMP-SMX is not clearly defined. Its use in the treatment of invasive infections has been discouraged because of a concern for therapeutic failures.¹⁸

Nevertheless, several case reports documented the successful use of TMP-SMX in the treatment of osteoarticular infections caused by CA-MRSA. Messina et al concluded that TMP-SMX appears to be a useful and well-tolerated therapy for the treatment of acute osteomyelitis in children.¹⁹ At our hospital in a series of 26 pediatric patients with osteoarticular infections with a documented CA-MRSA infection, 13 were treated with oral TMP-SMX to complete treatment. No relapse or complications were reported.²⁰

This review has several limitations. The first limitation is the low number of studies found that complied with the selection criteria. The second is the lack of quality studies beyond those on skin and soft tissue infections. The third limitation is the lack of evidence on the role of TMP-SMX as the first-choice treatment in systemic CA-MRSA infection in children. Additionally, in most studies included the presence of CA-MRSA was not confirmed. Nevertheless, to the best of our knowledge, our study is the first systematic literature review on the potential effectiveness of TMP-SMX as an alternative to treat CA-MRSA-related infections in children. However, based on the limited availability of literature on the issue and the heterogeneity of the included studies it was not possible to perform a quantitative summary of the data or to present categorical recommendations.

Currently, studies showing TMP-SMX as the treatment of choice in the era of CA-MRSA are not sufficient to make strong recommendations on its use. This study confirms the paucity of evidence to support the prescription of TMP-SMX as a first-choice treatment in CA-MRSA infections in children. Nevertheless, we cannot conclude that TMP-SMX should be avoided. It is important to point out that the available studies did not show any relevant difference in efficacy of TMP-SMX against the tested alternatives. Additional well-designed studies are required to further elucidate this issue.

Declaration of Conflicting Interests

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