CJEM Journal Club

Comparison of trimethoprim-sulfamethoxazole versus placebo for uncomplicated skin abscesses

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Clinical question
In patients with uncomplicated abscesses receiving incision and drainage, does the addition of trimethoprim-sulfamethoxazole result in improved clinical resolution at 7 to 14 days after treatment when compared with placebo?

Article chosen
Talan DA, Mower WR, Krishnadasan A, et al. Trimethoprim-sulfamethoxazole versus placebo for uncomplicated skin abscess. *N Engl J Med* 2016;374(9):823-32.

Objective
The primary objective of this study was to compare the clinical cure rates at 7 to 14 days after the end of the treatment period among patients receiving either trimethoprim-sulfamethoxazole (TMP-SMX) or placebo. Secondary outcomes included composite cure; surgical drainage procedures; change in erythema size; presence of swelling, induration, or tenderness; invasive infections; skin infections at the same site and different sites; hospitalizations; similar infections in household contacts; days missed from normal activities; days missed from school or work; and days of analgesic use.

Keywords: antibiotics, abscess, infection, SSTI, skin and soft tissue infection, trimethoprim-sulfamethoxazole

BACKGROUND

Skin and soft tissue infections comprise a significant number of health care visits, resulting in 3.4 million emergency department (ED) visits and 6.3 million primary care visits annually.[1,2] Over the past several years, community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) has emerged as the most common cause of purulent skin and soft tissue infections.[3,4] Trimethoprim-sulfamethoxazole (TMP-SMX), which has retained very low resistance rates for CA-MRSA treatment, has become one of the most commonly prescribed antibiotics to treat these infections.[3,4]

The primary treatment of cutaneous abscesses is incision and drainage.[5] However, whether adjunctive antibiotics will significantly improve outcomes has been unclear. Prior studies demonstrated no significant difference in cure rates between antibiotic and placebo groups, but were limited by small sample sizes and use of antibiotics ineffective against CA-MRSA.[6] Because drainage alone will result in cure rates in excess of 85%, very large sample sizes are required to demonstrate a significant difference.[6]

POPULATION STUDIED

The study enrolled patients older than 12 years of age who presented to the ED with a cutaneous lesion suspected to be an abscess by physical examination and ultrasonography or examination alone and found to have purulent material on surgical exploration. Patients were included if the lesion had been present for less than 1 week, the lesion was at least 2.0 cm in diameter by examination or ultrasonography, and the treating clinician intended outpatient treatment. Exclusion criteria included presence of an indwelling device, presence of an organic foreign body, associated mammalian bite, underlying skin condition, immunodeficiency, renal dysfunction, endocarditis risk factors, allergic reaction or intolerance to TMP-SMX, current antibiotic use, pregnancy or lactation, enrollment within the prior 12 weeks, or perirectal, perineal, or paronychial location.

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STUDY DESIGN

This was a multicentre, double-blind, randomized, placebo-controlled trial that enrolled patients presenting to five different U.S. EDs with abscesses treated with incision and drainage. All patients received standardized training on abscess drainage techniques prior to the study. Patients were allocated to twice daily TMP-SMX (320 mg of trimethoprim and 1600 mg of sulfamethoxazole) or placebo in a 1:1 ratio by a remote, Web-based randomization system featuring randomly permuted blocks. Each study participant received 56 identical-appearing capsules and was instructed to take four pills twice daily for 7 days.

OUTCOMES MEASURED

The primary outcome measured in this study was the rate of clinical cure, defined as not meeting any of the criteria for treatment failure (Table 1), at 7 to 14 days after the end of the treatment period (14 to 21 days after ED presentation). Secondary outcomes included composite cure (resolution of all symptoms and signs of infection or improvement such that no additional antibiotics or procedures were necessary); surgical drainage procedures; change in erythema size; presence of swelling, induration, or tenderness; invasive infections; skin infections at the same site and different sites; hospitalizations; similar infections in household contacts; days missed from normal activities; days missed from school or work; and days of analgesic use.

Table 1. Criteria for treatment failure

Assessment time	Criteria
Day 3 or 4	Fever (attributable to the infection)
	Increase in the maximal dimension of erythema ≥25% from baseline
	Worsening of wound swelling and tenderness
Days 8-10	Fever (attributable to the infection)
	No decrease in the maximal dimension of the erythema from baseline
	No decrease in swelling or tenderness
Days 14-21	Fever (attributable to the infection)
	More than mild erythema, swelling, or tenderness
Trial completion	Withdrawal from the trial
	Loss to follow-up
	Missing outcomes

RESULTS

Between April 2009 and April 2013, 1265 patients were enrolled and 1247 (98.6%) were randomly assigned to TMP-SMX (630 patients) or placebo (617 patients) and received at least one dose. The average age was 35 years. The median length, width, and depth of the abscesses were 2.5 cm, 2.0 cm, and 1.5 cm, respectively. The median length and width of the erythema were 6.5 cm and 5.0 cm, respectively. There were no significant differences in the baseline characteristics. MRSA was found in 45.3% of the participants, and 97.4% of MRSA isolates were susceptible to TMP-SMX.

There was a statistically significant 6.9% (95% confidence interval 2.1%-11.7%) increase in the clinical cure rates among the TMP-SMX group compared with the placebo group when assessed with both modified intention-to-treat and per-protocol analyses, resulting in a number needed to treat of 14 (Table 2). TMP-SMX was superior to placebo with respect to most secondary outcomes in the per-protocol analysis, resulting in lower rates of subsequent surgical drainage procedures, skin infection at new sites, and infections in household members. TMP-SMX was associated with slightly more gastrointestinal side effects, but there were no cases of *Clostridium difficile*-associated diarrhea or serious adverse events.

Table 2. Cure rates among patients with drained cutaneous abscesses treated with antibiotics compared with placebo

Trial population	TMP-SMX cure rate (%)	Placebo cure rate (%)	Difference (95% CI)	*p*-value
Modified ITT	507/630 (80.5%)	454/617 (73.6%)	6.9% (2.1-11.7%)	0.005
Per-protocol	487/524 (92.9%)	457/533 (85.7%)	7.2% (3.2-11.2%)	<0.001

CI = confidence interval; ITT = intention-to-treat; TMP-SMX = trimethoprim-sulfamethoxazole.

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STUDY CONCLUSION

In settings in which MRSA was prevalent, TMP-SMX treatment resulted in a higher cure rate among patients with drained cutaneous abscesses than placebo.

COMMENTARY

Most abscesses are successfully treated with incision and drainage.[5,6] Multiple studies have evaluated the utility of adjunctive antibiotics in the management of abscesses in conjunction with surgical drainage.[6] However, only two randomized, controlled trials, comprising 161 and 212 patients, have assessed TMP-SMX in the era after the emergence of CA-MRSA.[7,8] Unfortunately, given the the high baseline cure rates with incision and drainage alone, these studies were underpowered to detect a clinical difference, prompting the current study.

This study demonstrated an approximate 7% increase in cure rates with the use of adjunctive TMP-SMX. Among this group, there was a 5.2% increase in the total number of patients requiring additional incision and drainage, which may be an important patient outcome. It is important to weigh this potential benefit against risks associated with increased TMP-SMX use. While this study demonstrated no significant difference in adverse drug events, with the exception of slightly increased gastrointestinal symptoms, it was underpowered to identify serious, life-threatening infections, such as Stevens-Johnson syndrome.[9] Additionally, less than 65% of patients were 100% compliant with the medication and, although this may reflect real-life practice, it may also have underrepresented other known side effects of TMP-SMX, such as renal dysfunction, electrolyte abnormalities, and *Clostridium difficile* colitis. The authors also did not address the potential for antibiotic resistance with increased use, which can have significant public health consequences. Furthermore, it is important to note that the average abscess was 2 to 3 cm, but the majority had an associated cellulitis measuring more than 5 cm. This suggests that many cases may have been a combination of abscess with cellulitis (which many would already treat with adjunctive antibiotics), rather than simple uncomplicated abscesses. Because experts currently recommend adjunctive antibiotics for patients at the extremes of age and those with diabetes, systemic inflammatory response syndrome criteria, or with erythema extending beyond 5 cm, this study provides further support for the treatment of these patients.[10,11] Finally, MRSA rates may vary by location. Although this study demonstrated a 45.3% overall prevalence of MRSA, two other Canadian studies have demonstrated variations in the rates of MRSA. One study performed in Toronto, Canada demonstrated a 19% prevalence of MRSA among skin and soft tissue infections,[12] whereas another study in Vancouver, British Columbia, Canada demonstrated a prevalence of 54.8% with a threefold increase over the preceding 2-year period.[13] Therefore, it is important to consider the prevalence of MRSA at one's own institution when applying this study and selecting antibiotics.

CONCLUSION

Empiric TMP-SMX for all uncomplicated abscesses after incision and drainage may help increase clinical cure rates, but also may result in increased adverse drug events and may lead to increased TMP-SMX resistance.

Competing interests: None declared.

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