Trimethoprim-Sulfamethoxazole vs Placebo for Uncomplicated Skin Abscess 1

BOTTOM LINE

- Compared to incision & drainage (I&D) alone, outpatients presenting to the ER with uncomplicated skin abscesses (~45% MRSA) who underwent I&D & received high-dose TMP/SMX (=2 double-strength [DS] tablets BID) x 7 days had a:
  - higher rate of clinical cure at days 14 to 21 (80.5% vs 73.6%, NNT=14 for the MITT analysis)
  - higher discontinuation rate & more adverse events (see Table 1; p-values & confidence intervals not published)
  - note: the study was conducted at 5 sites over a 4 year period; impact on antimicrobial resistance was not reported

- Smaller previous studies (RCTs & observational) suggested standard doses do not provide additional benefit compared to I&D alone, & are as effective as high-dose regimens, except in patients who have a BMI >40kg/m². See Background section below.

- In Saskatchewan, ~30% of Staphylococcus isolates in SHR & RQHR are MRSA.
  - I&D is recommended for all abscesses, & is usually sufficient for clinical cure.
  - Systemic antibiotics, in addition to I&D, are recommended for large abscesses (>5cm) or abscesses in an area where I&D is difficult (e.g. face, hands, genitalia); for skin infections which are unresolving, rapidly progressing or with extensive cellulitis; systemic symptoms (e.g. fever); & in patients with significant comorbidities, immunosuppression or extremes of age.
    - If oral antibiotics are required, consider cephalaxin or cloxacillin. If MRSA coverage is required, consider TMP/SMX or doxycycline as both have good activity against MRSA in the province.

- Overall, the trial supports the use of TMP/SMX in areas with a MRSA rate of 45%. However, I&D is most important & high-dose TMP/SMX only made a difference in 1/14 patients versus placebo. If using antibiotics, consider patient characteristics, & high-dose TMP/SMX for those with a BMI >40kg/m².

BACKGROUND

Incision & drainage (I&D) ± antibiotic:

- The 2014 IDSA Skin & Soft Tissue Infection Guideline recommends I&D for abscesses, & note that the procedure alone is often all that is required for uncomplicated abscesses.2
- A small 2014 meta-analysis (4 RCTs, N=589) found no difference in clinical cure rates 7 to 10 days after treatment when I&D + antibiotics (cephalosporin or TMP/SMX) was compared to I&D alone for uncomplicated abscesses.3 The included TMP/SMX data was based on standard dose TMP/SMX (2 RCTs, n=161) versus I&D alone.4,5

Standard versus High-Dose TMP/SMX:

- A 2011 prospective observational single center study compared standard dose (i.e. TMP/SMX 1 DS po BID) to high-dose (i.e. TMP/SMX 2 DS po BID) in 291 patients with a MRSA skin infections (n=237, [81%] had an abscess). The authors concluded there was no difference in cure rates between the two doses. Those who received a higher dose of TMP/SMX were also more likely to have received surgical drainage.6
- A 2012 retrospective observational single center study sought to identify risk factors for clinical failure in patients hospitalized with cellulitis & cutaneous abscess (n=106). The authors concluded morbidly obese patients (BMI>40kg/m²) were at greater risk of clinical failure when prescribed the standard dose of TMP/SMX compared to high-dose.7

TRIAL BACKGROUND 1

DESIGN: randomized, placebo-controlled, multicentre 5 US ER departments, double-blind superiority trial with concealed allocation.

Enrollment: April 2009 to April 2013. Funding: grant from the National Institute of Allergy & Infectious Disease; medications were purchased (i.e. no pharmaceutical industry funding).

INTERVENTION: skin abscess incision & drainage, PLUS

- TMP/SMX 4 single-strength tablets (i.e. 4 x 80mg TMP/400mg SMX = 320mg TMP/1600mg SMX) po BID x 7 days, versus placebo

INCLUSION: outpatients presenting to ER who were ≥12 years of age with a purulent abscess (confirmed by physical exam & ultrasound or purulent material on surgical exploration) present for <1 week & measured ≥2 cm in diameter.

EXCLUSION: indwelling device; suspected osteomyelitis or septic arthritis; diabetic foot, decubitus or ischemic ulcer; mammalian bite; wound with organic foreign body; infection of another organ system/site; perineal or paronychial location; IV drug use within previous month & fever; underlying skin condition; LTC residence; incarceration; immunodeficiency (e.g. absolute neutrophil count <500/mm³), immunosuppressive drugs, active chemotherapy, or AIDS; creatinine clearance <50mL/min; cardiac condition with risk of endocarditis; taking warfarin, phenytoin, or methotrexate; known G-6-PD or folic acid deficiency; pregnant or lactating; TMP/SMX treatment within 24 hours; concurrent treatment with topical or systemic antibiotics.

POPULATION at baseline: n=1,265 outpatients presenting in ER

- median age 35 years (range 14 to 73) n=8 were <18 yrs, ~58% male, 11% DM, history of MRSA infection ~7.5%
- median days of symptoms: 4 days (IQR 3-5 days), ~18% fever in preceding week, 7.3% household contact with similar infection
- abscess location: arms/hands 23.5%; legs/feet ~22%; trunk, abdomen or back ~20%; groin or buttocks ~20%; head or neck ~13.5%
- median abscess length 2.5cm (IQR 2.3-3.5cm), width 2cm (IQR 1.5-3cm), depth 1.5cm (1-2cm)
- median erythema length TMP/SMX 7cm (IQR 4.3-10cm) vs placebo 6.5cm (IQR 4-10cm), width 5cm (IQR 3.5-8cm & IQR 3-7.5cm, respectively)
- wound culture results: MRSA TMP/SMX 43.5% vs placebo 47.2% (97.4% of the MRSA isolates were sensitive to TMP/SMX), MSSA 16%, coagulase-negative Staphylococcus TMP/SMX 12.7% vs placebo 9.9%, Streptococcal species TMP/SMX 6.5% vs placebo 3.6%, other ~14%

RESULTS

TABLE 1: EFFICACY & SAFETY CONTINUED ON NEXT PAGE

<table>
<thead>
<tr>
<th>CLINICAL ENDPOINTS</th>
<th>TMP/SMX 320mcg/1600mcg BID</th>
<th>PLACEBO</th>
<th>ARR/ARI (95% CI)</th>
<th>NNT/NNH /7 DAYS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MITT (n=630)</td>
<td>PPA (n=524)</td>
<td>FDAGEEP (n=601)</td>
<td>MITT (n=617)</td>
</tr>
<tr>
<td>PRIMARY ENDPOINT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical cure of the abscess at the test-of-cure visit (i.e. day 14 to 21)*</td>
<td>80.5% (n=507)</td>
<td>92.9% (n=487)</td>
<td>36.3% (n=218)</td>
<td>73.6% (n=454)</td>
</tr>
</tbody>
</table>

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## RXFiles Trial Summary

**L. KOSAR, S. TOEWS – MAY 2017 www.RXFiles.ca**

### TABLE 1: EFFICACY & SAFETY continued - SECONDARY ENDPOINTS (per-protocol analysis only)

<table>
<thead>
<tr>
<th>Clinical Endpoints</th>
<th>TMP/SMX (n=630)</th>
<th>Placebo (n=533)</th>
<th>ARR/ARI (95% CI)</th>
<th>NNT/NNH /7 DAYS</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite cure by test-of-cure visit *</td>
<td>86.5%</td>
<td>74.3%</td>
<td>12.2% (7.2 to 17.1)</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td>Additional surgical drainage procedure</td>
<td>3.4%</td>
<td>8.6%</td>
<td>-5.2% (-8.2 to -2)</td>
<td>19</td>
<td>-</td>
</tr>
<tr>
<td>Presence of tenderness</td>
<td>6%</td>
<td>10%</td>
<td>-4.1% (-7.5 to -0.6)</td>
<td>24</td>
<td>-</td>
</tr>
<tr>
<td>Skin infection at a new site</td>
<td>3.1%</td>
<td>10.3%</td>
<td>-7.2% (-10.4 to -4.1)</td>
<td>14</td>
<td>-</td>
</tr>
<tr>
<td>Invasive infections ¶</td>
<td>0.4% (n=2)</td>
<td>0.4% (n=2)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**SAFETY ENDPOINTS**

<table>
<thead>
<tr>
<th>Clinical Endpoints</th>
<th>TMP/SMX (n=630)</th>
<th>Placebo (n=617)</th>
<th>ARR/ARI</th>
<th>NNT/NNH /7 DAYS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation rates</td>
<td>1.9%</td>
<td>0.6%</td>
<td>1.3%</td>
<td>p-values &amp; CI not reported</td>
</tr>
<tr>
<td>Gastrointestinal AE</td>
<td>42.7%</td>
<td>36.1%</td>
<td>6.6%</td>
<td>-</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>0.2%</td>
<td>0%</td>
<td>0.2%</td>
<td>-</td>
</tr>
</tbody>
</table>

mITT: at least one dose of the study medication, including those lost to follow-up
PPA: took ≥75% of study medication during first 5 days & available for in-person follow-up
FDAGEEP: at least one dose of study medication & completed 48-72hr follow-up evaluation

*Clinical cure: did not meet criteria for clinical failure at or before the test-of-cure visit. The criteria for clinical failure were as follows: fever (attributable to the infection), an increase in the maximal dimension of erythema by >25% from baseline, or worsening of wound swelling and tenderness by the visit during the treatment period (day 3 or 4); fever, no decrease in the maximal dimension of erythema from baseline, or no decrease in swelling or tenderness by the visit at the end of the treatment period (day 8–10); and fever or more than minimal erythema, swelling, or tenderness by the test-of-cure visit (day 14–21).

¶ Composite cure: resolution of all symptoms & signs of infection, or improvement such that no additional antibiotic therapy or surgical drainage procedure was necessary

### STRENGTHS, LIMITATIONS, & UNCERTAINITIES

**STRENGTHS:**

- The largest RCT comparing I&D alone to I&D with an antibiotic. However, the study was originally powered for 590, & the sample size was recalculated during a pre-specified interim analysis to 1265 participants based on the observed cure rates between the two treatment arms.
- Investigators were blinded to C&S results.
- Trial personnel provided with standardized training on the general technique & trial-specific procedures for incision & drainage.
- Per-protocol analysis with adherence measured by inspecting medication blister packs or memory aid booklet with patient interview.
- Patients in the modified intention-to-treat analysis who were lost to follow-up (n=34) were categorized as a clinical cure, & the results were similar.
- Assessed clinical cure 1 to 2 weeks after incision & drainage, as skin may appear worse a few days after the procedure & takes time to heal.

**LIMITATIONS:**

- no subgroup analysis based on size of lesion, C&S results, test-of-cure results in those with shorter courses of therapy (i.e. non-adherent to 1 week)
- p-values & confidence intervals were not published for the safety analysis
- mean duration of therapy not reported for those who were non-adherent
- body weight & BMI was not reported (re: standard versus high-dose TMP/SMX)
- ~4% more of the patients in the placebo arm had MRSA infections (TMP/SMX 43.5% vs placebo 47.2%)

**UNCERTAINTIES:**

- the efficacy of standard dose TMP/SMX + I&D compared to I&D alone in a largeRCT
- efficacy of shorter courses of antibiotics (i.e. less than 1 week)
- efficacy of TMP/SMX + I&D compared to I&D in an area with MRSA rates of ~30% (i.e. Saskatchewan)

### RxFILES RELATED LINKS


**ARR=absolute risk increase  ARR=absolute risk reduction  BID=twice daily BMI=body mass index C&S=culture & sensitivity DM=diabetes mellitus DS=double strength ER=Emergency Room FDAGEEP=Food and Drug Administration Guidance Early Endpoint I&D=incision & drainage IQR= interquartile range IV=intravenous LTC=long-term care mITT=modified intention to treat MRSA=methicillin-resistant Staphylococcus aureus MSSA=methicillin-susceptible Staphylococcus aureus N=number NNH=number needed to harm NNT=number needed to treat NS=non-statistically significant PPA=Per-protocol analysis RCT=Randomized controlled trial RQHR=Regina Qu’Appelle Health Region SHR=Saskatoon Health Region TMP/SMX=trimethoprim-sulfamethoxazole**
REFERENCES


