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/m^2. 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 cephalexin 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/m^2.

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/m^2) 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/mm^3, 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 <18yrs, ~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 2-3.5cm), 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 *Staphylococci* 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

CLINICAL ENDPOINTS	TMP/SMX 320MG/1600MG BID			PLACEBO			ARR/ARI (95% CI)			NNT/NNH /7 DAYS		
	MITT (N=630)	PPA (N=524)	FDAGEEP (N=601)	MITT (N=617)	PPA (N=533)	FDAGEEP (N=605)	MITT	PPA	FDA-GEEP	MITT	PPA	FDA-GEEP
PRIMARY ENDPOINT												
Clinical cure of the abscess at the test-of-cure visit (i.e. day 14 to 21)*	80.5% (n=507)	92.9% (n=487)	36.3% (n=218)	73.6% (n=454)	85.7% (n=457)	33.7% (n=204)	6.9% (2.1-11.7%)	7.2% (3.2-11.2%)	NS	14	13	-

TABLE 1: EFFICACY & SAFETY continued - SECONDARY ENDPOINTS (per-protocol analysis only)					
CLINICAL ENDPOINTS	**TMP/SMX 320MG/1600MG BID (N=524)**	**PLACEBO (N=533)**	**ARR/ARI (95% CI)**	**NNT/NNH /7 DAYS**	**COMMENTS**
Composite cure by test-of-cure visit ‡	86.5%	74.3%	12.2% (7.2 to 17.1)	8	• The following endpoints were NS: - recurrent skin infection at original site, - presence of swelling or induration, - hospitalization by test-of-cure visit, - change in mean area of erythema • Similar infections in household members was statistically significant at test-of-cure visit (1.7% vs 4.1%, risk difference 2.4%, NNT=42), but not at extended follow-up (day 49 to 63). • Days missed from normal activities or work/school, & days of analgesic use was 0.5 days or less with TMP/SMX. • No treatment-associated serious or life-threatening AE occurred.
Additional surgical drainage procedure	3.4%	8.6%	-5.2% (-8.2 to -2.2)	19	
Presence of tenderness	6%	10%	-4.1% (-7.5 to -0.6)	24	
Skin infection at a new site	3.1%	10.3%	-7.2% (-10.4 to -4.1)	14	
Invasive infections ¶	0.4% (n=2)	0.4% (n=2)	-	-	
SAFETY ENDPOINTS					
CLINICAL ENDPOINTS	**TMP/SMX 320MG/1600MG BID (N=630)**	**PLACEBO (N=617)**	**ARR/ARI**	**NNT/NNH /7 DAYS**	
Discontinuation rates	1.9%	0.6%	1.3%	p-values & CI not reported	
Gastrointestinal AE	42.7%	36.1%	6.6%		
Hyperkalemia	0.2%	0%	0.2%		

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
¶ Invasive infections = sepsis, bacteremia, endocarditis, osteomyelitis, septic arthritis, necrotizing fasciitis, or pneumonia

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

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 failure. Additional analyses were conducted re-categorizing these patients 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%)

UNCERTAINITIES:

- the efficacy of standard dose TMP/SMX + I&D compared to I&D alone in a large RCT
- 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

- **RxFiles Skin & Soft Tissue Infection Chart:** http://www.rxfiles.ca/rxfiles/uploads/documents/members/ABX-Skin-Infections.pdf
- **RxFiles Trial Summary Clindamycin versus TMP/SMX for uncomplicated skin infections:** http://www.rxfiles.ca/rxfiles/uploads/documents/Trial%20Summary%20TMP-SMX%20Vs%20Clindamycin%20in%20Uncomp%20SSTI.pdf

ARI=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/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

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