Clindamycin vs TMP/SMX vs Incision & Drainage alone for Small Skin Abscesses [1]

A placebo-controlled trial of antibiotics for smaller skin abscesses

BOTTOM LINE:

- Compared to placebo, outpatients with a single small *S.aureus* (~50% MRSA) skin abscess who underwent incision & drainage & received an antibiotic clindamycin or TMP/SMX, were more likely to have clinical cure by test-of-cure visit (i.e. 7 to 10 days after treatment ended) NNT=7-8. The difference between clindamycin and TMP/SMX was non-statically significant.
  - Only 6.9% (13/188) of the participants *S.aureus* isolates were resistant to clindamycin, which is less than current SK rates.
- Individuals who were treated with clindamycin were more likely to have treatment-associated adverse events. There were no reported cases of *C. difficile*.
  - note: the study was conducted at 6 sites over a 6 year period; impact on antimicrobial resistance was not reported
- Overall, the trial supports the use of clindamycin or TMP/SMX in areas with a MRSA of ~50% and good *S.aureus* susceptibility to these antibiotics. However, I&D is most important & an antibiotic only made a difference in 1/7 to 1/8 patients versus placebo.

BACKGROUND

- Clinical practice guidelines/ references recommend incision & drainage (I&D) for abscesses, & note that the procedure alone is often all that is required for uncomplicated abscesses.[2,3,4]
- 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.[5]
- In 2016, a larger RCT (n=1,265) compared high-dose TMP/SMX (2 double-strength tablets BID) + I&D to I&D alone in outpatients presenting to the ER with uncomplicated abscesses. TMP/SMX had a higher rate of clinical cure 1 to 2 weeks after treatment ended (NNT=14), but also a higher discontinuation rate & more adverse events.[6]

TRIAL BACKGROUND

DESIGN: randomized, double-blind, placebo-controlled multicentre 6 U.S. sites ITT/PPA trial with concealed allocation. Enrollment May 2009 to January 2015. Funding: National Institute of Allergy & Infectious Diseases of the National Institutes of Health.

INTERVENTION: incision & drainage of abscess AND
- clindamycin 300mg po TID x 10 days (pediatric dose: 25-30mg/kg/day), or
- TMP/SMX 160mg/800mg po BID (i.e. 1 double strength tablet twice daily) x 10 days (pediatric dose: 8-10mg TMP/kg/day), or
- placebo

INCLUSION: outpatients with a single abscess (≤5cm, or ≤4cm for participants 1-8 yrs old, or ≤3cm if 6-11months old) with ≥2 of the following signs or symptoms for ≥24hrs: erythema, swelling or induration, local warmth, purulent drainage, and tenderness to pain or palpation.

EXCLUSION: superficial skin infections (e.g. impetigo), infection at a body site requiring specialized management (e.g. perirectal, genital, or hand infection), human or animal bite, oral temperature >38.5° (or >38° for children 6-11 months old), presence of systemic inflammatory response syndrome criteria, immunosuppressive therapy or an immunocompromising condition (e.g. DM, CKD), BMI >40kg/m^2, surgical site or prosthetic device infection, systemic antistaphylococcal antibacterial therapy in the previous 14 days; & required hospitalization, LTC resident, cancer, inflammatory disorder or major surgery in the past 12 months.

POPULATION at baseline: n=786
- adults 64.2%, children 35.8% (~21% 1-8yrs, 12.5% 9-17yrs, 2.2% <1yr), mean age 25.5 years
- ♂ 57%, Black / African American ~62%, Caucasian ~30%
- body temperature 36.6°±0.47°, area of wound 3.89cm^2±4.3cm^2, area of surrounding erythema 27.44cm^2±86.82cm^2
- culture obtained 99.4%, positive culture results 91.3%, *Staph aureus* isolated 67% (MRSA 49.4%), coagulase-negative staphylococcus 13.2%, Streptococcus species 6.9%, other 15%

RESULTS

TABLE: EFFICACY & SAFETY

CLINICAL ENDPOINTS	CLINDAMYCIN 300MG PO TID	TMP/SMX 1 DS BID	PLACEBO	ARR/ARI			NNT/NNH /10 DAYS		
				Clinda vs TMP/SMX	Clinda vs Placebo	TMP/SMX vs Placebo	Clinda vs TMP/SMX	Clinda vs Placebo	TMP/SMX vs Placebo
PRIMARY ENDPOINT: CLINICAL CURE BY TEST-OF-CURE VISIT (i.e. 7 to 10 days after the end of treatment)									
Intention-to-treat population	83.1% (221/266)	81.7% (215/263)	68.9% (177/257)	NS	14.2%	12.8%	-	7	8
Population that could be evaluated [‡]	92.9% (221/238)	92.7% (215/232)	80.5% (177/220)		12.4%	12.2%		9	9
SECONARY ENDPOINTS (ITT Analysis; results were similar for the population that could be evaluated)									
Cure rate at 1 month follow-up	78.6% (209/266)	73% (192/263)	62.6% (161/257)	NS	16%	10.4%	-	7	10
Cure rate in *S.aureus* infections	83.5% (157/188)	83.2% (149/179)	63.8% (102/160)		19.7%	19.4%		6	6
Cure rate in MRSA infections	81.7% (116/142)	84.6% (110/130)	62.9% (73/116)		18.8%	21.7%		6	5
Cure rate in MSSA infections	89.1% (41/46)	79.6% (39/49)	65.9% (29/44)		23.2%	NS		5	-
Cure rate in non-*S.aureus* infxns	83.8% (57/68)	81.9% (59/72)	83.1% (69/83)		NS	NS		-	-
ADDITIONAL ANALYSES (population that could be evaluated, or took ≥1 study doses)									
New or recurrent infection at 1 month follow-up	6.8% (15/221)	13.5% (29/215)	12.4% (22/177)	6.7%	NS	NS	15	-	-
Treatment-associated adverse events	21.9% (58/265)	11.1% (29/261)	12.5% (32/255)	10.8%	9.4%	1.4%	p-values & CI not reported for AE no cases of *C. difficile* reported		
Diarrhea	16.2% (43/265)	5.4% (14/261)	6.7% (17/255)	10.8%	9.5%	1.3%			

[‡] Participants who received treatment or placebo & completed the end-of-treatment and test-of-cure visits.
S.aureus isolates resistant to clindamycin 4.9% (n=13/266)

Age groups: for the population that could be evaluated, children had a higher cure rate with clindamycin than with TMP/SMX or placebo (versus adults, p≤0.04). This outcome was non-statistically significant for the ITT analysis.

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:

- Study protocol included a standardized incision & drainage procedure.
- Funded by the National Institute of Allergy & Infectious Diseases of the National Institutes of Health.
- Investigators were blinded to C&S results.
- Intention-to-treat analysis with a "population that could be evaluated" analysis. For the latter, adherence was assessed by self-report and drug accountability for participants who returned blister packs / suspension bottles.
- Primary endpoint was assessed 7 to 10 days after treatment ended (i.e. 17 to 20 days after I&D).
- Subgroup analysis based on culture results.
- Duration of therapy was reported for non-adherent patients (in supplement).

LIMITATIONS:

- Less than half (43.6%) of participants were fully adherent to the study regimen (majority of the non-adherent patient population took 76-99% of the doses).
- p-values & confidence intervals were not published for the safety analysis.
- Subgroup analyses were underpowered, and therefore can only be hypothesis generating.

UNCERTAINITIES:

- Efficacy of doxycycline in comparison to clindamycin or TMP/SMX.
- Efficacy of shorter courses of antibiotics (i.e. ≤1 week).
- Ideal dose of TMP/SMX (individuals with a BMI >40kg/m^2 were excluded).
- For new or recurrent infections at the 1 month follow-up, the difference between clindamycin vs TMP/SMX was statistically significant (in favour of clindamycin) but the difference between clindamycin vs placebo was non-statistically significant (p=0.06) [see Results Table on first page]. As noted about, all secondary endpoints were underpowered. Query if the difference between clindamycin vs TMP/SMX was a chance finding.

RxFILES RELATED LINKS

- **RxFiles Skin & Soft Tissue Infection Chart:** http://www.rxfiles.ca/rxfiles/uploads/documents/members/ABX-Skin-Infections.pdf
- **RxFiles Trial Summary TMP/SMX vs Placebo for uncomplicated skin abscesses:** http://www.rxfiles.ca/rxfiles/uploads/documents/TMP_SMX%20vs%20Placebo%20for%20Uncomplicated%20Skin%20Abscess_Trial_Summary.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

♂=male **AE**=adverse events **ARI**=absolute risk increase **ARR**=absolute risk reduction **BID**=twice daily **BMI**=body mass index **C&S**=culture & sensitivity **CKD**=chronic kidney disease **DM**=diabetes mellitus **DS**=double strength **ER**=Emergency Room **I&D**=incision & drainage **LTC**=long-term care **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 **SK**=Saskatchewan **TMP/SMX**=trimethoprim/sulfamethoxazole

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2. Stevens DL, Bisno AL, Chambers HF, Dellinger EP, et al; Infectious Diseases Society of America (IDSA). Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014 Jul 15;59(2):e10- 52.
3. Bugs & Drugs 2012.
4. Anti-infective Review Panel. Anti-infective guidelines for community-acquired infections. Toronto: MUMS Guideline Clearinghouse; 2013.
5. Singer AJ, and Thode HC Jr. Systemic antibiotics after incision and drainage of simple abscesses: a meta-analysis. Emerg Med J.
6. Talan DA, Mower WR, Krishnadasan A, Abrahamian FM, et al. Trimethoprim-Sulfamethoxazole versus Placebo for Uncomplicated Skin Abscess. N Engl J Med. 2016 Mar 3;374(9):823-32.