Clindamycin versus Trimethoprim-Sulfamethoxazole for uncomplicated skin infections

BOTTOM LINE

- In this trial of healthy patients with uncomplicated skin and soft tissue infections (SSTIs), there was no significant difference in efficacy or adverse events between clindamycin and trimethoprim-sulfamethoxazole (TMP-SMX).[5]
- In patients with skin infections and MRSA risk factors, either TMP-SMX or clindamycin may be an efficacious choice depending on resistance rates. HOWEVER, MRSA resistance to clindamycin is often higher in the real world than this study. In Saskatchewan, MRSA resistance to clindamycin is 30-40%, much higher than the 4% in this study. Thus TMP-SMX is preferred over clindamycin.
- Two important treatments for skin infections - beta-lactam antibiotics, and incision and drainage alone without antibiotics - were not examined in this study. However, beta-lactam antibiotics remain first-line therapy for non-purulent skin infections, and incision and drainage alone remains first-line therapy for mild purulent skin infections.

BACKGROUND

- SSTIs are common reasons for visits to outpatient clinics and emergency rooms, as well as hospital admissions, and may result in significant morbidity and mortality. Classically, it is thought that beta-hemolytic streptococci are the causative organism for non-purulent SSTI and staph species are implicated in purulent SSTI.
- Trimethoprim-Sulfamethoxazole and clindamycin are two antibiotics commonly used to treat purulent SSTI where CA-MRSA is suspected as the likely causative pathogen.
- Historically, TMP-SMX is thought to have less Group A strep coverage and may not be as effective as clindamycin for empiric coverage of non-purulent SSTI caused by *Beta-hemolytic streptococci* or mixed infections. However, there is recent evidence that group A strep may be more susceptible than thought.[6]

TRIAL BACKGROUND

- **DESIGN**: Randomized, double-blind, interventional assessment trial; multisite (4 centers in US).[5] Patients stratified based on prespecified criteria. ITT analysis for primary and secondary endpoints. Population that could be evaluated also included superiority based study. Study sponsored by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health.

INTERVENTION: trimethoprim/sulfamethoxazole 160mg/800mg twice daily (pediatric dose: 8-10mg/kg/day) vs. clindamycin 300mg three times daily (pediatric dose: 25-30mg/kg/day) for 10 days.

Follow up: Test of cure visit (TOC) (7-10 days after completion of 10 day course of therapy) and at the one month follow up (day 40)

INCLUSION: Age 6 months to 84 years old, with at least two localized clinical signs or symptoms for SSTI for at least 24 hours, and able to take medication orally (tablet or suspension)

EXCLUSION: Hospitalization required, hospitalized or treatment with anti-staphylococcal antimicrobial therapy in previous 14 days, long term care resident, superficial skin infection (impetigo, folliculitis), psychiatric disease, active alcohol or drug use, documented or witnessed animal bite in previous 30 days , breast feeding, morbid obesity (BMI >40), history of immunocompromising condition (e.g. HIV, diabetes, chronic renal failure), complicated skin or soft tissue infection, infection at anatomical site requiring specialist management (e.g. hand, foot, genital, perirectal, periorbital)

POPULATION at baseline: n=524: age 27 +/- 17; Female (47.7%)

- Ethnicity: White 40.3%, Asian 1.7%, Black 53.2%, American Indian or Alaskan native 0.6%, other 4.2%
- Type of lesion: Abscess only (30.5%), Cellulitis (53.4%), and mixed abscess and cellulitis (15.6%)
- Area of wound (Cm^2) 39.62 +/- 111.28
- Purulent drainage present 45.2%, incision and drainage performed 44.5%
- Positive culture 52.9%, no culture obtained 43.5%, no growth 2.3%, no results 1.3%
- *Staph aureus* (41.4%) MRSA 31.9% (Clindamycin resistance 4%, TMP-SMX resistant 0.2%)
- *Strep pyogenes* 1.5%, Group B Strep 0.4%, *viridans Streptococci* 3.4%

RESULTS

TABLE 1: EFFICACY OF THE ITT POPULATION & SAFETY OF THE SAFETY POPULATION (DEFINED AS SUBJECTS WHO TOOK 1 OR MORE DOSES OF STUDY MEDICATION)

CLINICAL ENDPOINTS	TMP-SMX n=202	CLINDAMYCIN n=212	ARR/ARI	COMMENTS
Clinical cure at 17-20 days	80.3%	77.7%	2.6%	All results statistically non-significant. No treatment- associated serious adverse events No reported cases of *C.difficile* associated diarrhea
Clinical cure at one month follow up	73.1%	67.7%	5.4%	
Clinical cure in adults	77.6%	76.3%	0.3%	
Clinical cure in pediatrics	86.4%	81.1%	5.3%	
Clinical cure rate of abscess at TOC	78.8%	80%	1.2%	
Clinical cure rate of cellulitis at TOC	80.9%	76.4%	4.5%	
Clinical cure rate of mixed abscess and cellulitis at TOC	83%	80%	3.0%	
Adverse-event rates (total)	18.9%	18.6%	0.3%	
Diarrhea	10.1%	9.7%		
Vomiting	2.3%	1.6%		
Dyspesia	0.4%	0%		
Rash	1.2%	0.8%		
Pruritis	1.2%	1.5%		

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:

- Well-designed trial: large sample size, multi-centre, well-balanced treatment groups.
- Examined an important clinical question surrounding two common non-patent medications.

LIMITATIONS:

- Extensive exclusion criteria (3 pages in supplement) limit generalizability. Mostly enrolled young, healthy patients with no comorbidities; therefore cure rate (clindamycin 77.7%, TMP-SMX 80.3%) may be higher than seen in the real world.
- 4% of MRSA isolates in trial had clindamycin resistance. This is less than reported provincial susceptibilities and thus the study cure rate for clindamycin is likely to be higher than seen in real world. (In Saskatchewan *Staph aureus* resistance to clindamycin is around 30-40%).[11]
- Nearly all patients in this study with purulent infections received incision and drainage. Incision and drainage has been shown to be highly effective, particularly in mild abscesses, and may render antibiotics unnecessary.[12] Thus this could have artificially increased the cure rate in this study.
- Use of a 10 day course does not provide insight into the current recommendation of a shorter, 5 day course.
- This study did not differentiate uncomplicated SSTI secondary to trauma, which can influence dosing and agent choice.
- Study location included emergency department, urgent care clinics, and affiliated clinics. Did not include hospitalized patients. May be harder to generalize findings to a pure ED setting.

UNCERTAINITIES:

- Due to exclusion criteria did not analyze more complex patients or more complicated forms of SSTIs.
- Historically, *Streptococci* are believed to be the predominant causative pathogen in non-purulent infections, and TMP-SMX is believed to have minimal activity. However, in this study, TMP-SMX was equally effective to clindamycin. (Note: 80% of non-purulent infections did not have a culture taken, as this is a difficult sample to collect. We presume most of these patients had *Streptococci* infections, but it is possible this wasn't the case.)
- Guidelines generally do not recommend empiric MRSA coverage in this patient population.[12] How would a beta-lactam antibiotic have performed in this study? While there were a large amount of MRSA isolates identified, most MRSA samples came from patients who had received incision and drainage ... and thus antibiotic therapy may have been unnecessary.

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ARI=absolute risk increase **ARR**=absolute risk reduction **CA-MRSA**=community-associated MRSA **ED**=emergency department **MRSA**=methicillin-resistant *Staph Aureus* **SSTI**=skin and soft tissue infection **TOC**=test of cure **TMP-SMX**=trimethoprim-sulfamethoxazole

ACKNOWLEDGEMENTS: Contributors & Reviews: Loren Regier, Alex Crawley **Prepared By**: Jeff Herbert