**Title:**
Efficacy of preoperative intranasal povidone-iodine in comparison to standard protocol or no antibiotics to prevent surgical site infections in patients undergoing Mohs micrographic surgery: A three-arm randomized clinical trial

**Specific Aims:**
1. Primary aim: to evaluate the effectiveness of preoperative intranasal povidone-iodine for surgical site infection prevention after Mohs micrographic surgery.
2. Secondary aims: evaluate 1) aforementoined povidone-iodine SSI prevention strategy in comparison to 2) "standard" protocol per 2008 Advisory Statement (PMID: 18694679) and 3) no prophylactic antibiotic.
3. Additional aims: Identify prospective infection rates and qualitative data in each trial arm, substratified based on: anatomic site, reconstruction type, total surgical sites, and subpopulation (immunosuppressed patients).

**Background and Significance:**
Mohs micrographic surgery (MMS) has been reported to have overall low rates of surgical site infection (SSI), ranging from <1% to 4-5%(1), with variable definitions of SSI and follow-up. An Advisory Statement on Antibiotic Prophylaxis in Dermatologic Surgery (2008) recommended that antibiotic prophylaxis should be considered in patients at high risk for SSI or at high risk for serious complications and morbidity after SSI (prosthetic valve or joint replacement <2 years PLUS mucosal breech or infected site) (2). Despite efforts to standardize prescribing habits, there remains controversy and heterogeneity in antibiotic prophylaxis practices and preferences amongst Mohs surgeons (3,4). In 2019, Mourad et al. published a meta-analysis that included RCTs and found no benefit to oral antibiotics versus placebo for SSI prevention after MMS, although some benefit to the use of intraincisional antibiotic compared with placebo (4). A 2023 systematic review and meta-analysis by Chen et al. further quantified SSI among 2252 flap/graft closures, 3818 primary closures, and 1434 secondary intention healing cases demonstrating: 1% SSI rates for flaps/grafts and <1% for primary/secondary closures of the head and neck (H/N) compared to pooled lower extremity SSI rates of 11% for flap/graft closures, 5% for primary closures, and 4% for secondary intention healing (5). Aizen et al. demonstrated that Mohs surgeons desire further clinical trials to elucidate the role of antibiotic prophylaxis for SSI prevention after MMS (4).

Studies and meta-analyses demonstrating the potential lack of benefit of oral antibiotics brings into question whether we can optimize SSI prevention strategies in a cost-effective and generalizable way. For example, the application of nasal mupirocin to decolonize and

prevent SSI has been shown (6,7). Preoperative intranasal povidone-iodine solution appears to be an even more promising and cost-effective regimen, achieving similar results to mupirocin but in less time and minimal adverse effects (8) based on prospective and randomized trial data from orthopedic surgery (9,10). While the povidone-iodine strategy has become the standard for many orthopedic practices, this has not yet been studied in dermatologic surgery. Our proposed study seeks to explore this novel SSI prevention approach in comparison to current prophylaxis practices. Specifically, we have designed a 3-arm randomized clinical trial to investigate SSI rates between patients undergoing MMS with: 1) standard prophylaxis per 2008 Advisory statement based on pre-defined SSI risk and morbidity risk or 2) no antibiotic prophylaxis or 3) a novel approach with preoperative intranasal povidone-iodine (no antibiotic).

**Preliminary Studies:**
Our division colleagues published the updated guidelines for antibiotic prophylaxis in dermatologic surgery in 2005 and the 2008 advisory statement (Wright et al. 2008 JAAD). This is our first study on the use of povidone-iodine. We did discuss beginning with a proof-of-concept study investigating only povidone-iodine, but the bioethics and research committee felt the current 3-arm design would provide more valuable insight with potential for impact on clinical practices.

**Methods:**
A randomized, non-blinded, multi-arm clinical trial will be conducted. Patients will be randomized to one of three arms: 1) preoperative application of intranasal 10% povidone-iodine, 2) preoperative prophylactic antibiotic protocol (as defined by the 2008 advisorystatement), or 3) no prophylactic antibiotics. Inclusion criteria includes any patient > 18 that is consentable who is undergoing MMS at our institution, including immunosuppressed patients and all anatomic sites, but excluding patients with a high-risk of infective endocarditis or hematogenous total joint infection undergoing surgery involving/breeching mucosa. All patients will undergo Mohs stages with clean technique, and sterile closure as is the standard in our practice.

Detailed sociodemographic and procedural/clinical information will be recorded. All enrolled patients will undergo nasal swab culture before surgery to assess nasal carriage of S. Aureus. The primary outcome of our study will be SSI developed between day of MMS (day 0) and 30 days after MMS, following the criteria of CDC (National Healthcare Safety Network) guidelines. Approximately 45% of our patients are non-local from other parts of the country, so requirement for in-person follow-up would make the trial infeasible at our institution. Instead, SSI within 30 days of MMS will be determined through meticulous chart

review (or obtaining outside records) and phone call. Other outcomes such as the rate of wound dehiscence, S. Aureus infection, hospitalization, and emergency department visit/admission will be measured.

We estimated a sample size of 2298, with 766 patients assigned to each arm, to detect a clinically significant difference of at least 2% in SSI rates between the arms through pairwise comparisons. SSI rates will be calculated for each group and pairwise comparisons will be made between each arm using two-sample proportion tests. Additionally, relative risk estimates with their respective 95% confidence intervals will be calculated for each pairwise comparison. The same calculations will be performed in predetermined subpopulations of interest such as immunosuppressed patients and of higher risk anatomic sites (lower extremities).

**Organizational Structure:**
A research fellow will be dedicated to this study (Dr. Rios) and is currently funded by the PI's Totz Benefactor Award, and supplemented by the Department of Dermatology, with the possibility of extension of time and funding for continuity of projects. In addition, the Department has shared experienced personnel dedicated to clinical research and who will be available to assist with study coordination of funded protocols. Our institution also offers consultations across disciplines to assist with details of planning a successful investigator- initiated clinical trial. Of note, this proposal has already undergone rigorous review and feedback from members of the Division of the Dermatologic Surgery (7 board-certified MDS surgeons who will be participating), research committee, IRB, bioethics, and statistics with plans for ongoing guidance to further refine design. We discussed initially performing a proof-of- concept study investigating only povidone-iodine (given novelty to our literature) versus a 2-arm design; however, universal feedback was that there would be more value and potential for impact on clinical practice to proceed as a 3-arm trial.

**Literature cited:**

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