Title: Use of Perioperative Antibiotics in Endoscopic Sinus Surgery

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Title of Study: Use of postoperative antibiotics in endoscopic sinus surgery: A multi-institutional prospective randomized controlled trial
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Background/Significance:

Endoscopic sinus surgery (ESS) is commonly performed by otolaryngologists for chronic rhinosinusitis (CRS) that is refractory to medical management. Given that human sinonasal tracts are colonized by bacteria, ESS is considered to be a clean-contaminated procedure as outlined by Waddell and Rotstein.[1] These types of surgery are known to carry a higher risk of infection than surgeries in a clean or sterile part of the body. Otolaryngologists often prescribe prophylactic antibiotics for their patients following ESS. The benefits of antibiotic use following ESS are still unknown. There are known risks however of inappropriate antibiotic use. Inappropriate antibiotic prescribing is thought to be the primary cause of antibiotic resistance.[2] Adverse events such as allergic reactions and *Clostridium difficile* infections are also known risks of antibiotic use.[3] In the ambulatory care setting, acute sinusitis has been shown to be the leading diagnosis associated with inappropriate antibiotic use.[4] With regards to ESS, culture-inappropriate antibiotic therapy has been shown to lead to less quality of life improvement following surgery.[5]

To date, the standard of care for prescribing perioperative antibiotics for ESS has not been established. In 2012, evidence-based practice guidelines concluded that there may be some benefit in prescribing postoperative antibiotics following ESS, although this conclusion was based on the results of a single prospective study.[6] There is a general consensus among otolaryngologists that further studies are necessary to elucidate the role, if any, of perioperative antibiotics for ESS. There have been three prospective randomized trials examining the use of oral postoperative antibiotics following ESS. Two of these studies found that the use of postoperative antibiotics did not significantly impact the rate of postoperative infection or sinonasal symptoms.[7,8] The most recent randomized double-blinded placebo-controlled trial showed that a 2-week course of postoperative amoxicillin-clavulanate resulted in a statistically significant reduction of observed postoperative sinus endoscopy scores, nasal discharge, and nasal blockage on postoperative day (POD) 5.[9] These benefits of antibiotic therapy with regards to symptoms and endoscopy scores were not significant by POD 12 and 21, respectively. However, this study only had a sample size of 75 patients.

Given the mixed results regarding antibiotic use and postoperative patient-related outcomes currently present in the literature, the evidence supporting the use of postoperative antibiotics following ESS remains equivocal. Our proposed multi-institutional prospective randomized controlled trial aims to determine whether postoperative antibiotics are beneficial in patients undergoing ESS.

Study Design

Objective

The objective of this study is to determine whether the use of postoperative antibiotics following ESS decreases postoperative infection rates. This is a multi-institutional prospective study involving Albert Einstein College of Medicine/Montefiore Medical Center, Columbia University

Medical Center, Weill-Cornell Medical College, Mount Sinai Health System, and New York University Langone Medical Center.

The study design will be a multi-institutional prospective randomized controlled trial with parallel random groups assigned to receive antibiotics or no antibiotics. Patients will undergo simple randomization into either group. Physicians and patients will not be blinded. Noncompliant patients will be kept in their assigned groups in accordance to the intention to treat principle.

Hypothesis

We hypothesize that patients who receive postoperative antibiotics will have lower postoperative infection rates and improved postoperative sinonasal symptoms and nasal endoscopy scores than those who do not receive postoperative antibiotics.

Research Protocol

Patient Randomization

Patients will undergo simple randomization and be assigned to either receive antibiotics immediately prior to surgery and for 10 days following surgery or no antibiotics. Patients will undergo 1:1 randomization into the 2 arms so that group assignments will be balanced between all sites.

Patients assigned to the antibiotic group will receive cefazolin 1-2g immediately prior to surgery and then amoxicillin-clavulanate 875mg/125mg twice daily for 10 days starting on POD 1. The rationale behind using amoxicillin-clavulanate postoperatively is the flora of bacteria that has been commonly identified in patients with CRS, which most commonly include *Staphylococcus and Corynebacterium*, and less commonly *Streptococcus, Moraxella and Haemophilus*.[10,11] The spectrum of amoxicillin-clavulanate is appropriate for all bacterial species mentioned above and is the optimal choice for postoperative prophylaxis for patients with CRS. Concern for beta-lactam resistance is low in the ambulatory patient population specified in this study proposal. In the 2015 Clinical Practice Guidelines for Adult Sinusitis, the American Academy of Otolaryngology – Head and Neck Surgery Foundation recommended use of amoxicillin or amoxicillin-clavulanate for the treatment of acute bacterial rhinosinusitis which is also consistent with our rationale.[12]

Patients assigned to the no-antibiotic group will not receive antibiotics preoperatively or postoperatively.

Standardization of perioperative medical management

The following perioperative medical management protocol is considered standard clinical care.

- *Preoperative*
    - Steroids - Patients with nasal polyposis will be given prednisone 30mg x 5 days immediately prior to surgery. Patients without nasal polyposis will not be given preoperative systemic steroids.

- Antibiotics - Patients who are randomized to the antibiotic group will receive cefazolin 1-2g immediately preoperatively. Patients randomized to the no-antibiotic group will not receive antibiotics immediately preoperatively.

- *Intraoperative*
  - Antibiotics - No intraoperative antibiotics will be given.
  - Steroids - Patients with nasal polyposis will given a single dose of intravenous steroid at time of surgery (i.e. decadron 8-10mg).
  - Propel stents - The use of Propel steroid eluting stents will be left to the discretion of the attending surgeon.
  - Splints - The use of Doyle splints or silastic spacers will be left to the discretion of the attending surgeon.
  - Biomaterials – The use of absorbable biomaterials will be left to the discretion of the attending surgeon.
- *Postoperative*
  - Saline rinses - Nasal saline irrigations 3-4 times/day will be started on POD 1.
  - Intranasal steroids - Based on the specific patient pathology, intranasal steroid sprays or rinses may be started at the time of the first postoperative visit. Daily or twice daily use of intranasal steroid spray or rinses will be left to the discretion of the attending surgeon.
  - Steroids - Patients with nasal polyposis will given a 9-day prednisone taper (30mg x 3 days, 20mg x 3 days, 10mg x 3 days). Patients without nasal polyposis will not be given postoperative systemic steroids.
  - Antibiotic – Patients randomized to the antibiotic group will be continued on a 10-day course of amoxicillin-clavulanate following surgery. If a postoperative infection is identified on rigid nasal endoscopy at the time of the follow-up visit, a culture swab will be taken. If a bacterial source of the purulence is identified, the amoxicillin-clavulanate will be changed according to the culture sensitivities. Patients randomized to the no-antibiotic group will not be given antibiotics immediately preoperatively or postoperatively. However, if purulence is identified during postoperative nasal endoscopy, similarly, a culture swab will be taken. These patients will be started on an antibiotic of the physician's choice at the time of their postoperative visit. The antibiotic will be switched to a culture-directed antibiotic when results of the culture swab are available.

Outcomes

The primary outcome of this study is postoperative infection rate, as assessed by rigid nasal endoscopy in the office and culture of suspected infectious material noted within the paranasal sinuses. A postoperative infection is defined by having an infection at any of the postoperative visits and is detected initially by evidence of purulence on nasal endoscopy but will only be considered an infection if the culture swab from the site of purulence during that office visit determines that there is an actual bacterial source of the infection. This information will also be used to initiate appropriate antimicrobial management if indicated. This is considered to be standard clinical care.

Secondary outcomes include patient reported symptoms as assessed by the validated sino-nasal outcome test (SNOT-22)[13] and sinonasal crusting and inflammation as assessed by the validated perioperative sinus endoscopy (POSE) scoring system.[14]

Outcome Time Points

The outcome time points will be the first postoperative visit (POD 7-10), second postoperative visit (2-4 weeks), and the third postoperative visit (6-8 weeks). Symptoms (SNOT-22) and endoscopy scores (POSE and endoscopic evidence of purulence) will be obtained at all time points. Cultures will be obtained only if there is endoscopic visualization of purulence within a paranasal sinus as described above.

Study Population

The population for this study will be drawn from patients presenting to the otolaryngology clinics at the aforementioned medical centers. All patients who present to the otolaryngology clinic are potential candidates for ESS. Only patients who are diagnosed with CRS and deemed suitable surgical candidates for ESS will be recruited for this study. The study population size is intended to be a total of 426 patients across all sites. Suitable surgical candidates that agree to be in the study will be randomized into the antibiotic or no-antibiotic trial arms.

***Inclusion criteria*:** Patients with CRS with or without nasal polyposis or allergic fungal rhinosinusitis who present to the otolaryngology clinic who have been deemed suitable for bilateral ESS, and are over the age of 18 will be included.

***Exclusion criteria*:** Patients with sinonasal tumors, allergy to penicillin, adverse reactions to amoxicillin-clavulanate or penicillin, immunodeficiency, cystic fibrosis, pregnancy, or diabetes with nasal polyposis (inability to receive systemic steroids) will be excluded, as will patients who lack capacity to provide informed consent. Patients undergoing active treatment for malignancy will be excluded. Patients undergoing unilateral ESS or with nonabsorbable packing placed at the time of surgery will be excluded. Patients who have been on antibiotics within 2 weeks of the surgery date will be excluded. Patients with acute on chronic sinusitis or the presence of purulence at time of surgery will be excluded from the study.

Participant Recruitment

All patients who present to the rhinology clinic are potential candidates for ESS. Only patients who are diagnosed with CRS and deemed surgical candidates for ESS will be asked to participate in this study. Participants will be recruited during otolaryngology clinical office hours by attending physicians or residents. Patients who are interested in participating in the study will then be approached by study team members who have been instructed on the informed consent, risks/benefits of the study, and standard of care for postoperative antibiotics in ESS to obtain informed consent. Patients will be asked to sign the informed consent form during their preoperative visit. Patients will then be randomized to either trial arm by the researchers and either receive the antibiotic or no antibiotic following surgery.

Coercion will be avoided by guaranteeing the patient's access to otolaryngology care regardless of the decision to participate or not, and by offering no financial incentive to join the study.

Refusal to participate will in no way affect the patient's ability to receive the established standard of care at any of the participating institutions.

There will be no additional cost to the patient.

Informed Consent

Informed consent will be obtained by an attending physician or resident physician who have been instructed on the risks/benefits of the study, the objectives of the study, and the standard of care for postoperative antibiotics in sinus surgery, during otolaryngology clinic office hours. The research team will retain the original consent form and a photocopy will be provided to the participant.

Risks/Benefits

Risks of this study include the risk of an allergic reaction to the antibiotic, adverse reaction to medications, and change in the baseline risk of infection associated with ESS. Risks of amoxicillin-clavulanate include nausea, vomiting, headache, diarrhea, upset stomach, dark urine, skin rash or itching, jaundice, increased risk of bruising and very rarely, *Clostridium-difficile* associated diarrhea. Risks will be minimized by taking a thorough history from the patient regarding past allergic reactions and other adverse outcomes to medications. A separate informed consent will be obtained for the risks of the surgery itself. There are minimal additional risks to the patient beyond the risks associated with the study and those outlined prior.

The benefits of this study include the theoretical improvement in a patient's postoperative sinonasal symptoms and endoscopy exams.

Confidentiality

Patient records used for research will be de-identified and given a code number. This code number will be separate from any name or other information that could identify the patient. The form that links patient names to the code number will be kept in a secure manner and only the investigator and study staff will have access to the file. Patient data will be recorded into a password secured HIPAA compliant computer program only available to researchers or clinicians directly managing the patient's care during the course of the study. All information will be kept in a secure manner and computer records will be password protected. We will keep records relevant to the study until completion of this project (until completion of data analysis and manuscript publication).

Medical information collected during the research, such as test results, may be entered into the secure electronic medical record and will be available to clinicians and other staff who provide care to the patients.

Time to Complete

This study will start as soon as ORP and local IRB clearances are obtained, and is expected to take 12 months to complete.

Statistical Analysis

Sample Size Calculation

We are planning a study of independent cases and controls with 1 control(s) per case. In the absence of data reporting the baseline postoperative infection rate in ESS patients, the consensus rate agreed upon by the sub-specialist, fellowship-trained rhinologists at each of the study sites is 0.1. If the true failure rate for experimental subjects--those that are given postoperative antibiotics is 0.03--we will need to study 194 experimental subjects and 194 control subjects to be able to reject the null hypothesis that the failure rates for experimental and control subjects are equal with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05. We anticipate an attrition rate of 10 percent and accounting for this would need a total of 426 subjects.

Data Analysis

The primary outcome will be statistically analyzed with the confidence level set to 5% and effect size of 20%. We will utilize binomial logistic regression for analysis. As stated, the dependent variable (primary outcome) is binary and we can, therefore, use this technique to determine the influence of independent variables on the primary outcome. Secondary outcomes of SNOT-22 and POSE scores will compared between the two groups by means of multivariable linear regression analysis. Demographics such as age, gender, presence of asthma or nasal polyps, and preoperative disease severity will be controlled for using these analyses. We will be working with a biostatistician for our data analysis and will add their expertise to our data analysis.

Compensation for Participation

No payment or compensation will be received by subjects.

Adverse and/or Unanticipated Events

All adverse and/or unanticipated events will be reported to PI/study staff and the Einstein IRB as per IRB guidelines. Given the low risk and non-invasive nature of this study for those involved, however, this is unlikely to occur.

Departure/Deviation from Protocol

Both the ORP/HSRRB offices and local IRB will be notified prior to protocol deviations by email and written notice.

Amendments/Addendums/Modifications (Including Termination of the Study)

Any modification or amendment to the protocol will be submitted to the ORP/HSRRB and local IRB offices for review and approval prior to implementation by email and written notice.

Sponsors

None

Data Safety Monitoring Plan

The PI, who is an attending physician will monitor the data collected for adverse events and will report any adverse events including data breach immediately upon determination of adverse events. There is minimal risk of adverse events from digital imaging except breach of confidentiality which will be carefully monitored, and name/date of birth

identifiers which will be removed. In addition, only close-up views of the intranasal cavities will be recorded, avoiding any recognition by imaging.

The PI at each site will monitor subject outcomes to determine if one group is suffering undue complications at an increased rate by reviewing the data collected every month. There is no published or known rate of postoperative infection following ESS; however, if the group that is assigned to not receive any postoperative antibiotics is found to have a postoperative infection rate of > 10%, the protocol will be terminated. If the group that is assigned to receive antibiotics has an increased rate of complications related to the antibiotic, specifically if >10% of patients develop an allergic reaction to the antibiotic, then the protocol will be terminated.

Each institutional site involved in this study will have their own IRB approved data safety monitoring plan, and each individual site will likely be monitored by their own PI/research team. Every quarter, all of the PIs will meet to share safety data and discuss any adverse events. Any serious adverse event will be immediately reported to the primary PI at Albert Einstein for review. At each meeting, minutes will be taken and include attendance, summary of the discussion, and any pertinent findings.

Roles and Responsibilities of Team Members:
Nadeem A. Akbar, MD (Principal Investigator)
Waleed M. Abuzeid, MD (Co-Principal Investigator)
Christina H. Fang, MD (PGY-3, Research Staff)
Priya Nori, MD (Infectious disease/antibiotic expert)

Other Sites
Columbia University Medical Center
- David Gudis, MD (Principal Investigator)

Weill-Cornell Medical College
- Abtin Tabaee, MD (Principal Investigator)

Mount Sinai Health System
- Satish Govindaraj, MD (Principal Investigator)
- Anthony Del Signore, MD (Co-Investigator)
- Alfred Iloreta Jr., MD (Co-Investigator)
- Patrick Colley, MD (Co-Investigator)
- Madeleine Schaberg, MD (Co-Investigator)

New York University Langone Medical Center
- Seth Lieberman, MD (Principal Investigator)
- Richard Lebowitz, MD (Co-Investigator)

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