

Oral vs. Topical Antibiotic Therapy for Treatment of Chronic Rhinosinusitis Exacerbations

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Background

Chronic Rhinosinusitis (CRS) is a common condition that affects approximately 13 percent of the United States population annually.¹ CRS is a persistent symptomatic inflammation of the nasal cavity and paranasal sinuses due to a variety of host and environmental factors.² According to the American Academy of Otolaryngology-Head and Neck Surgery definition, the diagnosis of CRS requires that patients have at least 2 signs or symptoms of rhinosinusitis (mucopurulent drainage, nasal obstruction, facial pain, pressure, fullness, or hyposmia) for at least 12 weeks as well as documented inflammation on nasal endoscopy or radiographic imaging.³ Treatment is focused on decreasing mucosal inflammation, controlling infection, and improving mucociliary clearance.² Patients who are symptomatic despite medical therapy may undergo endoscopic sinus surgery (ESS). Given the chronic nature of the disease, CRS patients who have undergone endoscopic sinus surgery may continue to have intermittent, acute exacerbations of rhinosinusitis.

There are no FDA approved treatments for acute exacerbations of chronic rhinosinusitis. The mainstay therapy is topical nasal steroids and culture-directed oral antibiotics.⁴ Recent studies suggest that topical antibiotics may provide a more potent and targeted therapeutic option for CRS exacerbations.⁵⁻¹⁵ In post-ESS patients, the open paranasal sinuses result in improved penetration of topical medical therapies, making topical antibiotics an attractive treatment option.¹⁶ Available delivery methods include irrigation, nebulization, atomization, and spray.^{5-14,17} Overall there has been no improvement demonstrated by the use of topical antibiotic sprays, but there has been low-level evidence to support the use of topically irrigated and nebulized antibiotic therapies with overall improvement in patient outcomes.⁴ To our knowledge, there have been no studies comparing nebulizations to irrigations in the treatment of chronic or acute or chronic rhinosinusitis, thus indicating one method of delivery is superior to another. Nebulized therapies have the benefit of a predictably large particle size that results in high intranasal retention.¹⁸ Treatment is well tolerated overall with no major adverse effects reported in the literature.¹⁶ Minor side effects are rare and include local irritation, cough, headache, and sore throat.^{12,16,19} Despite gains in popularity, there is currently little evidence to support the efficacy of topical antibiotic treatments in comparison to oral antibiotics.^{4,17}

Antibiotic treatment of chronic rhinosinusitis is currently based on the organisms that are cultured from the sinonasal cavity. The most prevalent organisms cultured from patients in acute bacterial rhinosinusitis include *Streptococcus pneumonia*, *Haemophilus influenza*, *Moraxella catarrhalis*, and *Staphylococcus aureus*.²⁰ The bacteria involved in chronic rhinosinusitis are similar, with *Staphylococcus aureus* being most prevalent, and *Pseudomonas aeruginosa*, *Haemophilus spp*, and

Streptococcus pneumonia also contributing to the disease etiology.²¹ The microbial contribution to chronic rhinosinusitis is not limited to these pathogens. Considerable interest has been shown in the role of bacterial biofilms to disease. Composition of these biofilms, as well as total bacterial population, has been elucidated using molecular tools with the capability of identifying all bacteria present in a sample.²²⁻²⁴ These techniques have been used previously to compare the bacterial communities of patients with CRS to healthy patients. There have not been any previous studies that have compared patients with acute exacerbations of CRS pre- and post- antibiotic treatment.

Purpose

1. Evaluation of the efficacy of culture-directed sinonal antibiotic nebulizations in treating post-endoscopic sinus surgery CRS patients with active rhinosinusitis compared to conventional treatment with oral antibiotics.
2. Determination of changes in the total bacterial community of the sinonal cavity following oral antibiotic therapy vs. topical antibiotic treatment.

Methods

Subjects

The rhinology clinic at the University of Rochester Medical Center routinely follows CRS patients with nasal endoscopy and with disease-specific quality-of-life questionnaires. Our current clinical standard of practice includes obtaining a sinonal culture directed by nasal endoscopy and making treatment decisions based on the culture results. We will recruit post-ESS CRS patients with worsening symptoms and mucopurulence in the paranasal sinuses seen on nasal endoscopy. Up to 100 potential subjects meeting the defined inclusion criteria will be approached during routine clinic visits with a goal for enrollment of 70 patients. Enrollment is defined as entering the study and receiving treatment. We will screen more patients than will be enrolled, anticipating that approximately 30 patients will not be eligible for inclusion based on their culture results. Patients will not be eligible for inclusion if they are systemically ill at the time of their initial visit or if they require antibiotic treatment prior to finalization of culture data. Justification for a sample size of 70 (35 subjects per treatment group) is based on the assumptions that (1) 90% of patients taking culture-directed oral antibiotics will experience a clinical and statistically significant improvement in Rhinosinusitis Disability Index (RSID) score at the end of therapy, and (2) The non-inferiority limit of topical therapy is 20% of oral therapy. Using a standard deviation of 20% and a power of 0.9, 26 subjects will be required in each treatment group. We will enroll more subjects than required to compensate for any exclusions made once treatment is initiated and for subjects who drop out of the study.

Male and female adults of any race will be considered for inclusion. Mentally and physically disabled persons will be allowed to participate if they exhibit the capacity to consent to participate in the research, to carry out the treatment regimen, and to accurately communicate and record their symptoms, which will be based on the physician's assessment at their initial visit. There will be no exclusion based on economic or educational disadvantage. Prisoners will not be included in the study population due to difficulties coordinating care and administering nebulization therapy.

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Inclusion criteria

1. Adults (age ≥ 18).
2. Diagnosis of CRS.
3. Worsening sinonasal symptoms.
4. Previous bilateral ESS (including maxillary antrostomy and anterior ethmoidectomy).
5. English speaking.
6. Open sinuses (open middle meatus bilaterally; determined on endoscopy).
7. Positive sinonasal culture (1+ or greater) with sensitivity to Levofloxacin.
8. Individuals must have the ability to understand the requirements of the research and be able to provide consent to participate.

Exclusion criteria

1. Patients < 18 years of age.
2. Treatment with systemic or topical antibiotics within the last 1 month.
3. Pregnant women.
4. Non-English speaking persons.
5. Systemically ill at initial visit necessitating treatment prior to culture data.
6. Allergy to Levofloxacin or other fluroquinolones
7. Patients with a history of long Q-T syndrome.
8. Patients currently taking medications that prolong the Q-T interval.
9. Sinonasal culture with less than 1+ growth.
10. Multiple organisms grown on culture that are not sensitive to a single antibiotic.
11. Patients with ciliary function disorders (cystic fibrosis, Kartagener's syndrome, ciliary dyskinesia).
12. Patients with immunodeficiencies.

Study Design

Sinonasal cultures guided by nasal endoscopy via aspiration with a Tami Sinus Secretion Collector (Medtronic, Minneapolis, MN) will be performed. Aerobic cultures will be obtained, according to the clinical standard of care. If bilateral sinuses appear infected, representative cultures will be taken from each side. After suctioning purulent material, a sterile swab with flocked nylon fiber will be brushed along the mucosa in bilateral maxillary sinuses. The swabs will be placed into separate storage buffers for transport to the laboratory for further molecular analysis. Positive cultures will be defined as 1+ or greater organism growth. Patients with positive cultures will be randomized to one of two treatment groups:

- (1) Daily oral Levofloxacin with twice daily nebulized intranasal placebo for 14 days, or
- (2) Daily oral placebo with twice daily nebulized intranasal topical Levofloxacin for 14 days.

Each nostril will be irrigated with approximately 120 mL of saline solution prior to administration of the nebulized placebo or antibiotic. Patients will not be eligible for enrollment into the study if any organisms are not susceptible to Levofloxacin. Additionally, if bilateral cultures are obtained, the patient will only be eligible for inclusion if all cultures are susceptible to Levofloxacin.

Subjects will enter the blinding process after culture data has been reviewed. A sealed envelope blinded to the investigators selecting either an oral or topical antibiotic will be sent to the participating pharmacy (Professional Arts Pharmacy, Lafayette, LA). This will be based on a separate key that has been blinded to the investigators that will randomly assign a study participant to either an oral or topical antibiotic with the appropriate corresponding placebo. The list will be maintained by the study coordinator. A saline rinse kit (Sinus Rinse, NeilMed, Santa Rosa, CA) and isotonic salt preparation will be supplied to the patient at their initial visit. A nasal nebulizer (NasoNeb, Medinvent, White Bear Lake, MN) and the topical antibiotic with oral placebo or topical placebo with oral antibiotic will be mailed to the subject by the participating pharmacy. Alternatively, instead of the pharmacy shipping to the subject's home, subjects may pick up the appropriately randomized medication regimen from the otolaryngology clinic at Clinton Woods, with the prescription then sent to the participating pharmacy (PAP) to refill the stock. The clinical technician at the clinic in charge of ordering and receiving will be responsible for receipt and storage of the study medication, under the direction and supervision of the PI. The medication will be stored securely in the Clinical Trials office at Clinton Woods. The study drug will be labelled as "Regime A" or "Regime B" corresponding to the randomization scheme in order to ensure that the subject receives the correct medication. The study drug will be dispersed to the subject at the clinic by the PI, or by medically qualified study personnel who receive the culture results (ENT attending, resident or mid-level provider). Patients will be contacted by telephone by study personnel approximately 3 days following delivery of antibiotics to ensure the medications were received and approximately one week later to assess compliance with twice-daily irrigations and nebulizations and to evaluate for any side effects the patient may be experiencing. The participating pharmacy will also contact the patient prior to and following the delivery of medication to instruct the patient on use of the nebulizer, per their current clinical standard of care. A diary will also be given to the patient at their initial visit to assist with compliance.

At the end of treatment, an otolaryngologist blinded to the treatment will repeat nasal endoscopy, cultures, and sinusal brushings to assess response. If there is no mucopurulent drainage within the sinusal cavity, 3 cc of normal saline will be irrigated into the maxillary sinus and sent for culture. Change in Rhinosinusitis Disability Index (RSDI) scores will serve as the primary outcome. The RSDI is a validated, rhinosinusitis-specific 30-item quality-of-life questionnaire.²⁵ It relates the physical, functional, and emotional quality-of-life domains to rhinosinusitis. The survey is set up as an equal-appearing five point scale designated by the words "never", "almost never", "sometimes", "almost always", and "always". Total scores range between 0 and 120 with high scores indicating greater burden of disease. Secondary outcomes will be change in Sinusal Outcome Test (SNOT)-22 scores,²⁶ change in nasal endoscopy findings using Perioperative Sinus Endoscopy (POSE) scores²⁷, post-treatment culture negativity defined as less than 1+ growth of organisms, and change in the total bacterial community following treatment as determined by RNA pyrosequencing. The study participants will be routinely followed in clinic with nasal endoscopy at 2 month intervals for

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up to 6 months from the time of enrollment, or until the study is closed, to evaluate for disease recurrence or progression.

Molecular Analysis

For the molecular section of the study, samples will be collected via mucosal brushings and as detailed above in the Tami Sinus Secretion Collector. From the Collector, samples will be aseptically divided into two aliquots: one to the microbiology lab for conventional culturing, and one for molecular work. Each sample will be assigned a unique sample identification number (UID) that will be separated from the patient identification. This list will be administered by the study coordinator. Brushings and aliquots of the sample allocated to the molecular work will be transferred into lysis buffer for RNA pyrosequencing ²⁸. The remainder of the sample will be frozen, and maintained at -80C for the remainder of the study.

All of the collected samples of the study will be streaked for anaerobic growth in the research laboratory for speciation. The primary samples will then be analyzed for total bacterial 16s rRNA, allowing comparison of the microbiome within and between pre- and post-treatment in both study arms.

It is anticipated that there may be patients that may not respond to the antibiotic treatment in either the oral or topical antibiotic treatment groups. In this case, the samples that were banked at -80C would be submitted for bacterial RNA transcriptional profiling. Additionally, the correlating banked nasal swab sample would be submitted for human RNA transcriptional profiling. This will allow comparison of the genes expressed by the bacteria that evaded antibiotic therapy in the two treatment arms. Similarly, it will also allow comparison of genes expressed by human endonasal mucosa in response to infection and therapy. Numbers of patients for this part of the study will be determined based on the failure of therapy rate.

After original patient samples have been speciated, and antibiotic sensitivity has been assessed, cultures from the Microbiology Lab will be given the correlating deidentified UID, and frozen at -80C to allow potential future analysis of the isolated strains. Study of these strains will be conducted using the deidentified UID. Samples will be kept at -80 for the remainder of the study.

Timeline

Time (Weeks)	Steps	Notes
Date of enrollment (Week 0)	<ol style="list-style-type: none"> 1. Patient questionnaire completed in waiting room. 2. Patient examined with nasal endoscopy. 3. Cultures obtained. 4. Molecular analysis samples obtained and frozen. 5. Consent obtained. 6. Participant given sinus rinse bottle, and saline packets. 	<ul style="list-style-type: none"> • Part of current clinical practice. • Part of current clinical practice. • Part of current clinical practice.
Telephone call/Start of therapy (Day 3-7)	<ol style="list-style-type: none"> 1. Antibiotic, placebo and nebulizer mailed to subject, or picked up by subject at the clinic, depending on the subject's preference. 2. Subject instructed on use of nebulizer. 3. Therapy initiated. 	
Telephone call (Start of therapy + 7 days)	<ol style="list-style-type: none"> 1. Compliance check. 	
Follow-up (start of therapy +14 days)	<ol style="list-style-type: none"> 1. Patient questionnaire completed in waiting room. 2. Patient examined with nasal endoscopy. 3. Cultures obtained 4. Molecular analysis samples obtained and frozen. 5. Therapy terminated. 	
Routine follow-up (every 2 months)	<ol style="list-style-type: none"> 1. Patient questionnaire completed in waiting room 2. Patient examined with nasal endoscopy. 	<ul style="list-style-type: none"> • Part of current clinical practice. • Part of current clinical practice.

Data Collection, Analysis and Monitoring

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Data including patient demographics, endoscopic results, culture data, and quality of life questionnaire scores will be collected and stored on a password protected, encrypted share drive. Any printed data will be stored in the study personnel's office in a locked file cabinet. Only the study personnel will have access to identifying information. Research subjects will be given a unique study number that is stored separately from collected data. The results will be analyzed at the study's completion. A data safety monitoring plan will be ongoing and performed by the investigators. Any adverse events will be recorded and monitored for trends throughout the entire study period. Any serious adverse events will be scrutinized by the principal investigators and study termination will be considered if indicated.

Risk/Benefit Assessment

Risk Category

This is a greater than minimal risk study since it is not necessarily routine to repeat a nasal endoscopy and culture following completion of antibiotic treatment, particularly if the patient is symptomatically improved.

Potential Risk

Potential risks to the subject include mild discomfort and nasal irritation secondary to nasal endoscopy, in addition to any added inconvenience for having to return to the clinic for re-examination. There is a small risk of loss of privacy to the subjects. Genetic information obtained from human subjects will be limited to genes that are currently being expressed.

The remainder of the study is within accordance to the current standards of clinical practice and will not add any additional risk to the patients. The oral and topical treatments proposed are generally safe without any major adverse events reported in the literature.¹⁶ There are no anticipated benefits for the patients participating in the study. Non-participation will not affect the patient's care and they will be treated according to the current standard of care employed by the University of Rochester's Rhinology clinic.

Protection Against Risk

Study participants will be deidentified using a unique study number. All protected health information will be securely stored on a password-protected, encrypted share drive. Any written information will be stored in a locked filing cabinet in the PI's office and will be disposed of in a protected health information bin after 5 years has elapsed.

Safety Monitoring

The principle investigators will be responsible for safety monitoring. All adverse events related to a subject's participation in the research study will be reported to the University of Rochester's Research Subject Review Board (RSRB) as a summary in the annual progress report for the study. Serious, unexpected, and related to the study adverse events will be reported to the RSRB in a

written report within ten calendar days of the study team being notified of the adverse event occurrence.

Sample storage and confidentiality

Collected samples will be assigned a unique sample identification number (UID) and placed into storage at -80° C. It will be the responsibility Dr. Gill or his designee to ensure that all samples are stored under appropriate conditions according to type. Samples will be stored indefinitely unless a subject requests, in writing, that their sample(s) be destroyed.

A database will be developed to accompany the sample. Each case will be assigned a unique ID number and all identifiers will then be deleted, except for a single copy (key) containing the ID number, and medical record number. This database would provide clinical and pathological parameters and contain the following information: date of collection, initials of attending physician, gender, date of birth, type of antibiotic used, clinical response to therapy and final microbial diagnosis. It may also contain pertinent medical history and comorbidities, as well as social aspects of history, including tobacco use. Collection of information for the database will be the responsibility of Dr. Strohl. Study records will be kept in a locked filing cabinet in the Principal Investigator's office in the Department of Otolaryngology at the University of Rochester or on a password-protected encrypted share drive. The results of any research studies performed with the banked samples may be presented at meetings or in publications without disclosure of subject identity.

Subject Identification, Recruitment and Consent

Study subjects meeting the defined inclusion and exclusion criteria will be recruited from the rhinology clinic at the University of Rochester Medical Center. In addition, patients with a diagnosis of CRS that are status post bilateral sinus surgery but are not currently infected will be offered a flyer outlining the specifics of our study. The flyer will instruct the patients to call our research coordinator for a telephone screening. If eligible, they will be contacted by an investigator for an examination. Eligible patients will also have information about the study printed in their checkout materials via eRecord smartphrase, with instructions to contact Dr Man prior to taking antibiotics for a flare up. Similarly an eRecord smartphrase will be used to inform PCP that the patient may be study eligible if they present with a CRS flare up.

Treatment options proposed are routinely used for CRS patients. This decreases the risk of any undue influence, as patients would be receiving one of these treatment regimens regardless of their inclusion in the study. Patients electing to participate will undergo an informed consent process by one of the investigators. The study will be explained at length and the consent form will be reviewed with the patient. All questions or concerns will be addressed to the patient's satisfaction. The subject will be given the option of reviewing the consent form at home if desired. The decision to participate or not to participate will not alter their care in any way.

Costs

Costs to the patients will be minimal. The initial visit, nasal endoscopy, and culture are current clinical standards of practice and will be billed to the patient's insurance. The patient will not be charged for follow up visits, repeat cultures, medical supplies for the study, or medications prescribed.

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