Topical Antibiotics in Chronic Rhinosinusitis

NCT03673956

August 26, 2018

Topical Antibiotics in Chronic Rhinosinusitis

v3 8-26-18

PRÉCIS

Study Title

Topical Antibiotics in Chronic Rhinosinusitis

Objective

The primary objective is to show that the use of topical antibiotics in the treatment of chronic rhinosinusitis does not lead to antibiotic resistant organisms. The secondary objectives are to investigate the effects of topical antibiotics on patient symptoms as measured by the validated Sino-Nasal Outcomes Test (SNOT-22) and physical exam endoscopic findings as documented by Lund-Kennedy endoscopic scoring system.

Design and Outcomes

This is a prospective pilot study to evaluate development of antibiotic resistance in patients with chronic rhinosinusitis who are being treated with topical antibiotics.

Interventions and Duration

Intervention includes 28 days of culture directed antibiotic therapy with one of the following four topical antibiotics: Tobramycin, Mupirocin, Gentamicin or Levofloxacin

Sample Size and Population

There will be 20 participants total in the study and they will all receive the intervention.

STUDY TEAM ROSTER

Principal Investigator: **Garret W Choby, MD**

Phone: 507-284-2533
Choby.Garret@mayo.edu

Co-Investigators: **Erin K. O'Brien, MD**
Phone: 507-284-2533
[redacted]

Janalee K. Stokken, MD
Phone: 507-284-2533
[redacted]

Study Team: **Christopher M. Low, MD**
Low.Christopher1@mayo.edu

Zhuo Li, MS
Biostatistician
Phone: [redacted]

Melanie A. Thompson, CCRP
Research Coordinator
[redacted]

Nicole M. Tombers, RN
Research Coordinator
Phone: [redacted]
Pager: [redacted]

1 STUDY OBJECTIVES

1.1 Primary Objective

The primary objective is to describe the results of antibiotic resistant organisms after the use of topical antibiotics in the treatment of chronic rhinosinusitis.

The secondary objectives are to investigate 1) the effects of topical antibiotics on patient symptoms as measured by the validated Sino-Nasal Outcomes Test (SNOT-22) and physical exam endoscopic findings as documented by Lund-Kennedy endoscopic scoring system. 2) the adherence to study intervention

2 BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

There is a population of patients who have chronic rhinosinusitis that is refractory to maximal medical therapy including treatment with saline and steroid nasal irrigations as well as with oral steroids and antibiotics.

The evidence for use of topical antibiotics in current literature is conflicting. The few double blind randomized control studies cited have significant limitations including small sample size, variable intervention medications and delivery methods as well as variable outcomes measured[1-5]. Other studies have shown that use of topical antibiotics in CRS has trended toward positive change in symptom score and endoscopic physical exam findings[6]. In addition, topical antibiotics are currently being used commonly at this institution for patients with recalcitrant chronic rhinosinusitis with good clinical anecdotal result. A well designed study is warranted to further investigate the utility of topical antibiotics in chronic rhinosinusitis.

One concern with topical antibiotics limiting widespread use is perceived increased risk of causing antibiotic resistance. Non-standardized dosage patterns has led to the concern that patients are potentially being treated with subtheraputic dosages. Others postulate that treatment with topical antibiotics against susceptible bacteria may have the effect of inducing biofilm production from resistant bacteria[7]. In contrast, advocates for topical antibiotics expect topical delivery to deliver high concentrations of antibiotics to the sinonasal cavity where they may penetrate a bacterial biofilm, and avoid the systemic effects of enteral or parenteral antibiotics[7]. Further study is warranted to further describe the potential association of topical antibiotic treatment of the sinonasal cavity with antibiotic resistance.

Our department has developed in conjunction with the infectious disease department and the Mayo pharmacy, an easy to implement set of topical antibiotics with easy to use capsules and set dosages for use by our patients. This is a pilot study designed with the hypothesis that topical antibiotics do not cause antibiotic resistance. In addition, data will be collected to investigate symptom and physical exam outcomes in patients undergoing topical antibiotic therapy as secondary outcomes. The study will be conducted on existing patients who would otherwise receive treatment with topical antibiotics as standard of care.

Moreover, many of patients who have recalcitrant chronic rhinosinusitis are infected by the bacteria pseudomonas aeruginosa. The use of the fluoroquinolone class of antibiotics is a treatment of choice for this pathogen. In 2008, the US Food and Drug Administration issued a "black box" advising manufacturers to warn providers and patients of risk increased risk of tendinitis, tendon rupture, peripheral neuropathy. A well-studied, viable alternative to oral fluoroquinolone that works well without the associated risks is warranted.

Finally, poor penetration of oral antibiotics to the sinonasal cavity due to the infection being within a space may limit the efficacy of oral antibiotics as a treatment. In contrast use of topical antibiotics in a patient who has previously undergone sinus surgery, provides a potentially more effective delivery of medication to the infected space[8].

2.2 Study Rationale

The interventional regimen is as follows.
Patient will undergo pre-intervention nasal swab from the affected sinus that will be sent for gram stain and bacterial culture and sensitivities.

If pathogen identified in the bacterial culture is pseudomonas aeruginosa, topical tobramycin or gentamycin will be assigned as first line agent pending culture profiles and cost factors. If the sensitivities show resistance to both tobramycin and gentamycin, then levofloxacin will be prescribed.

If the pathogen identified in the bacterial culture is other than pseudomonas aeruginosa, mupirocin will be prescribed. If the pathogen shows resistance to mupirocin, then the patient will be prescribed one of the other three antibiotics will be prescribed pending culture profiles and cost factors

The patient will use the topical antibiotic twice a day for 28 days. This will be accomplished by first proceeding with their normal nasal rinse regimen as prescribed by their physician (this may include saline alone, or saline with budesonide). Twice per day, at the end of each regimen, they perform one additional nasal saline rinse using the Neil Med sinus rinse bottle in the manner outlined on the packaging instructions. However, with this last additional nasal saline rinse, they will open their antibiotic capsule and drop the contents into the rinse bottle prior to rinsing.

Known and potential risks are as follows:
Potential risks of nasal saline irrigation is stinging sensation and burning
Potential risks of filling the nasal saline irrigation rinse bottle with water that is too hot is mucosal burns
Potential risks of topical antibiotic administration include local pruritis and inflammation
Potential risks of selection antibiotic resistant organisms.
Potential risk for hearing loss

3 STUDY DESIGN

This is a prospective, pilot study to investigate the presence or absence of antibiotic resistant organisms after treatment of chronic rhinosinusitis with topical antibiotics. In addition, therapeutic effects of the topical antibiotics will be investigated via assessment of patient symptoms, and physical exam endoscopic findings.

There will be 1 study group with 20 patients.

The patients will first undergo pre-intervention assessment in the outpatient setting. This will occur in the Department of Otorhinolaryngology on the 12th floor of the Gonda building in Rochester, MN with one of the staff rhinologists. Patients will be selected to participate if they have active mucopurulence on their endoscopic examination. The assessment will consist of 1) obtaining a nasal swab of mucopurulence from the affected sinus to be sent for gram stain, culture and sensitivity, 2) assessment of patient symptom severity score as measured by the self-administered Sino-Nasal Outcomes Test (SNOT-22) survey, and 3) assessment of patient physical exam as evaluated by rigid nasal endoscopy and documented in Lund-Kennedy endoscopic findings form.

The study intervention is the administration of culture directed topical antibiotics over 28 days. These antibiotics will prescribed to the patient in capsule form as compounded by the Mayo Clinic pharmacy, or suitable licensed compounding pharmacy. One capsule will subsequently be added to a nasal saline irrigation bottle, and the patient will administer this irrigation to him or herself in the usual fashion twice per day.

- The dosages of the antibiotic capsules were determined by the Mayo Clinic pharmacy team with input from infectious disease, based upon available published data, and will be as follows, dissolved in a standard 240mL saline irrigation rinse
    - Mupirocin: 30 mg
    - Tobramycin: 192 mg
    - Gentamicin: 192 mg
    - Levofloxacin: 250mg

After the completion of the study intervention (within 21 days), the patient will undergo post-intervention assessment in the outpatient setting, again in the Department of Otorhinolaryngology with one of the staff rhinologists. The patient will again be assessed with 1) nasal swab from the affected sinus sent for gram stain, culture and sensitivity 2) SNOT-22 symptom scores and 3) Lund-Kennedy endoscopic exam scores.

4 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

All participants in the study must meet all of the following inclusion criteria to participate in this study.

- Male or female, between 18-80 years old, diagnosed with chronic rhinosinusitis who have undergone previous functional endoscopic sinus surgery including at minimum maxillary antrostomy and anterior ethmoidectomy
- Active mucopurulence on endoscopic examination with corresponding culture demonstrating pathogenic bacterial growth
- Completion of written informed consent
- No prior enrollment into this study
- Refractory to maximal medical therapy

4.2 Exclusion Criteria

Candidates meeting any of the following exclusion criteria at baseline will be excluded from study participation.

- Patient has not had prior endoscopic sinus surgery consisting of at minimum bilateral maxillary antrostomy and anterior ethmoidectomy
- Patient is currently being treated with oral antibiotics
- Patient has been treated with oral or topical antibiotics within the past 14 days
- Participation in an investigational drug study simultaneously with participation in this study
- Concurrent use of oral steroids
- Allergy to Tobramycin, Mupirocin, Gentamicin and Levofloxacin
- Known to currently be pregnant

4.3 Study Enrollment Procedures

Garret Choby, MD or study staff will consent and enroll potential participants from the pool of principal and co-investigators patients.

Recruitment will take place in Gonda 12 Otorhinolaryngology department during the patient's clinical visit.

There will be no screening log or other documentation of reasons of ineligibility.

The consent and enrollment process will occur in a private patient room on Gonda 12. When the consultant has completed discussing different treatment options with the patient, and the patient and the physician have decided on to pursue treatment with topical antibiotics, the study staff member will inform the patient that he/she meets the criteria for this study and describe the study to the patient. Total time of discussion is expected to be 10 minutes. The patient will be given adequate time to decide whether or not to participate in the study.

The patient will be informed by the study staff member of the possible risks and benefits of participation and study staff member will reinforce that this is a decision only the patient can ultimately make. The study staff member will also inform the patient that declining participation in the study will in no way affect the quality or duration of their care. Only patients who can consent for themselves will be enrolled in this study.

If the potential participant is a women age 18-50, the Mayo Clinic "Pre-Procedure Pregnancy Reasonably Excluded Guide (PREG)" will be administered. If pregnancy is reasonably excluded according to the guide, the patient will qualify for enrollment. If the patient is found to be pregnant, she will be excluded from the study.

5 STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

The pre-intervention assessment will occur during the enrollment visit as part of routine clinical care. Once the results of the gram stain, culture and sensitivities are known, the patient will be prescribed the appropriate topical antibiotic for the study. They will be notified of the result of the gram stain, culture and sensitivities as well as their pending prescription via a phone call or other electronic means, as per study subject preference. The intervention will take over the course of 28 days as the patient uses the medication as an outpatient. There will be only one 28 day duration study intervention administered after the enrollment visit. There will be no modifications to this study intervention.

5.2 Handling of Study Interventions

After completion of the intervention, the patient will present for post-intervention assessment in the Department of Otorhinolaryngology on the 12th floor of the Gonda building in Rochester, MN with one of the staff rhinologists. This assessment will be exactly the same as the pre-intervention assessment. Specifically, this assessment will consist of 1) obtaining a nasal swab of mucopurulence from the affected sinus to be sent for gram stain, culture and sensitivity, 2) assessment of patient symptom severity score as measured by the self-administered Sino-Nasal Outcomes Test (SNOT-22) survey, and 3) assessment of patient physical exam as evaluated by rigid nasal endoscopy and documented in Lund-Kennedy endoscopic findings form.

5.3 Concomitant Interventions

5.3.1 Allowed Interventions

Any additional medications prescribed to the patient as part of their ongoing therapy for chronic rhinosinusitis including nasal saline irrigations, steroid irrigations, or topical sprays.

5.3.2 Required Interventions

None

5.3.3 Prohibited Interventions

Patients will be excluded if they are prescribed concomitant oral steroids

5.4 Adherence Assessment

Definition of adherence to study intervention will study subject attestation that they completed at least 48 / 56 dosages of nasal saline irrigation with topical antibiotic and presentation for one post-intervention assessment. Patient will record topical antibiotic use in a daily log. This log will be used by the investigators to assess adherence. These available endpoints will be taken and incorporated into analysis.

6 STUDY PROCEDURES

6.1 Schedule of Evaluations

Pre-Intervention assessment: to be completed before starting intervention

- Nasal swab: Obtain swab from affected sinus and send for gram stain, culture and sensitivity
- Patient symptom evaluation as assessed by SNOT-22 symptom scores
- Patient endoscopic physical exam as assessed by Lund-Kennedy endoscopic exam scores. Documentation photos will also be obtained with two endoscopic photos per side, one from the head of the inferior turbinate into the nasal cavity and one from the head of the middle turbinate towards the middle meatus.

Post-Intervention assessment: to occur after the completion of the 28 days of intervention with topical antibiotics

- Nasal swab: Obtain swab from affected sinus and send for gram stain, culture and sensitivity
- Patient symptom evaluation as assessed by SNOT-22 symptom scores
- Patient endoscopic physical exam as assessed by Lund-Kennedy endoscopic exam scores. Documentation photos will also be obtained with two endoscopic photos per side, one from the head of the inferior turbinate into the nasal cavity and one from the head of the middle turbinate towards the middle meatus.

6.2 Description of Evaluations

6.2.1 Screening Evaluation

Consenting Procedure

There will be a single informed consent form that describes both the screening and study procedures.

Garret Choby MD or study staff will consent potential participants from the pool of principal investigator's and co-investigators' patients. When the staff member has completed discussing the intervention with the patient, the provider will inform the patient that he/she meets the criteria for this study. Total time of discussion is expected to be 10 minutes. The patient will be given time to decide if they would like to participate in the study.

Documentation of signed consent will be maintained through monitoring by Garret Choby MD and study staff and/or ENT Committee. The documentation will be kept in a secure, locked cabinet in the Department of Otorhinolaryngology's Research office only accessible to PI and study staff.

Screening

Screening will be based on procedures that are part of standard patient care, and therefore, informed consent will not be obtained by study staff prior to screening

patients. Potential participants will come from the pool of patients diagnosed with chronic rhinosinusitis that the principal investigator and co-investigator consultants have treated.

Screening evaluation for patients in both groups includes:

- Patient Demographics
- Diagnosis of chronic rhinosinusitis
- Assessment of symptom score with SNOT-22 survey
- Physical Examination-Involves examination of the patients bilateral nasal cavities and paranasal sinuses with rigid endoscopy
- Pre-Procedure Pregnancy Reasonably Excluded Guide (PREG)

If the potential participant is a women age 18-50, the Mayo Clinic "Pre-Procedure Pregnancy Reasonably Excluded Guide (PREG)" will be administered. If pregnancy is reasonably excluded according to the guide, the patient will qualify for enrollment. If the patient is found to be pregnant, she will be excluded from the study.

The study staff will review these tests from the patient's medical records to determine eligibility. Time prior to enrollment within which the screening tests and evaluations must be performed is within 28 days of study enrollment.

6.2.2 Enrollment and Baseline

Enrollment

Enrollment will be defined as the date all screening criteria are met and individual agrees to participate. There will be a single informed consent form for both screening and study procedures. Enrollment and screening will be conducted during the same visit.
The criteria used for inclusion and exclusion will be collected from the patient on this date using the following tests:

- medication reconciliation
- Review of medical record

6.2.3 Post-treatment assessment

Post-treatment assessment must be performed after the completion of the intervention

7 SAFETY ASSESSMENTS

7.1 Specification of Safety Parameters

Safety will be assessed for administration of topical antibiotic via nasal irrigation that is the subject of the intervention under investigation. Assessment will include details of any adverse reaction at the site of irrigation.

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

Assessment of adverse reaction at the post-intervention visit.

7.3 Adverse Events and Serious Adverse Events

An **adverse event (AE)** is generally defined as any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the study, having been absent at baseline, or if present at baseline, appears to worsen. Adverse events are to be recorded regardless of their relationship to the study intervention.

A **serious adverse event (SAE)** is generally defined as any untoward medical occurrence that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly.

No serious adverse event out of character with nasal irrigations is expected.

Adverse events captured during interval clinical visit are captured as unsolicited events, but if patient reports by calling PI directly using number on the consent form it will be captured as a solicited event. The events will be recorded as such so that there are no double collection systems.

If there are any adverse events or serious adverse events reported by the patient to the co-investigators at any point post-interventional procedure throughout the study, the Principal Investigator will be notified within 24 hours.

7.4 Reporting Procedures

If there are any adverse events or serious adverse events reported by the patient to the co-investigators at any point (post-interventional procedure) throughout the study, the Principal Investigator will be notified within 24 hours. The co-investigator will record the occurrence in the patient's research file within 24 hours of report of the incident.

Decision of relatedness and severity will be made by the Principle Investigator.

Details of the adverse event will be maintained in the Reportable Event Tracking Log for this study.

7.5 Follow-up for Adverse Events

Adverse events involving infection will be followed up with appropriate treatment involving wound cultures, broad spectrum antibiotics, and narrow spectrum once the species is identified. Follow up will continue as needed (acute debilitating event), until resolution for chronic AD from the occurrence of adverse event.

8 INTERVENTION DISCONTINUATION

Participants may withdraw voluntarily from participation in the study at any time and for any reason. Participants should continue to be followed, with their permission, after study intervention has been administered.

Replacement of participants who discontinue early is allowed. The participants who are replaced will not be counted in the study and replacement can occur if participants do not complete the at least 48 / 56 dosages of intervention with topical antibiotics.

It is vital to collect safety data on any subject discontinued due to an AE or SAE. In any case, every effort will be made to undertake protocol-specified safety follow-up procedures. If voluntary withdrawal occurs, the subject will be asked to continue scheduled evaluations, complete an end-of-study evaluation, and be given appropriate care under medical supervision until the symptoms of any AE resolve or the subject's condition becomes stable.

9 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

This will be prospective single arm pilot study. We propose enrolling 40 patients in this study.

Measure of success is post-treatment assessment with nasal swab sent for gram stain, culture and sensitivity.

9.2 Sample Size and Randomization

We propose enrolling 40 patients in this study. Since this study is a pilot study where we aim to describe the results and collect data for future larger study, sample size calculation is not required.

9.3 Interim analyses and Stopping Rules

Safety findings that would temporarily suspend enrollment and/or study intervention until a safety review is convened (*either routine or ad hoc*) to determine whether the study should continue per protocol, proceed with caution, be further investigated, be discontinued, or be modified and then proceed are as follows:

-Number of SAEs overall

-Number of occurrences of a particular type of SAE

-Severe AEs/reactions

-Increased frequency of events

Such findings are presented to the Data and Safety Monitoring Board (DSMB) statistician

to review the events by group to determine whether there are statistical as well as clinical concerns. The statistician reports his findings to a closed session of the DSMB (or to the Safety Officer and/or NIA.) The findings are used to determine what steps will be taken.

9.4 Outcomes

9.4.1 Primary Outcome

Post treatment assessment of presence of antibiotic resistant organism as assessed by nasal swab sent for gram stain, culture and sensitivity

9.4.2 Secondary outcomes

The secondary outcomes are measurement of patient symptoms as measured by the validated Sino-Nasal Outcomes Test (SNOT-22) and physical exam endoscopic findings as documented by Lund-Kennedy endoscopic scoring system

9.5 Data Analyses

Statistical Methods

Continuous patient characters will be summarized with means and standard deviations for features that are approximately normally distributed and with medians, interquartile ranges, and ranges otherwise. Categorical features will be summarized with frequency counts and percentages.

Primary endpoint:
Number and proportion of patients who developed antibiotic resistance organism will be summarized. 95% confidence intervals will be provided for the proportion.

Secondary endpoint:

1) SNOT-22 symptom scores and Lund-Kennedy endoscopic exam score will be summarized as mean (standard deviation) and median (range).

2). Definition of adherence to study intervention will be to complete 25 of 28 days of topical antibiotics and attend the pre-intervention / enrollment visit as well as the post-intervention assessment visit. Number and proportion of patients with adherence will be reported.

3) Audiometric data will be summarized as a mean (standard deviation) and median (range)

10 DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Information will be collected on Case Report Forms (CRFs) by study staff. Participant CRFs will be kept in a locked cabinet in the Department of Otorhinolaryngology and only study staff will have access to this cabinet to maintain confidentiality of participant records.

Data Management

All data is checked for completeness and for accuracy on data ranges.

Data collection forms will be organized in the following categories:

-Enrollment / Pre-intervention assessment

-Post-intervention assessment

Data will be collected and stored using excel file.

10.2 Quality Assurance

10.3.1 Training

Co-investigators will be briefed on the study primary and secondary objectives, the study design and all information in this protocol will be reviewed in person by the Principal Investigator.

10.3.2 Quality Control Committee

ENT Research Committee is the study control committee. Jeffrey Janus, MD is Chair of this Committee.

10.3.3 Protocol Deviations

Protocol deviations will be captured by the PI or study staff at the time of occurrence, during surgery or during follow up. Information on deviation will be documented. The study will only use data that is coherent with protocol.

11 PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the IRB.

11.2 Informed Consent Form

A signed consent form will be obtained from each participant. Participants who cannot consent for themselves will not be enrolled in this study. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant and this fact will be documented in

the participant's record.

11.3 Participant Confidentiality

All records will be kept in a locked file cabinet. All computer entry and networking programs will be done by either the Principal Investigator or Study Staff using secure login information only. Information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the FDA, OHRP.

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NIA, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected.

12 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures developed by the ENT Research Committee. Any presentation, abstract, or manuscript will be made available for review to them by PI prior to submission.

13

References

1. Wei JL, Sykes KJ, Johnson P, He J, Mayo MS. Safety and efficacy of once-daily nasal irrigation for the treatment of pediatric chronic rhinosinusitis. *Laryngoscope.* Sep 2011;121(9):1989-2000.
2. Jervis-Bardy J, Boase S, Psaltis A, Foreman A, Wormald PJ. A randomized trial of mupirocin sinonasal rinses versus saline in surgically recalcitrant staphylococcal chronic rhinosinusitis. *Laryngoscope.* Oct 2012;122(10):2148-2153.
3. Desrosiers MY, Salas-Prato M. Treatment of chronic rhinosinusitis refractory to other treatments with topical antibiotic therapy delivered by means of a large-particle nebulizer: results of a controlled trial. *Otolaryngol Head Neck Surg.* Sep 2001;125(3):265-269.
4. Videler WJ, van Drunen CM, Reitsma JB, Fokkens WJ. Nebulized bacitracin/colimycin: a treatment option in recalcitrant chronic rhinosinusitis with Staphylococcus aureus? A double-blind, randomized, placebo-controlled, cross-over pilot study. *Rhinology.* Jun 2008;46(2):92-98.
5. Sykes DA, Wilson R, Chan KL, Mackay IS, Cole PJ. Relative importance of antibiotic and improved clearance in topical treatment of chronic mucopurulent rhinosinusitis. A controlled study. *Lancet (London, England).* Aug 16 1986;2(8503):359-360.
6. Lee VS, Davis GE. Culture-directed topical antibiotic treatment for chronic rhinosinusitis. *Am J Rhinol Allergy.* Nov 1 2016;30(6):414-417.
7. Barshak MB, Durand ML. The role of infection and antibiotics in chronic rhinosinusitis. *Laryngoscope investigative otolaryngology.* Feb 2017;2(1):36-42.
8. Liang J, Lane AP. Topical Drug Delivery for Chronic Rhinosinusitis. *Current otorhinolaryngology reports.* Mar 1 2013;1(1):51-60.