Dear Friends and Colleagues,

We are excited to provide you this update on what's happening in the Rhinology Division at MUSC as we strive to work with you to provide our patients with the best possible care. Clinically, our division now consists of two rhinologists supported by Brittany Crosby, PA-C, Heather Levy, RN and Cornette Flanning, CMA. Our research laboratory is headed by Jennifer Mulligan, PhD who brings her expertise in sinonasal immunology to our basic science studies. Jennifer supervises three full time technicians and is also assisted by Tina Storck, MPH, who coordinates our rhinology clinical trials.

Our center continues to search for better treatments for the patients with difficult inflammatory conditions, such as nasal polyposis, that we all face every day in our practices. The included article on current research into nasal polyposis highlights an increasing demand for evidence-based treatment approaches. Our team is at the forefront of this movement, having led a number of multi-institutional studies examining the quality and strength of the research regarding polyposis management. We hope that the studies highlighted in the attached article will prove useful in your daily practice.

In addition to examining evidence based treatments for chronic rhinosinusitis (CRS), the MUSC Sinus Center is active in a number of clinical and basic science trials for CRS patients. Our goal is to examine adult and pediatric CRS in a comprehensive fashion, including underlying immune dysfunction and pathophysiology, novel medical and surgical treatment options, and the impact of CRS and its treatments upon quality of life, cognition and economic parameters. We have highlighted a few ongoing studies in this issue. If you have any interest in taking part in these studies please let us know.

The clinical disorders treated by our team encompass the entire spectrum of rhinology and skull base disease. Our close collaboration with the Department of Neurosurgery, led by W. Alex Vandergrift III, MD, enables us to tackle the most complex skull base pathology using minimally invasive, endoscopic approaches. We have included a brief article on the important role the pedicled nasoseptal flap has played in allowing us to reconstruct the skull base in these patients and improve outcomes. We are excited to welcome Andrew Eiseman, MD from the Department of Ophthalmology to our collaborative team. Andrew is an oculoplastics surgeon with extensive experience and is a great addition to our multi-disciplinary, endoscopic approach to patients with orbital and lacrimal pathology.

Finally, our educational efforts remain very busy. Over the last year, we have served as faculty for several courses, including Adelaide, Australia, San Diego, Chicago, University of Pennsylvania and University of Southern California with upcoming trips to University of Pittsburgh and Korea. We will also be bringing experts from Northwestern University, Mayo Clinic and Mt. Sinai to MUSC for a variety of CME events this spring, so please contact us if you are interested.

We appreciate the opportunity to work together with you to optimize the care of your rhinology patients. Please don’t hesitate to contact us. Appointments can be scheduled at 843-792-3531 and we can be reached directly at the numbers with our photos.
Recent American and European guidelines have recommended classifying patients with chronic rhinosinusitis into subgroups either with (CRSwNP) or without nasal polyps (CRSsNP). Although this simple classification is important for research purposes, it also informs therapeutic decision-making. A large body of scientific research has focused on patients with CRSwNP, including epidemiology, pathophysiology, and both medical and surgical treatments.

Epidemiology

The prevalence of CRSwNP in the United States is often estimated between 1-5% of the population. This estimate represents an extrapolation of data gathered from large-scale population studies done in several European countries, including France (2.1%), Sweden (2.7%), and Finland (4.3%). Interestingly, cadaver studies have typically found higher rates of nasal polyposis, suggesting that up to 1/3 of patients with polyps remain asymptomatic and may not be identified in basic surveys without detailed nasal examination. Based on the state’s population and the figures above, it can be estimated that between 46,000 and 230,000 South Carolina residents have nasal polyps.

Pathophysiology

Most studies suggest that nasal polyps are the result of chronic inflammation of the sinonasal mucosa. Over the last decade or so, researchers have documented dysregulation of a wide host of inflammatory markers and cell types in patients with nasal polyps. The identification of so many inflammatory mediators is exciting; however, it has also proven difficult to determine which are principally-involved and clinically-relevant and which are not. We recently performed a systematic review of all published gene and gene products which are differentially found in CRSwNP as compared to controls—identifying 97 individual genes. This data was supplemented with results from our own study wherein gene expression was compared between polyp specimens and controls for over 47,000 genes using a “gene chip.” With the help of a bioinformatic program called Ingenuity, we performed a pathways analysis in order to determine which genes appeared to be most critical to CRSwNP (Figure 1).

Interestingly, the gene products we found are also commonly implicated in other chronic inflammatory conditions (asthma, rheumatoid arthritis, inflammatory bowel disease) for which targeted therapeutics are either already available or are in development. It remains possible that many of these medications may one day be modified for use in patients with CRSwNP. The MUSC Sinus Center has embarked on an ambitious study to collect DNA via salivary samples from several thousand patients with polyps in order to better understand the genetic polymorphisms which may predispose to polyp development.

Medical Treatment

Otolaryngologists oftentimes must practice without the benefit of high-level clinical evidence; however, nothing could be further from the truth with regard to nasal polyps. We recently performed a meta-analysis identifying 19 double-blind, randomized, controlled trials evaluating the efficacy of topical intranasal corticosteroids in patients with CRSwNP (Figure 2). When these trials were combined statistically, patients using nasal steroids were 72% more likely to have improved nasal congestion as compared to those on placebo (RR=1.72; 95%CI: 1.41-2.09). Of note, these studies were mostly of short duration (range 4-270 weeks) and no one steroid type was found to be superior to another. Recently, corticosteroid formulations delivered via high-volume saline irrigations have become popular. Enthusiasm for this method of administration is based in part upon studies...
showing high-volume devices (squeeze bottles) are more likely to deliver medication to the sinus mucosa as compared to low-volume modalities (sprays, nebulizers, and drops).6 Although anecdotal evidence abounds, to date no high-level studies have been performed proving the efficacy of steroid irrigations.

Oral corticosteroids are another popular treatment option for CRSwNP. A recent evidence-based review was performed by Poetker et al identifying 16 published studies, 5 of which were high level.7 Although studies varied in steroid dosage and outcome measures, improvements were seen both in subjective symptoms and objective measurements such as polyp size or CT scores. An excellent example is a study by Vaidyanathan in which patients with CRSwNP were randomized to prednisone 25mg/day for 2 weeks (or placebo) followed by topical steroid sprays.8 Those patients receiving just 2 weeks of oral steroids had benefits which persisted for close to 6 months. Based on the aggregate of these studies, use of oral corticosteroids has been strongly recommended as a short-term therapy in patients with CRSwNP.

Many clinicians routinely treat polyp patients with antibiotic regimens. We recently performed an evidence-based review with recommendations examining the efficacy of antibiotics for CRS, including patients with polyps.9 Overall, the evidence is quite weak that antibiotics can be used to treat nasal polyps, including antibacterial or antifungal formulations. In fact, there is just a single study out of Belgium which suggested that oral doxycycline may have some benefit in patients with CRSwNP.10 In this double-blind, randomized, controlled study, patients on doxycycline 100mg/day for 20 days had decreased polyp size at 12 weeks as compared to placebo, as well as less postnasal drainage. It was unclear whether patients reported improved nasal congestion or whether results would be durable beyond 12 weeks. The authors hypothesized that results were secondary to intrinsic anti-inflammatory effects of doxycycline as opposed to an antibacterial mechanism. Based on this evidence, use of oral antibacterial antibiotics in patients with CRSwNP is not formally recommended, but is instead considered an option.

Surgical Therapy

Surgical treatment of nasal polyps extends as far back as the time of Hippocrates in 400BC and has evolved considerably over the last 30 years with the advent of endoscopic visualization and instrumentation such as the microdebrider. The quality of research documenting the efficacy of surgery has also strengthened substantially during the last decade. We recently took part in a multi-institutional study which demonstrated that endoscopic sinus surgery (ESS) results in clinically- and statistically-significant improvements in patient-reported quality-of-life over and above that seen for many other expensive chronic disease treatments (Figure 3).11 This was followed by a second long-term study which demonstrated that these improvements are maintained up to 5 years after surgery. Despite the proven efficacy of surgery, it is well accepted by most sinus surgeons that ESS alone is rarely curative. Instead, surgery is best thought of as an adjunctive treatment, which clears polyps, widely opens sinus ostia, and allows for effective delivery of long-term topical anti-inflammatory medications to polyp-forming

Visit our website www.muscENT.org to view related videos, listen to our podcasts, read about our doctors, and learn more about what the MUSC Nose & Sinus Center has to offer.
mucosal surfaces (Figure 4). We are currently 1 of 4 sites participating in an NIH-sponsored study comparing the efficacy of ESS plus ongoing medical management to that of ongoing medical management alone in those patients who have failed initial medical therapy—data from this study will help us better appreciate the benefits of surgery for patients with CRSwNP.

References


Take Home Points:

- 1-5% of the US population has CRSwNP.
- Hundreds of inflammatory genes are either up- or down-regulated in CRSwNP, with several being most important to polyp formation (TNF-a, NFKB, EGFR, JNK). We are leading a multi-institutional effort to collect salivary DNA to further investigate genetic contributions to disease.
- The highest level evidence supports the efficacy of long-term topical nasal steroids and short bursts of oral steroids for patients with CRSwNP. There is little evidence to support the use of antibiotics (oral, intravenous, or topical).
- Prospective, multi-institutional studies have consistently found that endoscopic sinus surgery results in improved patient-reported quality-of-life that extends up to 5 years in duration.
- The most effective maintenance therapy is thought to be corticosteroid formulations delivered postoperatively to widely opened sinuses via high-volume delivery devices.
The Pedicled Nasoseptal Flap:
The Reconstructive Workhorse for the Endoscopic Skull Base Surgeon

The interest and ability of otolaryngologists and neurosurgeons to perform endoscopic, minimally invasive approaches to the skull base has exploded over the last decade. A number of advances in equipment, experience and technique have permitted this development. Increasing comfort of endoscopic, two surgeon techniques, image guided surgery and improved instrumentation were critical. Just ten years ago, skull base series were plagued by unacceptably high rates of postoperative CSF leaks, pneumocephalus and other intracranial complications directly attributable to failure of the skull base reconstruction. These early attempts utilized common techniques based upon the use of free tissue grafts of mucosa, fat or fascia. While these free grafting techniques had a high success rate when used for simple CSF leaks, they did not have similar success rates when treating larger skull base defects or high flow, intraventricular leaks often seen when operating upon skull base neoplasms. Initial reports of postoperative leak rates using free tissue grafts were as high as 40% and failure of the skull base reconstruction is/was a major cause of peri-operative morbidity. The development of vascularized, pedicled mucosal flaps was a huge advance for endoscopic skull base surgeons. Recent reviews have demonstrated that large skull base defects secondary to endoscopic resection of tumors can be repaired without lumbar drains using pedicled flaps with a postoperative CSF leak rate of 0-4%.

In addition to successfully stopping CSF leakage, it is critical that endoscopic skull base repairs also prevent intracranial complications, to include meningitis, seizure, abscess and pneumocephalus. Back in 2008 we reviewed over 100 consecutive patients who had undergone endoscopic skull base reconstruction and were able to demonstrate that such endoscopic repairs do decrease the rate of intracranial complications, both in the peri-operative period, as well as long term.

When faced with a skull base defect, the most commonly used pedicled flap is the nasoseptal flap, supplied by the posterior septal branch of the sphenopalatine artery. This is a large flap that can be easily raised using standard septoplasty techniques familiar to most otolaryngologists. Typically, a multi-layer repair using subdural free grafts of fat or dermal/collagen allografts is performed with the septal flap serving as the final intranasal layer. Other pedicled flaps using the inferior turbinate, middle turbinate, nasal floor and lateral nasal wall have all been described as well and each has its advantages and disadvantages. Other uses we have found for pedicled flaps include coverage of pseudoaneurysms, coverage of neurovascular structures in planned radiation fields, closure of septal perforations and choanal atresia repair.

The field of endoscopic skull base surgery continues to evolve rapidly and it is likely that robotic surgery, 3D endoscopes and other technologic developments will permit us to push the envelope even further. Vascularized skull base reconstruction has been a major advance in improving patient outcomes and is a versatile technique with a variety of uses outside the skull base.

Take Home Points
- Failure of successful skull base reconstruction is a major cause of morbidity
- Pedicled flaps reduce failure rates to 4% or lower
- Endoscopic skull base repair successfully prevents intracranial complications
- Pedicled flaps are versatile and have a variety of uses
Clinical Research

**Determinants of Medical and Surgical Treatment Outcomes in Chronic Rhinosinusitis**

**Overview:** MUSC is one of only three centers in the US participating in this 5-year NIH supported study. The goal is to evaluate and compare outcomes of sinus surgery versus medical management for sinusitis and to develop a predictive model of surgical outcomes utilizing a multi-institutional, prospective cohort of patients with CRS undergoing those treatments.

**Why it matters:** Payers (government and private) are increasingly demanding proof of efficacy for commonly used treatments, including sinus surgery. When complete, this study will provide the critical data comparing surgery to ongoing medical management in patients who have already failed standard medical treatments.

**Intranasal Corticosteroid via Novel Bi-directional Device for Chronic Rhinosinusitis**

**Overview:** This open-label multicenter Phase III study will examine a new device developed in Europe for delivering topical steroid medications to sinonasal mucosa.

**Why it matters:** Standard nasal sprays deliver very little medication to sinonasal mucosa, even after sinus surgery. Devices such as this attempt to increase the mucosal surface reached by medication.

**Development of Nanoparticles for Drug Delivery to Sinonasal Mucosa**

**Overview:** This 4-year VA supported study is a collaboration between researchers at Clemson University and the MUSC Sinus Center. The goal is to create a nanoparticle which can deliver a targeted, sustained medication to the sinonasal mucosa without disrupting normal mucociliary movement.

**Why it matters:** Novel topical medications delivered after surgery represents the future of chronic rhinosinusitis treatment. Nanoparticles may allow medications to be targeted to specific cells, delivering a set dosage over a particular time frame without altering normal function.

**Cognitive Function in Chronic Rhinosinusitis**

**Overview:** This 3-year FAMRI supported study will examine cognitive function in patients with CRS using validated questionnaires and computerized neurocognitive testing and compare it to matched healthy controls. Mechanisms by which cognitive dysfunction likely occurs will be examined including sleep quality, depression, and systemic cytokine levels.

**Why it matters:** Many patients with chronic rhinosinusitis complain of severe fatigue, difficulty concentrating, and even impaired memory. If subtle cognitive function is truly present, this has important implications for patients, physicians, employers, and public policy makers.

**Genome-wide Analysis of Nasal Polyps**

**Overview:** This 4-year, multi-center study will collect salivary samples in order to analyze DNA from 2000 patients with nasal polyps and compare it to 2000 controls without polyps. Whole genome analysis will examine differences in single nucleotide polymorphisms at half a million genetic loci.

**Why it matters:** Except for corticosteroid medications, the medical treatment of nasal polyps has changed little over the last 50 years. Understanding the genetic contributions to nasal polyps should lead to novel, targeted therapies, similar to current treatments for breast cancer?

**Randomized Clinical Trial of Vitamin D for Nasal Polyps**

**Overview:** This multi-center trial will explore whether high-dose vitamin D therapy improves olfactory, endoscopic, quality-of-life, or mucosal inflammation in patients with nasal polyps.

**Why it matters:** Nasal polyps often result in olfactory dysfunction, immune dysregulation, and overall poor quality-of-life. Development of a safe, long-term treatment option would revolutionize care of these patients.