IAPO Interamerican Association of Pediatric Otorhinolaryngology

XI IAPO Manual of Pediatric Otorhinolaryngology

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Pediatric Chronic Rhinosinusitis: Mucosal Inflammation and not a Bacterial Infection?

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Foreword

An excellent chapter summarizing differential diagnosis, medical, and surgical treatments on "Pediatric Acute and Chronic Rhinosinusitis: The ENT Perspective", by Dr. Scott Manning and Dr. Luiz Bellízia Neto can be found in the Xth IAPO Manual of Pediatric Otorhinolaryngology. This chapter is specifically written to suggest an alternative way we perceive pediatric chronic rhinosinusitis in relatively healthy children. I am referring to children who do not have cystic fibrosis, immune deficiency or disorders, aspirin hypersensitivity, or severe nasal polyposis. The suggested approach for diagnosing pediatric chronic sinusitis as well as using nasal irrigation as a primary and only initial treatment is based on the authors' clinical experience with successful treatment in over 200 children as well as based on the authors research findings. [1]

Introduction

Acute and chronic sinusitis are common clinical problems with significant morbidity affecting the quality of life for both pediatric and adult populations. From 1985 to 1992 sinusitis was the 5th most common diagnosis for which antibiotics were prescribed, and the number of U.S. chronic sinusitis cases in 1994 was estimated at 35 million.[2] Along with upper respiratory tract infections, rhinosinusitis and allergic rhinitis are among the most common reasons cited for work absenteeism and need for physician visits.[2] Direct medical costs for treatment of sinusitis alone is estimated at $2.4 billion annually and reported to affect 15% of the population.[2] In the pediatric population, rhinosinusitis is a common concern resulting frequently in the overuse of systemic oral antibiotic therapy. Children typically experience an estimated 6-8 upper respiratory illnesses per year, usually viral, and only 13 % are estimated to result in true sinusitis. True acute and chronic sinusitis, if not adequately treated, may result in long term symptoms including nasal airway obstruction, nasal congestion, persistent mucopurulent rhinorrhea, daytime and nocturnal cough, headaches, daytime fatigue, and even exacerbation of poorly controlled underlying asthma.

Most research studies that evaluate the medical and surgical treatments for chronic sinusitis are in adult patients. Many of these studies evaluate the efficacy of nasal irrigation for the alleviation of sinonasal symptoms.[3-7] Chronic and acute rhinosinusitis can negatively affect the quality of life of children and their caretakers because of days of missed school and frequency physician visits. The multiple courses of systemic oral antibiotic therapy and all of the associated negative side effects not affect quality of life but are costly and will ultimately result in the development of resistant organisms. Intranasal saline irrigation is underutilized in the pediatric population, most likely due to the presumption that

children will not cooperate nor tolerate the act of irrigation. In children, nasal irrigation is mostly likely prescribed by surgeons as a temporary adjunctive treatment after functional endoscopic sinus surgery (FESS). Healthy children may develop chronic inflammation of their sinuses due to impaired mucociliary clearance after viral upper respiratory tract infection or allergic rhinitis. If acute inflammation, nasal congestion, and airway obstruction does not resolve within the expected 1-2 weeks after a viral URI, then children may likely develop prolonged symptoms of nasal congestion with or without other symptoms.

Over the past decade, the author has made many observations about the similarities between otherwise healthy children who presented to the pediatric otolaryngologist with symptoms of chronic cough, nasal congestion, and what other physicians or parents have labeled as chronic "sinus infection". It was the diagnostic dilemma, observations of excessive yet often unsuccessful use of systemic antibiotics, and observations of consistent correlation between computed tomography findings to patient symptoms before and after nasal irrigation which led the author to conduct a prospective clinical trial studying these patients in order to prove the efficacy of saline irrigation in the treatment of pediatric chronic rhinosinusitis (CRS). This chapter hopes to increase the diagnostic accuracy of CRS and the utilization of nasal saline irrigation in children, and subsequently decrease unnecessary medical and surgical intervention.

Intranasal Irrigation

Intranasal saline irrigations have been advocated by otolaryngologists as adjunctive therapy because medical and surgical treatments are not universally successful. Saline irrigation of the nose is an inexpensive and generally well tolerated treatment with very few side effects or risks. Rigorous data evaluating the efficacy of saline irrigation has become more available in the past decade, with most studies demonstrating a clear improvement in patient quality of life as measured by various study instruments or outcome surveys.[3-7]

As with any intervention for chronic or acute disease, objective and subjective measures intervention outcome are important. Objective efficacy of treatment of rhinosinusitis can be determined using the Lund-McKay scoring system assessing computed tomography (CT) scans.[8] Subjective quality of life assessments for any chronic disease can be determined using the validated and reliable measure of Health-related Quality of Life (HRQoL) instrument, the Sinonasal (SN-5) Quality of Life survey.[9]

Efficacy of Nasal Irrigation in Children

Our prospective, randomized, double-blinded, placebo-controlled clinical trial evaluating the safe and efficacy of once daily intranasal irrigation comparing saline to saline plus gentamycin was conceived based on serial consecutive anecdotal successes of the author treating children with CT scan proven evidence of circumferential mucosal thickening. Both objective and subjective measures were obtained before and after 6 weeks of once daily irrigation in order to assess true efficacy of nasal irrigation in children. The key finding of our study was that once daily intranasal irrigation with saline alone or saline plus gentamycin were equally efficacious and safe for the treatment of pediatric CRS. We found

that maximum benefit of once daily irrigation with either solution was achieved after 3 consecutive weeks of once daily irrigation, and treatment success was demonstrated by both the SN-5 survey as well as CT scans post irrigation. While further improvements were noted after an additional 3 weeks of irrigation for a total of 6 weeks, the differences in improvements after 6 weeks compared to after 3 weeks were not statistically significant as measured by SN-5 QoL survey. In order to avoid unnecessary radiation exposure, CT imaging was not repeated after 3 weeks of daily irrigation at the midpoint of the study, but only after the study period of 6 weeks. The reported subjective and objective improvements are based on intranasal irrigation as the only intervention during the study period.

This is the first randomized prospective double-blinded, placebo-controlled clinical trial evaluating efficacy of non-surgical treatment for pediatric chronic rhinosinusitis based on both subjective and objective outcomes. Based on our results, adding what is considered a very low dose of gentamycin in the saline did not appear to result in any additional benefits as measurable by SN-5 survey and imaging study. However, due to the small sample size, we may not be able to detect even a small difference between the 2 groups. Based on the results of this trial, the author stopped adding gentamycin into saline for intranasal irrigation since 2009, but recommend using isotonic saline only. In addition to no increased benefit as based on the study, when a child has not had endoscopic sinus surgery, very little irrigation solution can reach each sinus through the miniscule natural ostia.

To determine if intranasal irrigation resulted in objective improvement based on CT findings pre-treatment and post-treatment CT scans for each patient were scored by a to a radiologist using the Lund-McKay scoring system. The CT scores were documented for each sinus and the ostiomeatal unit on each side. The CT scans were reviewed and scored in random order with identifying information concealed. The radiologist was blinded to which CT scan was pre-treatment and which was post-treatment scan, as well as which treatment arm the patient belonged to. The primary investigator was not involved in the scoring of the CT scans.

To determine if intranasal irrigation resulted in subjective improvement of chronic rhinosinusitis, each child had a total of 3 SN-5 QoL surveys completed during the study by their primary caregivers. The first SN-5 was completed at baseline prior to starting irrigation, a second one was performed over the telephone at midpoint of treatment period (after 3weeks) and finally a post-treatment survey was completed at the time of the follow-up visit after 6 weeks of once daily irrigation.

Sinus Mucosal Thickening on Computed Tomography

Despite evidence of significant mucosal thickening and opacification in the paranasal sinuses in our study, only 50% of saline group and 75% of gentamycin group reported rhinorrhea. By far the most bothersome symptom was nasal congestion, reported in 100% of patients in the saline group and 95% of the gentamycin group. In otherwise healthy, school-aged children who are referred to the author for evaluation of chronic “sinusitis”, the patient and parents rarely

report mucopurulent rhinorrhea. In fact, despite reports of consistent and prolonged constant nasal congestion, often for months to years without regard for season, commonly "nothing comes out" when the child blows their nose. Interestingly, the author has observed clear stringy thin strands of mucous between the inferior turbinate and the septum. The significant of this clinical exam finding and whether it would correlate well to CT findings warrants further investigation. Every patient in our study had a baseline CT scan confirming that there were findings of mucosal thickening which served as objective evidence of imperfect physiology. Almost always one or both ostiomeatal complex are opacified, and again the mucosal thickening in the maxillary sinuses are circumferential, indicative of mucosal thickening and not air fluid levels nor liquid "pus". This is important to recognize since otolaryngologists typically do not routinely strip the maxillary sinus of its edematous and thickened mucosa, but rather goals of endoscopic surgery is to restore ostiomeatal patency to allow reversal of inflammatory changes and improve natural mucociliary clearance. It is important to recognize that for non-otolaryngology physicians, they may not differentiate between CT findings of acute versus chronic sinusitis and often prescribe prolonged course of systemic antibiotics if there is any sinus opacification at all. Radiology reports often state "pansinusitis" or "chronic rhinosinusitis", with or without specific mentioning of degree of mucosal thickening, i.e., 2mm or 4mm mucosal thickening.

Dilemma and Historical View of "Chronic Sinusitis' as a Bacterial Infection

There is much to debate regarding the definition of the term "sinusitis". "Sinus infection" as a term mandates belief that the pathophysiology of the disease involve an infection, in which both medical and nonmedical people associate with the acceptance that the "infection" is caused by bacterial organisms so logically treating this diagnosis demands the use of antibiotics in order to eradicate the causative organisms. In fact, "sinusitis" as a term, is meaningless without clarification with other descriptive such as "acute", "subacute", "chronic", and recently "fungal", and "allergic fungal", terms all of which provide further description as to the duration of symptoms as well as potential etiologies. These various types of "sinus" disease states are in fact variations of disease processes requiring specific treatment(s) that all address the common underlying pathology, which is inflammation. For physicians and other health care providers, if the term "sinusitis" is accepted to be synonymous with "infection", then logically there is the natural tendency to prescribe oral antiobiotics especially if one assumes that the patient's symptoms are attributed to acute bacterial infection. For the patient there is also a perhaps erroneous assumption of bacterial infection and therefore unfortunate expectation to receive antibiotic prescription since they may have already arrived at the conclusion that without antibiotics, their "infection" will not resolve. One significant problems this paradigm creates is that if patient's symptoms do not clear with a 7 or 10 day course of oral antibiotics, the conclusion drawn by both the health care provider as well as the patient in this scenario is that the "infection" must be too strong and the medication too weak, so the further "logical" conclusion to be drawn is likely further prescription of a second and "stronger" or broader spectrum antibiotic.

In the author's clinical experience, otherwise healthy children who are referred to a pediatric otolaryngologist for the evaluation of "chronic" or 'recurrent' sinus infections have already been treated with multiple courses of systemic oral antibiotics, with many courses equal to at least 14-21 days each. In our clinical trial, parents and caregivers were specifically asked to recall how many courses of antiobiotics their child had been prescribed in the previous 6 and 12 months prior to the referral to the pediatric otolaryngologist. Most parents had difficulty remembering how many courses total over a 12 months period, but 14/19 and 17/21 in the saline and gentamycin group, respectively, reported completing as many as 9 course of antibiotic therapy in a previous 6 months period. Despite difficulty in reporting exact number of days of systemic antibiotics consumed, since a single course may include 21 days of therapy as prescribed by their primary care physician or allergist, these children definitely consume more systemic antibiotics than the parents and caregivers desired. It was very common for parents and caregivers to report that while on systemic antibiotics, the symptoms may be improved, but never resolve completely, and as soon as antibiotics were discontinued, the symptoms resumed as quickly as in a few days. Correlation of such feedback to actual bacterial load in the nasopharynx or nasal cavity was beyond the scope of our study, but studies have demonstrated that nasopharyngeal colonization is significant altered due to selective pressures of systemic antiobiotic therapy. Average duration of symptoms was over 2 months in both groups, with standard deviation of 10 weeks for both groups, reflecting the chronicity of this disease and it being refractory to routine medical therapy including antibiotics, antihistamines, OTC decongestants, and even leukotriene-receptor antagonist which near 50% of this study group was taking at the time of enrollment.

Underlying Atopy and Allergies as Predisposing Factor to Pediatric CRS

In the author's clinical experience as well as the clinical trial findings, children who present with chronic history of nasal congestion, cough, and history of previously diagnosed "chronic sinusitis" have a high likelihood of having underlying allergies to multiple aeroallergens proven by skin testing. In fact, 72.5% (29/40) of our study patients had skin test proven allergies with high prevalence of allergies to mold and pollen. Over 50% of patients in our study also had history of asthma proven by bronchodilator challenge on pulmonary function tests, and required medications for the management of their asthma. As would be expected, often these patients asthma were not well controlled but improved significantly after successful treatment and reversal of CRS as proven by reversal of sinus mucosal thickening in CT scan. Clinical and research studies have supported the theory that the sinopulmonary reflex stimulates a neural arc that involves cellular, humoral, and immunologic factors which all play a pivotal role in perpetuating bronchial hyperresponsiveness.[10]

Current Understanding of "Sinusitis" as a Disease of Inflammation

It appears that the word "sinusitis" has become synonymous with 'infection", instead of being understood as a state of inflammation with possibility of secondary acute infection. Until such distinctions are made, patients will continue

to expect that they need to be treated with antibiotics since symptoms must be caused by acute bacterial infection. Equally challenging, is the otolaryngologist's constant need to explain to patients that there are other causes of nasal congestion, rhinorrhea, chronic cough, and other upper airway symptoms which are not simply a reflection of active bacterial infection. Naclerio et al reviewed in excellent detail the pathophysiology of nasal congestion, and summarized a wide range of biologically active agents (eg, histamine, tumor necrosis factor-α, interleukins, cell adhesion molecules) and cell types which contribute to inflammation.[11] Whether it is viral initiated, allergic or nonallergic rhinitis, or chronic rhinosinusitis, inflammation is the underlying basis for clinical symptoms. In some cases symptoms are mediated by the actions of distinct neural pathways such that vasomotor, idiopathic, or "irritant" rhinitis may result from increased sensitivity of afferent fibers to irritant stimuli.[10] All the above will manifest as venous engorgement, increased nasal secretions and tissue swelling/edema, ultimately leading to decreased or altered nasal airflow and the sensation of nasal congestion.

Recent research has reported on the presence of biofilm on sinonasal mucosa and its potential role in the pathophysiology of CRS and inflammation. Smith and Buchinsky performed a systematically review on advances in biofilm treatment for ear, nose, and throat diseases, and report that antibiotic therapy is relatively ineffective against biofilms requiring markedly higher doses to reduce biofilm presence.[12] They suggest that clinical treatment may need to focus on nonantibiotic therapies that reduce, disrupt, or eradicate ENT biofilms.[12] Psaltis et al reported that genetic, transcriptional, or translational deficiencies in lactoferrin synthesis may reduce the functional level of lactoferrin, an important antimicrobial/antibiofilm peptide in the nasal secretions of CRS patients.[13] This may predisposing certain individuals to bacterial colonization, biofilm development, and recalcitrant sinus disease.[13] Using polymerase chain reaction assays on nasal mucosal tissue, it appears that paranasal sinuses are in fact not "sterile", even healthy sinus cavities may be colonized with bacteria. Inflammation which resulting from a variety of etiologies, eosinophils, and a complex list of mediators such as interleukins and cytokines, undoubtedly lead to venous congestion, temporary impairment of mucociliary clearance, impaired airflow mechanics and nasal physiology, all lead to symptoms of rhinorrhea and congestion.

Compliance of Using Nasal Irrigation in Children

To determine compliance and safety of intranasal irrigation, the primary caregivers were given a calendar sheet and asked to document compliance and whether irrigation was performed during each day of the 6 week study period. Caregivers were also asked to log any adverse events associated with the nasal irrigations. Study personnel called the caregivers weekly to assess adverse events and/or problems with compliance.

Compliance was extremely high at almost 90% in all subjected who completed the study. Out of 42 possible days of once daily irrigation regimen in a 6 week treatment period, no parent/caregiver reported missing irrigation more than 5 days, and over 50% reported completing all 42 days. The most common reasons

cited for missed days of irrigation are due to travel or being away from home, thus avoiding the inconvenience of transporting the irrigation solution and bottle. It is the investigator opinion that high compliance for this regimen reflects not only ease of use, but more importantly the desire of caregivers to give a best attempt of following a non-surgical treatment plan in order to avoid sinus surgery for their child. During the patient visit encounter and informed consent process, parents and caregivers are told that irrigation may or may not resolve their child's chronic symptom, and that sinus surgery may be necessary if the child fails irrigation treatment. Furthermore, the investigator emphasize the immense value of having the family and child learn this effective, non-invasive, and inexpensive treatment modality for future use on an as needed basis for onset of sinonasal symptoms due to upper respiratory tract infections or allergy exacerbations. Families are relieved to have an alternative treatment method which may eliminate multiple physician visits and use of systemic oral antibiotics. Intranasal irrigation therapy will likely reduce morbidity which directly impacts and decrease overall health care expenditure for this disease.

Children as young as preschool age were able to not only tolerate intranasal irrigation, the parents commonly report that after the first week of daily use many are able to irrigate independently. In fact, parents often report that children preferred to do it themselves so as to have better control of how quickly the solution comes out of the irrigation squeeze bottle. Anecdotal feedback include one child who declared regaining the ability to smell again after one week of irrigation, and many who tell their parents they like how it makes them feel since they regain ability to breathe through their nose again.

Comparing Outcomes Between Irrigation Using Saline vs. Saline and Gentamycin

The average age of our study patients was approximately 7.5 in the saline group and 8.5 in the saline plus gentamycin group. The only difference between the two groups was that there were predominantly more males in the saline group (84%) compare to the saline plus gentamycin group (43%, p=0.007). Approximately half of the patients in this study were referred from asthma/ allergy specialists, and 40% were referred by pediatricians (**Table 1**). History and presenting symptoms are presented in **Table 2** with congestion, cough and nasal airway obstruction being the top three symptoms reported. There were no differences between the two groups with respect to all symptoms reported, the number of course of antibiotics consumed in previous 6 and 12 months, duration of symptoms, and history of gastro-esophageal reflux disease (GERD) requiring medical treatment. Atopic allergy history is presented in **Table 3**. Over 50% of patients had previously undergone allergy testing (78.9% saline group, 66.7% saline+ gentamycin group), and there were no differences with respect to positive allergies to mold, trees, pollen, and animals in both groups. Approximately 58% of the saline group and 48% of the gentamycin group were diagnosed and actively treated for asthma. **Table 4** summarizes all medications used prior to otolaryngology visit and did not differ between the 2 groups. Over 80% reported using nasal steroid spray, and 57% of patients in both groups were also on

systemic antihistamines. Approximately one third of patients in both groups had been on oral steroids within the past 6 months most commonly for severity of asthma. Almost 50% of patients in the saline group and 57% of patients in the gentamycin group had been on montelukast, a leukotriene receptor antagonist.

Table I. Baseline Characteristics

	Saline (n = 19)	**Gentamycin (n=21)**	**p-value‡**
Age	8.53 ± 3.79 yrs.	7.68 ± 2.38 yrs.	0.76
Gender			
M F	16 (84 %) 3 (16 %)	9 (43 %) 12 (57 %)	0.007*
Race			
White African American Asian Other	18 (95 %) 0 0 1 (5%)	17 (81 %) 1 (5 %) 1 (5 %) 2 (9 %)	0.345
Referral			
Asthma/allergy Pediatrician Self Other	10 (53 %) 8 (42 %) 1 (5 %) 0	10 (50 %) 8 (40 %) 1 (5 %) 1 (5%)	1.00

Pre and Post-Treatment CT Scores

CT scans were scored using the Lund-Mackay Staging system. After 6 weeks of once daily irrigation, both groups demonstrated statistically significant reduction in CT scores for every sinus, the OMC, and the total score for each side. There were no differences observed between the two treatment groups except for the right frontal sinus (p=0.04).

Safety of Nasal Irrigation

Our clinical trial measured distortion product otoacoustic emissions (DPOAE) in all subjects before and after irrigation, primarily to ensure no evidence of ototoxicity for the children who irrigated with saline with gentamycin. No change in DPOAE was found in the entire study group.

Nasal irrigation was well tolerated for all subjects and there were very few adverse events reported which included otalgia, acute otitis media (likely from irrigation solution refluxing into middl ear causing pain/discomfort), epistaxis, cough, and poison ivy (unrelated to study).

How Children can Learn to Perform Saline Irrigation

The author recommends using the NeilMed Sinus Irrigation Kit which has already prepared buffered sodium phosphate packets as well as a pediatric irrigation squeeze bottle (4oz). Generally children as young as age 4 are able to be taught how to perform nasal irrigation themselves. It is very important that the children have control of the squeeze bottle and the adult not be the one doing the irrigation in order to decrease anxiety and allow for full control of the force

Table 2. Presenting Symptoms and History

	Saline (n = 19)	Gentamycin (n=21)	p-value
Congestion	19 (100 %)	20 (95 %)	1.0
Cough	12 (63 %)	20 (90 %)	0.06
Nasal Airway Obstruction	16 (84.2 %)	15 (71.4 %)	0.33
Rhinorrhea	10 (52.6 %)	16 (76.2 %)	0.12
Fatigue	8 (42.1 %)	10 (47.6 %)	0.73
Headache	12 (63.2 %)	10 (47.6%)	0.32
Number of Courses of Antibiotic Therapy Completed in Previous 12 months	Saline (n = 3) 4 ± 1.73	Gentamycin (n = 7) 5.29 (± 2.0)	0.36
Number of Courses of Antibiotic Therapy Completed in Previous 6 months	Saline (n = 14) 9.1± 18.5)	Gentamycin (n = 17) 3.3 ± 0.92	0.10
Duration of Any or All Combination of Symptoms	Saline (n = 9) 8.7 ± 10.3 weeks	Gentamycin (n = 8) 9.3 ± 10.3 weeks	0.85
GERD	8 (44.4 %)	9 (45 %)	0.97

applied for irrigation. It is especially useful for pre-school aged children that for the first few days, parents allow the child to play with the squeeze bottle at bath time, so that the child is completely confident in the nonthreatening nature of this bottle and becomes comfortable with it. When starting irrigation, parents are encouraged to be next to the child, have the child lean over the sink with the neck flexed and chin down. Parents can count out "1, 2, 3, 4, 5…." until saline comes out the other nostril. The child then repeats motion with the other side.

Table 3. Atopic History

	Saline (n = 19)	Gentamycin (n=21)	*p*-value
History of Positive Allergy testing	15 (78.9 %)	14 (66.7 %)	0.75
Mold	6 (51.6 %)	8 (38.1 %)	0.67
Trees	5 (26.3 %)	7 (33.3 %)	0.63
Pollen	5 (26.3 %)	8 (38.1 %)	0.43
Animals	6 (31.6 %)	6 (28.6 %)	0.84
Asthma	11 (57.9 %)	10 (47.6 %)	0.52

Table 4. Medications Used

	Saline (n = 19)	Gentamycin (n=21)	p-value
Nasal steroid spray	15 (79 %)	18 (85.7 %)	0.69
Oral antihistamines	11 (57.9 %)	12 (57.1 %)	0.96
Oxymetazoline nasal spray	0 (0%)	3 (14.3 %)	0.23
Oral OTC decongestants	3 (15.8 %)	2 (9.5 5)	0.65
Oral steroids	5 (26.3 %)	7 (33.3 %)	0.63
Montelukast (leukotriene receptor antagonist)	9 (47.4 %)	12 (57.1 %)	0.54

Observations Regarding Irrigation in Children

Almost all parents and caretakers report the following. For the first 4-5 days, there will be no mucous, secretions, or "snot" that the child will blow out of the nose after once daily irrigation. However, after the day 5 or 6 of consecutive daily use, they notice the child will blow out much material. This is always welcomed and psychologically reassuring that whatever is "stuck" in their head are now exiting, and continues only for 1-2 more weeks. Clinically, children report much improved nasal breathing after a couple of weeks of daily irrigations, as well as improved smell, decreased headache, improved sleep, and decreased coughing.

Discussion

This clinical trial was conceived and developed after the primary investigator noted fairly consistent anecdotal clinical success in consecutive patients after using intranasal gentamycin irrigation at the concentration of 80mg/1000ml. This concentration was chosen based on the investigator's previous experience during residency training having used it in adult patients after endoscopic sinus surgery. These patients had CT imaging following a 6- week trial of once daily irrigation, and CT scan demonstrated decrease in pre-treatment mucosal thickening and sinus opacification which correlated with clinical reports of resolution of ongoing symptoms such as cough, severe congestion, and headache. Despite a series of treatment successes with gentamycin irrigation, the purpose of this study was to definitively determine whether it is the volume of irrigation and the compliance with daily use which may be the most important for reversal of symptoms of chronic rhinosinusitis in children, or if adding an antibiotic like gentimicin is safe and increases efficacy. This study also demonstrated that while adding an antibiotic such as gentamycin to the saline is safe for topical irrigation, it does not increase efficacy. Many of these patients were already recommended to undergo FESS by other otolaryngologists prior to enrollment in this clinical trial, but were able to avoid surgery after completion of 6 weeks of once daily irrigation regardless of which group they were randomized to.

Treatment for Pediatric Rhinosinusitis

In 1997, Otten published a placebo controlled prospective study evaluating 4 conservative treatment methods for pediatric chronic maxillary sinusitis.[14] In that study, 141 children between ages 3 and 7 who were diagnosed by history,

exam, and positive sinus X-ray were randomized to either 1) physiologic saline nose drops 2) xylometazoline nose drops plus 10 days of amoxicillin, 3) drainage and irrigation of the maxillary sinus 4) 2 plus 3. All children were followed for 6 months, with follow up visits at 2, 6, 12, and 26 weeks after treatment. He reported 60% of the children had persistent purulent rhinitis at each follow up and there was no statistically significant difference between the 4 treatment groups. With limited explanation of the exact study procedures, he did conclude that symptoms generally disappear by age 7 and that amoxicillin and drainage have no permanent curative effect in these young children. He reported lack of explanation for persistent symptoms but postulate immaturity of the local immune system.

A decade later, it is common to see primary care physicians as well as allergists treat symptomatic patients who have CT evidence of mucosal thickening with at least 21 days of systemic broad-spectrum antibiotics recommended for acute sinusitis. Our patients and parents commonly reported that while on antibiotics, they feel slight improvement in symptoms but there is almost immediate return of symptoms within several days of discontinuing oral antibiotics. This is not entirely surprising since studies have demonstrated bacterial biofilm and its relationship to chronic rhinosinusitis.[15,16] However, it is widely accepted that prolonged systemic antibiotic therapy is associated with development of antibiotic resistance as well as systemic risks such as secondary *Clostridium difficile* infection.

Treatment recommendations for chronic rhinosinusitis in the pediatric population are often exactly the same as they are for acute rhinosinusitis, with frequent emphasis on use of systemic oral antibiotics.[17,18] Instead of a 10-day course of broad spectrum antibiotics with good coverage again *Streptococcus pneumoniae* and *Haemophilus influenza*, often patients are prescribed at least 14-21 days of continuous oral antibiotics and often even longer periods of treatment. Chronic rhinosinusitis in children may occur as a complication after severe viral upper respiratory illness or exacerbation of allergic rhinitis, both of which result in compromised mucociliary clearance. Many studies have shown that in patients with chronic rhinosinusitis there is a significant decrease in their sinonasal mucociliary clearance. [19] Impaired mucociliary clearance is the underlying pathophysiologic problem which leads to sinus mucosal thickening, subsequent obstruction of ostiomeatal complex and natural draining ostia of all sinuses, hypoxia, and hyperplasia of submucosal goblet cells and increased mucous production. This study demonstrates that first, atopic history is extremely common, with almost 80% of the patients in the saline group and 67% in the gentamycin group reporting history of a positive skin test to various aeroallergens. Almost all of these patients would have been deemed to have failed medical therapy and recommended to undergo FESS based on the history of already having had so many courses of systemic antibiotics as well as having tried nasal steroids, nasal and oral antihistamines medications.

The improvements reported based on SN-5 QoL survey and CT studies were strictly after once daily irrigation only, without addition of any systemic medications or intranasal sprays (decongestants, histamine, and/or topical steroid).

We did not control for these medications as the PI did not observe differences in children who present to the otolaryngologist because they have already failed all other medical therapy tried by primary physicians or their allergists. The majority of the patients and parents report being able to discontinue almost all systemic medications after the study period because of resolution of most if not all sinonasal symptoms, which were the reason for using other medications in the first place. Our data shows statistically significant improvements in both quality-of life with significant reduction in clinical symptom as well as CT evidence of reversal of mucosal thickening in almost all sinuses. Improvements in both CT scores and SN-5 QoL scores were statistically significant within each group when comparing baseline to after 3 weeks of once daily irrigation. .

Improvements in QoL scores for specific domains as well as the overall score were statistically significant comparing baseline to scores after 3 weeks of once daily irrigation and were seen in both treatment groups. The improvements continued after an additional 3 weeks of treatment in both groups, but the differences were not statically significant when compared to the scores after the initial 3 weeks of irrigation.

Mucociliary Clearance

Much has been reported on not only the efficacy of nasal irrigation comparing type of saline, techniques of irrigation as well as how irrigation affects mucociliary clearance. Several randomized trials reported statistically significant improvements in symptoms and in sinus-related quality of life scores after hypertonic or isotonic saline irrigation.[3-7] One randomized trial of 30 children age 3 to 16 reported hypertonic saline to be more efficacious than normal saline in reduction of cough and radiology score but not in postnasal drip score.[20] Daily nasal irrigation using either a bulb syringe, nasal irrigation pot, and daily reflexology massage were found to be equally efficacious and resulted in the improvement in symptoms of chronic sinusitis in over 70% of adult subjects.[4] Interestingly, one study showed buffered hypertonic saline irrigation improved mucociliary clearance in adults based on saccharin clearance test while buffered normal saline had no such effect.[21]

Correlation between ciliary beat frequency and structure of ciliated epithelia in human nasal mucosa was elegantly studied by Joki et al.[22] They found that ciliary disorientation and lack of ciliated cells seen in scanning electron microscopy (SEM) correlated with low ciliary activity. In cases where sinusitis secretions were not seen, CBF was slower than in cases with mucopurulent secretions. Sinusitis with disoriented cilia, loss of ciliated cells, and a lack of mucosal secretion s associated with a decrease in CBF, which may lead to impaired mucociliary clearance and increased risk of recurrent and chronic sinusitis.[22] Nasal mucociliary transport of chronic sinusitis in children was studied by Sakakura et al.[23] The mean value of saccharin transit time in the nose of children with chronic sinusitis was significantly slower than in controls of the same age.[23] In children with chronic maxillary sinusitis undergoing FESS, when compared to controls, cilia in antral mucosa were significantly regenerated compared to preoperative variants and significant differences in postoperative saccharin transit times were

demonstrated.[24] Since not all children who may experience episodes of chronic rhinosinusitis should undergo FESS, alternative methods of restoring mucociliary motility and clearance are preferable and necessary.

Finally, a comparison study looking at 3 methods of irrigation techniques (metered nasal spray, nebulization with RhinoFlow, and nasal douching while kneeling with the head of the floor) concluded that nasal douches are more effective in distributing irrigation solution to the maxillary sinuses and frontal recess based on Technetium 99m sulfur colloid distribution see on nuclear imaging.[25]

Even after completion of participation in this clinical trial, many parents report continued use of irrigation whenever the child developed recurrence of symptoms. In fact, the PI has often clarified to parents that permanent once daily irrigations are not recommended nor should be necessary in children who are otherwise immunocompetent. It is the author's experience that parents are often so anxious due to their prior experience of multiple physician visits, costs of treatment, and most importantly the child's prolonged symptoms, that once significant improvements are experienced by both patient and caregivers, it may be difficult to stop the successful treatment. Since daily irrigation generally is associated with minimal side effects, this is of less concern compared to parents who may be reluctant to stop systemic medications or antibiotics.

Summary

In children, prolonged cough and nasal congestion, especially in children with test proven allergies to aeroallergens, have a high likelihood of chronic rhinosinusitis as confirmed by mucosal thickening of the paranasal sinuses and secondarily obstruction of the ostiomeatal complex. Most children who present with these symptoms do not have acute symptoms suggestive of acute bacterial infection, therefore one or more courses of systemic oral antibiotics are unlikely to lead to long term resolution of symptoms. In these patients, once daily intranasal irrigation with saline is safe and effective in the treatment of pediatric CRS defined by reversal of disease on CT scan using the Lund-McKay scoring system. Furthermore, intranasal irrigation using the Neilmed Sinus Rinse squeeze bottle is well tolerated in children as young as 4 years of age, and we found extremely high compliance in this patient population. Parents and caregivers report significant improvement of their child's quality of life after only 3 weeks of daily irrigation.. Based on evidence of high compliance and effectiveness of intranasal irrigation, it should be recommended as a first-line treatment modality for treating pediatric rhinosinusitis, even before consideration of adenoidectomy (if it is not significantly enlarged), or endoscopic sinus surgery.

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Appendix Reference

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