

Medical therapy as the primary modality for the management of chronic rhinosinusitis

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ABSTRACT

Chronic rhinosinusitis (CRS) is a prevalent disease with many potential interventions including medical and surgical treatments. Because CRS is a chronic condition it is essential that therapy limits exacerbations. The purpose of this article is to show that literature supports the implementation of aggressive medical management as the mainstay of therapy for CRS. Scientific literature on the use of intranasal and systemic corticosteroids, antibiotics, nasal saline lavages, and unique therapies for individuals with CRS (both with and without nasal polyps) are reviewed. In addition, literature comparing outcomes of medical therapy versus surgical therapy are reviewed. There is ample evidence of the beneficial effects of intranasal corticosteroids (INCSs) in CRS. The literature also favors the use of systemic corticosteroids in acute exacerbations of disease in patients with nasal polyps. Although antibiotics are commonly used for acute sinusitis, there is also evidence of their potential value in CRS. The literature indicates that saline lavages show benefit in the treatment of CRS. In addition, there are promising new biological therapies on the horizon with mepolizumab and omalizumab. At least one study comparing medical therapy versus surgical therapy for CRS found no advantage for either modality. Treatment of CRS with aggressive medical management can potentially postpone the need for surgical intervention. Clinicians should use INCSs and nasal saline lavages as maintenance therapy. Systemic corticosteroids and antibiotics should be used for acute exacerbations, especially in individuals with nasal polyps.

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Chronic rhinosinusitis (CRS) is a group of disorders characterized by inflammation of the nasal mucosa and paranasal sinuses of at least 12 weeks duration.^{1,2} Recent estimates place the prevalence at ~5–15% of the general population in the United States and Europe, with a much lower prevalence of physician-diagnosed CRS at 2–4%.³ The health care costs of this disease are tremendous with estimates of 73 million restricted activity days and \$2.4 billion in direct medical costs annually.^{4,5} CRS can be classified into two main subtypes: CRS without nasal polyps (CRSsNPs) and CRS with nasal polyps (CRSwNPs), although this is an oversimplification of a complex disease that may actually comprise multiple phenotypes. There are no curative treatments for CRS, making it a chronic condition that requires long-term management that addresses the underlying pathogenesis of disease.

Current medical treatment options for CRS include corticosteroids (both intranasal and systemic), antibiotics, and nasal saline irrigations. Intranasal corticosteroids (INCSs) are the mainstay of therapy, and sys-

temic corticosteroids and antibiotics are often used for exacerbations of disease. Other treatment options often used for CRS include montelukast, decongestants (pseudoephedrine and oxymetazoline), and mucolytics. The primary surgical treatment option for CRS is functional endoscopic sinus surgery (FESS), which uses endoscopic visualization to locate obstructed drainage pathways of the paranasal sinuses, allowing for restoration of drainage and ventilation.⁶ The purpose of this article was to review the literature that supports the use of aggressive medical therapy as the primary modality for the management of CRS, with the goal of preventing, or at the very least limiting, the need for surgery.

PATHOGENESIS OF CRS

There is no single hypothesis on the etiology of CRS that is validated experimentally; however, there are two that highlight the mechanisms that may drive the disease process. The superantigen hypothesis proposes that exposure to exotoxins from pathogens, in particular, *Staphylococcus aureus* enterotoxins A and B, have untoward local effects. Exotoxins disrupt the local immune response resulting in skewing of T lymphocytes toward a Th2 phenotype, proinflammatory cytokine release, localized polyclonal IgE responses, and down-regulation of regulatory T- cells.⁷ In combination, these lead to recruitment of eosinophils with the resulting clinical and histopathological changes associated with CRS.⁸

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Although the previous hypothesis points to exogenous factors as the cause of pathology, the immune barrier hypothesis implicates preexisting host susceptibility. CRS occurs at the boundary of the sinonasal mucosa and external environment where the local host defenses are confronted with an innumerable number of pathogens, toxins, and other environmental stressors. Two crucial host defense mechanisms in the sinonasal mucosa are the mechanical barrier of the airway epithelium and the innate and adaptive immune system.⁹ In a subset of individuals, defects in these mechanical and immunologic barriers create an environment where persistent inflammation and possibly infection lead to CRS.^{7,9}

HOW STEROIDS WORK IN CRS

Although a unifying hypothesis that explains the pathogenesis of CRS remains elusive, a cardinal feature of the disease that is agreed on is persistent inflammation that, in the majority of cases, is dominated by eosinophils.^{1,3} Corticosteroids are traditionally understood to modify the disease process by reducing the number of inflammatory cells (eosinophils, T lymphocytes, dendritic cells, and mast cells) through inhibition of both their migration out of the circulation and survival in the tissues.¹⁰

Use of INCSs in CRS

Given the large number of studies establishing benefit of INCSs in individuals with CRSwNPs, the recent European Position Paper of Rhinosinusitis and Nasal Polyps (EPOS 2012) recommends their routine use after analyzing 38 randomized controlled trials.³ Meta-analyses of these studies characterized outcomes such as symptom scores, polyp size, and nasal breathing.³ In terms of symptom scores, data on change in combined symptom scores from seven studies were combined for a meta-analysis favoring the use of INCSs. Data on the proportion of responders in symptoms from four studies were used in a meta-analysis also showing benefit from INCSs.³ In terms of measures of polyp size: data on the final value of polyp score from three studies, data on the change in polyp score from three studies, and data on the proportion of responders in polyp size from eight studies were combined in meta-analyses, all of which showed benefit in the use of INCSs.³ In terms of measures of nasal breathing, data on peak nasal inspiratory flow from seven studies, data on the change in nasal airflow from three studies, and data on the proportion of responders in nasal airflow from two studies were combined in meta-analyses. As mentioned previously, these analyses significantly favored the use of INCSs.³

Subgroup analysis of the 38 trials compared factors such as CRSwNP patients with prior surgery versus

those without history of surgery, delivery methods (sprays versus drops), and modern corticosteroids (mometasone, fluticasone, and ciclesonide) versus first-generation corticosteroids (budesonide, beclomethasone, betamethasone, triamcinolone, and dexamethasone).³ In terms of history of surgery, patients with prior surgery responded better to INCS treatment with respect to polyp size but not symptom score or airflow. In terms of effect of delivery method, nasal aerosols and budesonide Turbuhaler (AstraZeneca, London, UK) were found to be more effective than nasal sprays in symptom control but not polyp size. In addition, in terms of the effect of modern corticosteroids versus first-generation corticosteroids, there was no significant benefit with modern corticosteroids.³

A large double-blind placebo-controlled (DBPC) trial by Stjarne indicated that mometasone furoate nasal spray (once or twice daily) significantly improved polyp grade and nasal congestion/obstruction scores (primary end points) and anterior rhinorrhea, post nasal drip, and loss of smell (secondary end points).¹¹ A similar DBPC trial by Small showed that mometasone nasal spray reduced polyp grade and improved symptoms of congestion and/or obstruction (primary end points) and significantly improved peak nasal inspiratory flow rate and sense of smell (secondary end points).¹² A follow-up study by Small to evaluate the onset of symptomatic effect of mometasone showed that twice-daily treatment improved rhinorrhea and peak nasal inspiratory flow by day 2 of therapy, nasal congestion by day 3, postnasal drip by day 5, and smell by day 13.¹³

Two additional studies worth noting address INCS delivery methods in individuals with CRSwNPs.^{14,15} Aukema used fluticasone propionate nasal drops in a DBPC trial to determine if their use could postpone or even prevent surgery in a subset of patients on the waiting list for FESS.¹⁴ These patients had been previously treated for 3 months with INCS sprays before the start of the study without adequate results. The use of fluticasone drops resulted in decreased symptoms (nasal obstruction, rhinorrhea, postnasal drip, and loss of smell), increased peak nasal inspiratory flow scores, and decreased polyp volume.¹⁴ After 12 weeks of treatment 13 of 27 patients treated with INCS drops no longer required FESS compared with only 6 of 27 patients in the placebo group.¹⁴ It should be noted that although this study did show benefit for nasal drops, the distribution of this formulation is limited in the nasal cavity compared with sprays. A pilot study by Steinke examined the effectiveness of budesonide inhalant suspension irrigations as a delivery method.¹⁵ Although it lacked a control group, the authors found that use of budesonide irrigations improved CT scores, sinus scores, and sense of smell over a ≥ 3 -month period. Interestingly, in seven asthmatic patients they found a trend toward a decrease in asthma scores after treatment with sinus irrigations,

which the authors speculated was an indirect effect of improved sinusitis.¹⁵

Although the literature also supports the use of INCSs in CRSsNPs, the evidence is less convincing. EPOS 2012 performed a meta-analysis of five studies comparing INCSs to placebo in patients with CRSsNPs and determined that there was significant benefit in terms of symptom scores and the proportion of responders.³ However, endoscopic scores from two studies did not reach significance in a meta-analysis and radiographic scores from three studies did not show benefit with INCSs.³

Oral Corticosteroids in CRS

Although topical corticosteroids should be considered as maintenance therapy for individuals with CRS, there is evidence that oral corticosteroids should be used for disease exacerbations in individuals with CRSwNPs. Oral corticosteroids are hypothesized to work as a “medical polypectomy.” Vaidyanathan performed the first randomized controlled trial examining the efficacy and safety of a burst of oral corticosteroids followed by sustained use of INCSs.¹⁶ The study group received 25 mg of oral prednisolone daily for 14 days, and the control group received placebo. After this 2-week period both groups received fluticasone propionate nasal drops (400 µg twice daily) for 8 weeks and then fluticasone propionate nasal spray (200 µg twice daily) for 18 weeks. The group that received oral corticosteroids had significant improvement, with decreases in both polyp grade and hyposmia score compared with the placebo arm. As far as side effects, there was temporary suppression of adrenal markers in the group that received oral corticosteroids, which returned to normal while on INCSs.¹⁶ A recent review of the literature on the use of oral corticosteroids in adult CRS strongly recommended their use in both the immediate and the short-term management of CRSwNPs based on evidence from 16 peer-reviewed articles, benefit/harm assessment, and value judgments.¹⁷ They found insufficient evidence from four articles on the use of oral corticosteroids in CRSsNPs and deemed it optional.¹⁷

ANTIBIOTICS IN CRS

There are no Food and Drug Administration (FDA)-approved antibiotics for CRS but antibiotics commonly used to treat acute rhinosinusitis are used to treat CRS, typically given for 3–6 weeks.¹⁸ The antibiotics that are currently approved by the U.S. FDA for acute rhinosinusitis are amoxicillin-clavulanate, clarithromycin, cefprozil, cefuroxime axetil, loracarbef, levofloxacin, azithromycin, trimethoprim-sulfamethoxazole, and moxifloxacin. A randomized controlled trial by Namyslowski compared the efficacy and safety of amoxicillin-clavulanate (875–125

mg twice daily for 14 days) to cefuroxime axetil (500 mg twice daily for 14 days) in patients with acute exacerbations of CRS.¹⁹ Clinical response was similar between the two (response rates of 95% for amoxicillin-clavulanate and 88% for cefuroxime, and bacteriological cure rate of 65 and 68%, respectively); however, clinical relapse was significantly higher in the group that received cefuroxime (7% for cefuroxime versus 0% for amoxicillin-clavulanate),¹⁹ which may be explained by the fact that amoxicillin-clavulanate has superior anaerobic coverage. A DBPC trial by Legent compared ciprofloxacin (500 mg twice daily for 9 days) to amoxicillin-clavulanate (500–125 mg three times per day for 9 days) for acute exacerbations of sinusitis in individuals with CRS.²⁰ As in the previous study, clinical response rates and bacteriological cure rates were similar for the two antibiotics; however, 40 days after the last dose of antibiotics the treatment cure rate was significantly higher in the patients who received ciprofloxacin (83.3% for ciprofloxacin versus 67.6% for amoxicillin-clavulanate).²⁰

Although the use of antibiotics for treatment of acute exacerbations in patients with CRS has been shown to be beneficial, there is less data on the use of long-term antibiotics.¹⁸ A DBPC study by Wallwork examined the efficacy of roxithromycin (150 mg daily) for 3 months versus placebo.²¹ The group receiving the macrolide had improved subjective measures (response rates and 20-item Sino-Nasal Outcome Test scores [Watsepik, Inc., Fort Collins, CO]), and objective measures (saccharine transit times and nasal endoscopy scores) at the end of the treatment period. Overall, the response rate was 67% in the treatment group versus 22% in the placebo group, which may be attributable to anti-inflammatory properties of the macrolide as well. However, no difference was seen in peak nasal inspiratory flow, olfactory function scores, or the levels of IL-8, fucose, or α2-macroglobulin in nasal lavages.²¹ The benefits were not sustained and were gone by 3 months after therapy, with the authors suggesting that longer, or multiple, courses of therapy may be indicated.²¹ Of note, our practice uses the above listed FDA-approved antibiotics as prophylactic treatment in individuals with refractory CRS and immunodeficiency, typically at half the normal dose. Although there are no guidelines on the use of prophylactic antibiotics in this disease, we feel it is beneficial in particular cases.

ANTIBIOTICS AND ORAL STEROIDS IN CRS

The combination of antibiotics and oral corticosteroids for acute exacerbations of CRS potentially targets two causes of pathology. A DBPC study by Ozturk compared oral corticosteroids (1 mg/kg per day for 10 days, 0.75 mg/kg per day for 2 days, 0.5 mg/kg per

day for 2 days, and 0.25 mg/kg per day for 1 day) along with amoxicillin-clavulanate (45/6.4 mg/kg per day for 30 days) versus placebo and antibiotic alone, in children with acute exacerbations of CRS.²² The authors found that the addition of oral corticosteroids to a course of antibiotics was more effective at reducing total and individual symptom scores, postnasal drip, and cough and resulted in a greater reduction in CT scores. Complete clinical recovery and clinically significant improvement were observed in the patients receiving systemic corticosteroids in addition to antibiotics.²²

NASAL IRRIGATION IN CRS

A prospective study by Tamooka sought to determine the efficacy of pulsatile hypertonic saline nasal irrigation in general sinonasal disease (CRS, allergic rhinitis, atrophic rhinitis, and postnasal drip).²³ Treatment consisted of nasal irrigation with hypertonic saline delivered *via* a Waterpik device twice daily for 3–6 weeks. Subjective outcomes of nasal disease-specific symptoms and a quality of life questionnaire were compared with a placebo group. The authors found significant improvements in 23 of 30 symptoms and quality of life with use of nasal irrigations, with 76% reporting overall improvement.²³ A Cochrane report on the use of nasal irrigations for symptoms of CRS concluded they were beneficial when used as the sole modality for symptomatic relief.²⁴ Although the use of saline irrigation was associated with minor side effects such as local irritation and burning, these were outweighed by their benefits. Topical antibiotics in nasal irrigations are often used for CRS; however, there are limited case reports and observational studies showing their benefit, and DBPC studies failed to show significant clinical benefit.^{18,25–28}

OUTCOMES OF MEDICAL MANAGEMENT

A study by McNally examined the records of 200 pediatric and adult patients with a history of CRS treated by an allergist with 4 weeks of oral antibiotics, INCSs, nasal lavages, and topical decongestants.²⁹ A goal of this report was to determine whether aggressive medical management would successfully treat symptoms and limit the need for surgical intervention. Patients were followed for a mean of 6 months during which the authors found that 23–75% of presenting symptoms (anosmia, postnasal drip, headache, facial pain, purulent drainage, and cough) improved, while 50–84% of physical exam findings (nasal polyps, purulent secretions, nasal mucosal edema, and abnormal transillumination) improved. Importantly, only 6% of the patients required surgery.²⁹

A retrospective study by Subramanian sought to determine the efficacy of intensive medical treatment for

CRS.³⁰ The intensive medical regimen consisted of oral corticosteroids (prednisone at 20 mg twice daily for 5 days and then once daily for 5 days), antibiotics for 4–8 weeks, and adjunctive therapy (INCSs and saline irrigations). This was one of the first studies to examine a combination of oral corticosteroids and antibiotics, and also one of the first to look at both symptomatic and radiographic responses. Thirty-six of 40 patients had significant improvement in symptom scores and CT scores after the treatment period. The majority of patients did not experience a relapse until well after 8 weeks of the last treatment. The two factors associated with relapse were a history of nasal polyps and prior sinus surgery.³⁰

MEPOLIZUMAB AND OMALIZUMAB FOR NASAL POLYPS

The majority of nasal polyps from white patients with CRS have a prominent local eosinophilic infiltrate and elevated levels of IL-5.^{3,31,32} With the introduction of biological agents to treat specific mechanisms driving disease processes, a new age of therapy guided by a patient's unique phenotype is up on us. A DBPC trial by Gevaert sought to characterize the therapeutic potential of anti-IL-5 therapy (mepolizumab) to treat severe, refractory CRS.³² This was a follow-up to an earlier study where the same group found that a single dose of mepolizumab successfully reduced polyp size in CRSwNP patients—with the affect most prominent in individuals with high local concentrations of IL-5 in the nasal cavity.³³ The newer study used 2 doses of mepolizumab (750 mg i.v. 28 days apart) versus placebo. The authors found significant improvement in their primary outcome measure (nasal polyp score by endoscopy) and their secondary outcomes (CT score, anosmia, postnasal drip, and congestion) in the group receiving mepolizumab.³² In addition, more recent data from Gevaert show promise for the use of anti-IgE therapy (omalizumab) for both atopic and nonatopic patients with nasal polyposis and asthma.³⁴

COMPARISON OF MEDICAL VERSUS SURGICAL TREATMENT IN CRS

A few studies compare medical versus surgical management of CRS. FESS has often been perceived as more effective than intensive medical therapy because there are few good trials of the latter modality, and the former has high success rates in the literature.³⁵ To address this, Ragab performed a prospective, randomized controlled trial to compare the medical and surgical treatment of polypoid and nonpolypoid CRS.³⁵ Ninety patients with CRS were randomized to get either intensive medical therapy or surgery. Intensive medical therapy consisted of a 12-week course of erythromycin (500 mg twice daily for 2 weeks, fol-

lowed by 250 mg twice daily for 10 weeks), alkaline nasal douche, and INCSs (dexamethasone at 20 μ g twice daily for 2 weeks followed by fluticasone propionate drops at 100 μ g twice daily for 10 weeks in CRSsNP patients, and fluticasone propionate drops at 100 μ g twice daily for 12 weeks in CRSwNP patients). Comparing the medical groups versus surgical groups posttreatment, there was no significant difference in subjective measures (visual analog scale and individual symptom score), quality of life (20-item Sino-Nasal Outcome Test score), or objective measures (endoscopic score). In addition, the study did not find a history of nasal polyposis as a poor prognostic factor for either medical or surgical therapy, because the measured parameters improved equally in individuals with CRSwNPs, regardless of treatment modality.³⁵

A recent prospective study by Smith sought to evaluate outcomes in CRS patients who failed initial medical management of their disease and elected to either continue medical therapy or pursue FESS in addition to medical management.³⁶ The results of the analysis favored surgery as the surgical cohort had greater improvement in quality of life, reduced exposure to antibiotics, and fewer missed days from work or school.³⁶ It should be noted that the study was not randomized (as treatment was based on clinical judgment and patient preference), and there were no objective measures quantified.³⁶

SUMMARY AND RECOMMENDATION

Although FESS has proven to be an effective option for individuals suffering from CRS, it should not be the mainstay therapy for disease management. CRS is, by definition, a chronic disease that currently has no curative options. As such, the most effective therapies for CRS are those that control mucosal inflammation and limit the overgrowth of pathogens that cause dysregulation of the immune response and disruption of the mechanical barriers of the epithelium. Because persistent inflammation is a hallmark feature of CRS, control of inflammation is essential with daily use of INCSs, especially in individuals with nasal polyposis. Exacerbations of acute sinusitis should be treated aggressively with antibiotics, and oral corticosteroids should be strongly considered, especially in individuals with CRSwNPs. The regular use of nasal saline irrigations should be encouraged as well.

Surgery should be implemented only when aggressive medical management has failed, because complications can occur.³⁷ Surgery alone is ineffective in managing this disease, because those with nasal polyposis frequently get recurrence of polyps and need repeat FESS.¹⁴ One of the most important outcomes of surgery is both restoring patency to drainage pathways in the sinus cavities and allowing access for topical cortico-

steroids. If surgery is required it is essential that aggressive medical therapy be implemented postoperatively to maintain the integrity of the nasal mucosa. CRS can be successfully managed when clinicians and patients understand the importance of controlling the disease process and quickly recognizing and limiting exacerbations.

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