Chapter 15
Medical Treatment of Pediatric Rhinosinusitis: Focus on Intranasal and Systemic Corticosteroids

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Rhinosinusitis is a commonly encountered problem in both pediatric and otorhinolaryngologic practices with a recent increase in the diagnosis of acute rhinosinusitis (ARS) and chronic rhinosinusitis (CRS) in both adult and pediatric patients. This is likely a consequence of an improved understanding of the etiology, pathophysiology, and microbiology of the disease. The exact prevalence of the disease in children is difficult to determine as only a small percentage of cases present to the physician's office. A recent analysis of national survey databases between 2005 and 2012 showed that CRS accounted for 5.6 million visits per year among patients 0–20 years of age [1]. CRS was diagnosed in 2.1% of all visits, ARS in 0.6% and as comparators, allergic rhinitis in 2.6%, upper respiratory tract infections (URI) in 8% and otitis media in 6.7%. In a Swedish population-based study of 3112 adolescents, Westman and colleagues estimated the 12-month prevalence of CRS based on questionnaire to be 1.5% and, after clinical follow-up with objective confirmation, to be 0.3–0.8% [2]. Prevalence of radiologically confirmed rhinosinusitis in patients presenting with chronic respiratory complaints is much higher and approaches 30–60% depending on the sinuses involved with younger children having a higher rate of abnormal imaging than older adolescents [3, 4].

The mainstay of treatment of rhinosinusitis in children is medical with nasal saline irrigation, antibiotics, and anti-inflammatory therapy with corticosteroids as the most common therapies. In this chapter, we will present the evidence, when available, that supports the use of these agents in the treatment of both acute and chronic rhinosinusitis in the pediatric age group.

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Intranasal Saline

Acute Rhinosinusitis Saline nasal irrigation has become mainstream in the treatment of rhinosinusitis in adults based on the presumption that it helps to clear debris and secretions from the nasal cavity. There is one trial in children that shows that adding saline versus placebo to decongestants and antibiotics in children with ARS resulted in greater improvement in nasal airflow and quality of life as well as better improvement of total symptom score [5]. Despite the lack of strong evidence, nasal saline irrigations are safe and are recommended if tolerated by the child with ARS.

Chronic Rhinosinusitis A Cochrane review analyzed randomized controlled trials in which saline was evaluated in comparison with either no treatment, a placebo, as an adjunct to other treatments, or against other treatments [6]. Overall there was evidence that saline is beneficial in the treatment of the symptoms of CRS when used as the sole modality of treatment. In a more recent trial, Wei and colleagues enrolled 40 children with CRS in a randomized, prospective, double-blind study comparing once daily irrigation with saline or saline/gentamicin for 6 weeks [7]. There were statistically significant improvements in quality of life scores at 3 and 6 weeks and a reduction of CT scores after 6 weeks in both groups with no significant difference between the groups, suggesting that the addition of gentamicin to saline irrigations provided no additional benefit. Contrary to what parents may think, saline irrigations were well tolerated by more than 80% of children and adolescents and when questioned, over 70% of patients/parents thought there was an improvement in nasal symptoms with irrigation [8]. Based on the above, saline nasal irrigation has become a mainstay of therapy of CRS in the pediatric age group [9].

Antibiotics

Acute Rhinosinusitis In the context of an upper respiratory tract infection, ARS can be diagnosed if there are persistent symptoms for more than 10 days, worsening of symptoms after initial improvement (double sickening), or severe symptoms at onset. The American Academy of Pediatrics guidelines recommend starting antibiotics when there is a severe onset of symptoms or worsening after initial improvement [10]. For persisting symptoms beyond 10 days, the guidelines recommend starting antibiotics or offering another 3 days of observation before doing so as symptoms might improve spontaneously [10]. A meta-analysis of randomized controlled trials evaluating antibiotic treatments for ARS, in which 3 of the 17 evaluated studies were performed in the pediatric age group, shows that antibiotics were associated with a higher rate of cure or improvement compared to placebo [11]. The rate of resolution of symptoms was faster with antibiotics in most randomized controlled trials. There are also a few trials where treatment with antibiotics in patients with ARS shows no added benefit over placebo [12, 13].

When considering antibiotic choices, one should keep in mind that over the past one to two decades, increasing resistance to antimicrobials has emerged among the organisms that are encountered in common upper respiratory infections in the pediatric age group. Furthermore, the routine use since 2000 of the 7-valent and, more recently, the 13-valent pneumococcal conjugate vaccine has been associated with a decrease in recovery of *S. pneumoniae* and an increase in recovery of *H. influenzae* [10, 14]. Extrapolating from what is known related to acute otitis media, it is estimated that *S. pneumoniae* and *H. influenzae* are currently each responsible for 30% of cases of ARS in children and *M. catarrhalis* for approximately 10%, also assuming that a quarter of aspirates, if done, would be sterile [10]. Risk factors for the presence of amoxicillin resistant organisms remain age under 2, recent antibiotic usage (within 30 days) and daycare attendance. Based on the above, the first-line treatment for uncomplicated ARS in a patient without risk factors remains amoxicillin at 45 mg/kg/day administered twice daily. Double that dose can be used in communities with higher incidences of *S. pneumoniae* resistance. In patients with severe disease or with risk factors for resistance, high dose amoxicillin clavulanate is recommended (dosed at 80–90 mg/kg/day of the amoxicillin component) and is also given twice daily. If the child will not tolerate PO antibiotics, ceftriaxone IV or IM at 50 mg/kg/day given as a single dose can be dosed for 1–3 days before switching to PO antibiotics to finish the course. Cephalosporins can be used in case of penicillin allergy and the favorite choices are cefdinir, cefuroxime, or cefpodoxime [15]. In case of lack of responsiveness and the suspicion of resistant organisms, a combination of clindamycin (or linezolid) and cefixime will provide the most comprehensive coverage for resistant *S. pneumoniae* and *H. influenzae*. Quinolones could also be used in exceptional circumstances [16]. Resistance trends of pneumococcus and *H. influenzae* to trimethoprim/sulfamethoxazole and azithromycin render their use unjustifiable in the treatment of ARS in patients with penicillin allergy [17, 18]. Duration of treatment varies widely, and a reasonable length would be for 7 days after the disappearance of symptoms, which usually averages about 10 days of therapy [10].

Chronic Rhinosinusitis There is no good evidence in the literature to support the use of antibiotics for CRS in children. Two clinical trials conducted by the same group do not show significant differences between treatment with placebo and systemic antibiotics in children with clinical criteria commensurate with CRS [19, 20]. The EPOS 2012 guidelines conclude as follows: "available data does not justify the use of short-term oral antibiotics for the treatment of CRS in children (Strength of recommendation: B)" [21]. In contrast, the consensus statement by the American Academy of Otolaryngology-Head and Neck Surgery supported the conclusion that "20 consecutive days of antibiotic therapy may produce a superior clinical response in pediatric CRS patients compared to 10 days of antibiotic therapy" [9]. In general clinical practice, antibiotics are used frequently as part of maximal medical management in children with CRS and treatment durations vary between 2 and 4 weeks. In many of these instances, treatment targets acute exacerbations on top of pre-existing chronic disease. The choice of antibiotics is similar to that described above for ARS.

Intravenous antibiotic therapy for resistant CRS has been advocated as an alternative to surgical intervention. Few studies evaluate this option [22] and they are limited by the presence of multiple variables that make it difficult to ascertain that the positive effect seen in CRS was related to the IV antibiotic use per se. Therefore, intravenous antibiotics are not routinely advocated for the treatment of CRS in children and are essentially reserved to treat the complications of ARS.

Intranasal Corticosteroids

Acute Rhinosinusitis The evidence for using INCS in acute rhinosinusitis is developing. Studies in adults with acute rhinosinusitis suggest that INCS may provide an additive benefit (versus placebo) when used in addition to antibiotic therapy [23, 24].

In the pediatric age group, Barlan et al. conducted a double-blind placebo-controlled trial in 89 children (age 1–15 years) with acute rhinosinusitis [25]. To be included in the study subjects had to have two of three major criteria (purulent nasal discharge, cough, purulent pharyngeal drainage) or one major and two minor criteria (facial pain, periorbital edema, earache, tooth pain, sore throat, headache, increased wheeze, fever, foul breath for more than 7 days). The children also had to have a positive Waters radiograph with complete opacification of the maxillary sinus or mucoperiosteal thickening >4 mm. All were treated with oral antibiotics; 43 also received intranasal budesonide (50 mcg), whereas 46 received a placebo saline spray. Budesonide was associated with greater improvements in nasal discharge and cough by the second week of treatment, but by the end of 4 weeks, both groups had a comparable improvement in symptom scores. In another pediatric study, children with ARS were treated with amoxicillin clavulanate with or without INCS and were stratified according to allergic rhinitis status [26]. There was no added benefit of using INCS in the patients with ARS without allergic rhinitis but in the rhinosinusitis with allergic rhinitis group, using an INCS improved the efficacy over the group with antibiotics alone.

Nayak and colleagues evaluated the effectiveness and safety of mometasone furoate nasal spray (MFNS) at two dose regimens as adjunctive treatment with oral antibiotics for ARS in a mixed population of adults and children (8–78 years of age) [27]. The diagnosis of ARS was made if the patients had purulent rhinorrhea with at least one moderate/severe nasal symptom (purulent rhinorrhea, congestion, post nasal drip, sinus headache, facial pain, cough). They also had to have the diagnosis confirmed by a CT scan. The study was multicenter, double-blind placebo controlled and enrolled 967 outpatients. All participants received amoxicillin/clavulanate for 21 days and either MFNS 200 mcg twice daily, MFNS 400 mcg twice daily or placebo nasal spray as adjunctive therapy. Both doses of MFNS resulted in significantly greater improvements in total symptom score compared to placebo which was significant by Day 4 of therapy and continued to be effective till day 21 of treat-

ment. Of note, is that both doses of MFNS used exceed the recommended dosage for allergic rhinitis in adults (200 mcg once daily) and children under age 12 years (100 mcg once daily).

To investigate the efficacy of INCS as monotherapy for ARS, Meltzer and colleagues conducted a randomized, placebo-controlled, double-blind, double-dummy trial in 981 patients older than 12 years with ARS [28]. Subjects were randomized to MFNS 200 mcg once daily or twice daily for 15 days, amoxicillin 500 mg three times daily for 10 days, or respective placebo. Subjects were recruited based on having uncomplicated rhinosinusitis based on symptoms (rhinorrhea, postnasal drip, nasal congestion/stuffiness, sinus headache, and facial pain/pressure/tenderness on palpation over the paranasal sinuses) for more than 7 days. The primary endpoint was mean (AM/PM) major symptom score over the 15-day treatment period. Mometasone furoate nasal spray 200 mcg twice daily (twice the allergic rhinitis dose) was significantly superior to placebo and amoxicillin at improving major symptom score. Starting on day 2, MFNS 200 mcg twice daily improved total symptom score throughout treatment versus amoxicillin and placebo. Although significantly superior to placebo, MFNS 200 mcg once daily was not superior to amoxicillin for the primary or secondary efficacy endpoints. In this study, amoxicillin was not shown to be more effective than placebo in controlling major symptom scores, a fact that has been previously demonstrated in placebo-controlled studies performed in both adults [29] and children [13].

In another prospective, randomized trial, children with ARS were treated with either antibiotics (amoxicillin clavulanate) and intranasal decongestants (xylometazoline) for 2 weeks ($n = 45$), or large volume low pressure nasal saline + fluticasone propionate combination (400 mcg of fluticasone diluted in 120 ml of saline twice daily) for 3 weeks ($n = 46$) [30]. Children in both treatment groups improved at the 21-day time point compared to baseline, and there were no significant differences between the groups in clinical scores, nasal peak inspiratory flow, or the radiologic resolution of ARS by Waters views.

Symptom scores tended to improve more quickly in the steroid irrigation group as a reduction from baseline was statistically significant at the 7-day time point whereas the antibiotic group symptom scores achieved significance compared to baseline at day 14. The only concern with this study is the use of saline irrigation in one arm but not in the other as it is conceivable that the more rapid improvement in the group with saline/steroid irrigations occurred because of the mechanical clearance effect of saline irrigation, not that of the intranasal steroid. Indeed, in children with CRS, saline nasal irrigation alone has been shown to be effective in resolving symptoms and CT findings of disease and the addition of gentamicin to the irrigation did not yield additional benefit [7].

Thus, there is some evidence in children that INCS are effective as adjuvants to antibiotics in the treatment of uncomplicated ARS, with one study showing the benefit specific to patients with concomitant allergic rhinitis. In studies including older children and adults, again the benefit of adding INCS to antibiotics was demonstrated but the doses of INCS used were higher than those approved for the treatment of allergic rhinitis in the pediatric age group. Finally, there is some evidence

supporting a high dose of INCS as monotherapy in patients with uncomplicated ARS. However, generalizing these conclusions to younger children is not justified in the absence of more evidence.

Chronic Rhinosinusitis INCS have become an important aspect of the treatment algorithm in light of increasing recognition of inflammation in the etiology of CRS. In a recent survey of pediatric otolaryngologists, Beswick and colleagues reported that 96% used nasal steroid sprays, 93% nasal saline irrigations, 91% oral antibiotics, and 43% oral steroids for maximal medical management of CRS in children [31]. In a similar survey of members of the American Rhinologic Society, the most frequently used therapies for maximal medical management of CRS in children were saline irrigation (97%), intranasal steroids (98%), oral antibiotics (90%), and oral steroids (72%) [32].

A Cochrane review evaluated the efficacy of intranasal steroids in CRS [33]. Eighteen randomized, controlled trials were included, with a total of 2738 participants. Fourteen studies had participants with nasal polyps and four studies had participants without nasal polyps. Only one study was conducted in children. Therefore, most evidence is inferred from patients with nasal polyps and does show some improvement in favor of intranasal steroids, especially as relates to the symptom of nasal congestion. The pediatric study included in this Cochrane review was primarily evaluating the safety of mometasone furoate nasal spray (MFNS) in children with nasal polyps [34]. Subjects aged 6–11 years with bilateral nasal polyps received MFNS 100 mcg once or twice daily or placebo; those aged 12–17 years received MFNS 200 mcg once or twice daily or placebo. Safety measures included a change in 24-h urinary free cortisol from baseline and change in 24-h urinary free cortisol. There were no differences between the treatment groups or placebo attesting to the safety of the intranasal steroid. Although the study was not powered for efficacy, information about polyp size, nasal symptoms, and investigator-evaluated therapeutic response was reported. MFNS given twice daily was associated with the greatest response in polyp size, congestion, and anterior rhinorrhea/postnasal drip. Groups that received MFNS once and twice daily showed numerically greater improvement in congestion compared with placebo. Moreover, subjects who received MFNS twice daily had better investigator assessed therapeutic response compared with those who received a placebo.

In the United States, it is the author's experience that most children with CRS present without nasal polyposis and the most frequent presentation of nasal polyps in children is in the context of cystic fibrosis or allergic fungal rhinosinusitis. Thus, the data from the above study are not very applicable to the typical presentation of pediatric CRS in the United States. However, the efficacy of INCS in CRS with/without polyps in adults, as well as their favorable safety profile, supports the recommendation that they be part of first-line therapy in children with CRS [9, 21].

Safety of INCS Most of the data available about the safety of INCS are from studies in patients with allergic rhinitis. The most common side effects are a result of local irritation and include dryness, burning, stinging, blood tinged secretions, and

epistaxis. The incidence of epistaxis with different preparations ranges from 4% to 8% over short treatment periods (2–12 weeks) with no differences between placebo and active therapy [35, 36]. In studies carried over a year, epistaxis is as high as 20% [37, 38]. Septal perforations are rare complications of INCS [39]. A systematic review of 34 published articles looking at biopsy studies in patients with allergic rhinitis or CRS using INCS did not show evidence of atrophy but a significant reduction in the odds ratio for the development of squamous metaplasia in patients using INCS, suggesting a favorable effect [40]. Studies in adults and children evaluating effects of INCS on the hypothalamic pituitary axis show no adverse effects [38, 41–52]. Although there has been a report of an association between the use of INCS and the development of posterior subcapsular cataracts [53], a systematic review of controlled trials did not demonstrate a clinically relevant impact of INCS on either ocular pressure, glaucoma, lens opacity, or cataract formation [54]. The effect of INCS on children's growth has been investigated in controlled studies using both knemometry in short-term studies (2–4 weeks) and stadiometry in long-term (12 months) studies. A meta-analysis of eight randomized controlled trials with appropriate controls showed that, compared to children using placebo, mean growth was significantly lower among children using INCS in trials using knemometry ($n = 4$) and that there was no significant growth difference in studies using stadiometry ($n = 4$) [55]. The data suggest that INCS might have deleterious effects on short-term growth in children, but the heterogeneity in the stadiometry studies makes the effects on long-term growth suppression unclear. Therefore, when using INCS in younger children, it is advisable to use the newer preparations that have been approved for the younger age groups (mometasone, fluticasone) and monitor growth carefully.

Systemic Steroids

Systemic steroids have also been used in children with CRS because of their potent anti-inflammatory properties. Ozturk and colleagues treated children with CRS with amoxicillin clavulanate for 30 days and with either a prednisone taper course for 15 days or placebo [56]. The steroid taper was given at the beginning of therapy. Compared to placebo, treatment with steroids resulted in significant improvements in CT scan score as well as symptoms of cough, nasal obstruction, postnasal discharge and total symptom score. In another study, primarily performed to evaluate mechanisms of inflammation in CRS, 30 children with asthma and CRS (mean age 9.1 years) were studied prospectively [57]. Sixteen were allergic and 14 were nonallergic. CRS diagnosis was confirmed by endoscopy showing purulence in the osteomeatal unit. All children were treated with amoxicillin-clavulanate and fluticasone propionate aqueous nasal spray (100 mcg daily) for 14 days; as well as a short taper course of oral corticosteroids for 10 days (deflazacort 1 mg/kg daily for 2 days, 0.5 mg/kg daily for 4 days, and 0.25 mg/kg daily for 4 days). Nasal lavage cytokine levels and cytology were evaluated before and after therapy. The results showed

normalized endoscopy in 25 children after treatment, a reduction in levels of IL4 in nasal lavages, as well as a significant reduction of the nasal inflammatory infiltrate in all the children. Although this study showed an improvement in clinical CRS after therapy, it is hard to glean the relative efficacy of systemic steroid administration as there was no placebo group and multiple other therapies were administered concomitantly. Therefore, evidence is scarce in support of systemic steroids in the treatment of CRS in the pediatric age group but using short courses is often added to other standard therapies.

In summary, corticosteroids are potent anti-inflammatory agents and are commonly utilized as adjuncts in the treatment of ARS and CRS in children. Antibiotics are frequently utilized and saline irrigations should be routinely included in the treatment of the child with chronic sinus problems.

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