



Pediatric Versus Adult Chronic Rhinosinusitis

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Abstract

Purpose of Review Pediatric and adult chronic rhinosinusitis (CRS) have some similarities but a number of differences. This article reviews the similarities and differences between pediatric and adult CRS.

Recent Findings Rhinosinusitis is an inflammatory disease of the nose and the paranasal sinuses. In adults, inflammation in CRS without polyps (CRSsNP) mainly manifests with T-helper 1 lymphocytes while in CRS with polyps (CRSwNP) manifests with T-helper 2 lymphocytes and eosinophilic inflammation. In children, CRS inflammation manifests with neutrophils, macrophages, and lymphocytes. The associations between the ostiomeatal complex occlusion and CRS are revealed in adults but are not so evident in children. Although the relationship between the CRS and allergic rhinitis is still controversial, recent findings have shown an association between allergen sensitization and a specific group of adults with rhinosinusitis. Intranasal corticosteroids and saline constitute the first-line of medical treatment for both pediatric and adult rhinosinusitis. Low-dose macrolides are used for immunomodulatory activities and beneficial effects to adult patients with CRSsNP were demonstrated by recent meta-analyses. For surgical treatment, adenoidectomy is a key strategy to eradicate mature biofilms in pediatric CRS and effective in treating children with CRS regardless of the adenoid size. Although endoscopic sinus surgery has been proven to improve quality of life outcomes in adult CRS, it should be only considered in the pediatric CRS after failure of adenoidectomy.

Summary Pediatric and adult CRS are different in many aspects, including immunopathogenesis and management. Investigations should be considered in specific cases. After failure of medical treatments, endoscopic sinus surgery is recommended for adults, while adenoidectomy is primarily considered for children.

Keywords Children · Adults · Intranasal corticosteroids · Saline · Adenoidectomy · Endoscopic sinus surgery

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Introduction

Rhinosinusitis is an inflammatory disease of the nose and the paranasal sinuses. It is a major health problem which causes a significant financial burden on society [1]. Chronic rhinosinusitis (CRS) is common in both pediatric and adult populations and more prevalent than acute rhinosinusitis in all age groups [2]. Although the presenting symptoms of CRS are similar, pediatric and adult CRS are different in many aspects. Pediatric CRS commonly eludes diagnosis [3••] and carries significant morbidity [4]. Knowledge gained from the literature published has been updated by the EPOS2020 position paper [5] and shows that knowledge in adult CRS cannot be applied to pediatric CRS patients in clinical practice and vice versa. This article reviews the similarities and the differences of the anatomy, epidemiology, immunopathogenesis, cause, comorbidities, clinical presentation, medical management, and surgical management between the pediatric and adult CRS.

Recent findings

Differences in the Anatomy of the Upper Airway

Development of the Paranasal Sinuses

The paranasal sinuses develop, at the eighth week of gestation, from the ethmoturbinals which are a series of ridges and folds on the lateral nasal wall. Around threefold to fourfold persist from the initial sixfold to sevenfold. The paranasal sinuses are formed by pneumatic extensions of the nasal cavity walls in the adjacent bones [6] and they grow rapidly during the first 3 years of life then grow slowly until the age of 7–12 years [7]. The maxillary sinuses are already present at birth, their floor reaching the nasal floor level by the age of 9 years. After a full pneumatization, the floor of adult maxillary sinus extends to about 1 cm below the level of the nasal cavity floor. The roof of the maxillary sinus slopes infero-laterally during childhood. When pneumatization progresses, the slope gradually becomes more horizontal in adulthood. The size ratio between maxillary and ethmoid sinuses is greater in childhood (2:1) compared with adulthood (4:5).

The ethmoid sinuses are formed by invaginations of the mucous membrane of the middle and superior nasal meatus into the ethmoid bone. They are also present at birth but not visible in plain X-rays until 2 years of age. The ethmoid sinuses begin to grow rapidly around 6 to 8 years of age [6] being fully mature at 12–14 years old. Anatomical variations in ethmoid air cells are common in adults but rare in children. Abnormal developments of ethmoid air cell include Haller, supraorbital, Onodi, supra agger, supra agger-frontal cell, and supra bulla-frontal and fronto-septal cells. The frontal sinuses are absent in neonates. Around 2 years of age, the most anterior ethmoidal cells of each side grow into the frontal bone, forming a frontal sinus of that side. The frontal sinuses are usually visible in plain X-rays by the age of 7 years [6] and fully developed at 12–14 years. Adults however may have unilateral or bilateral undeveloped frontal sinuses. The sphenoid sinuses are also absent in neonates. Pneumatization of sphenoid bone starts at 3–4 years. The most posterior ethmoidal cells of each side grow into the sphenoid bone forming a sphenoid sinus of that side [6] and the sinuses develop rapidly during the first 6–7 years of life and fully developed at 9–12 years old.

Differences between the anatomy of pediatric and adult paranasal sinuses raise several concerns regarding the comprehensive management of rhinosinusitis. In fact, poor pneumatization of the paranasal sinuses does not cause chronic refractory inflammation as long as the sinus outflow tracts are patent. Well-pneumatized paranasal sinuses may have poor ventilation and ineffective drainage. For example, highly pneumatized air cells around the opening may cause ineffective drainage resulting in chronic rhinosinusitis. Poorly

pneumatized paranasal sinuses are more difficult to approach in non-responsive or complicated rhinosinusitis that requires endoscopic sinus surgery. For example, if the ostia of poorly aerated maxillary sinuses are close to the orbital wall, the orbit may be injured during the operation. Another common complication is an injury of the lateral lamella of the cribriform plate during ethmoidectomy which may cause cerebrospinal fluid leakage. Injuries of the optic nerve and internal carotid artery are major complications of a difficult sphenoid sinus surgery. In addition, anatomical correction of poorly pneumatized paranasal sinuses may lead to a difficult sinus surgery causing fibrosis, scars, and poor outcomes. For instance, frontal sinusostomy may become a permanent stricture as a result of an inadequate operation.

Role of Adenoids in Rhinosinusitis

The adenoids are lymphoid tissue which form part of the Waldeyer ring. Adenoid enlargement continues until 5 to 7 years old. As the pharyngeal airway of the pediatric population is relatively narrow and the adenoids are close to the paranasal sinuses, adenoid hypertrophy may cause a bottleneck obstruction and compromise the drainage of postnasal discharge at the nasopharynx. The role of adenoids in pediatric rhinosinusitis has been demonstrated in many studies. Adenoid tissue was shown to be a bacterial reservoir that contains bacteria identical to the etiopathogenic bacteria of pediatric rhinosinusitis. Davcheva-Chakar et al. [8] found positive cultures in all adenoid tissue specimens from patients with recurrent rhinosinusitis. *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis* were the bacteria isolated in the adenoid specimens. Likewise, Elwany et al. [9] assessed the correlation between the microbiology of adenoid core specimens and middle meatal swabs in pediatric patients with rhinosinusitis. Adenoid core culture had a positive predictive value of 91.5% and a negative predictive value of 84.3% in forecasting the middle meatal culture. In addition, biofilms are more common in children with CRS than healthy children and children with ARS. A study of biofilms using electron microscopy was performed by Zuliani et al. [10] Mature biofilms were found in 95% of adenoids removed from patients with CRS, compared with 2% from patients with obstructive sleep apnea. These studies revealed the role of adenoids as a bacterial reservoir which may cause a higher chance of negative bacterial culture and resistance to antibiotics therapy. Thus, adenoidectomy has a potential role in the treatment of chronic or recurrent pediatric rhinosinusitis. Currently, numerous strategies are being utilized to eradicate the established biofilms of respiratory pathogens, including selective and non-selective inhibitors of adhesion. Adenoid removal is an effective strategy regardless of the adenoid size [11]. Shin et al. [12] retrospectively assessed adenoid microbiology and found that the bacterial isolation rate was

increased in association with rhinosinusitis severity but not with adenoid size.

Epidemiology

Despite the growing knowledge in clinical diagnosis and treatment, the epidemiology of both adult and pediatric CRS is difficult to assess. Because CRS is a heterogeneous disease, the diagnostic criteria used in different studies are varied. Nasal endoscopy and/or imaging and adequate evaluation of follow-up patients were not possible in most studies. In general, the prevalence of CRS in children is around 5–15% [13] compared with the prevalence of 11–12.8% in adults [14, 15]. The findings from different reports are varied because different questionnaires were used. The EPOS diagnostic criteria [2] was used in a questionnaire, conducted by the GA(2)LEN network of excellence [16], and the prevalence of CRS for Europe was estimated around 11%. This was highly correlated with the prevalence of physician-diagnosed CRS. Sami and Scadding [17] used the MSNOT-20 Young Persons Questionnaire (MSYPQ), a validated disease-specific quality of life questionnaire, to assess 213 adolescents in East London. Rhinosinusitis symptoms were reported by 13–15% of the participants which was comparable with an adult population. In contrast, Westman et al. [18] reported a low prevalence of CRS in adolescents from a Swedish population-based study. Based on the children's criteria from The European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) [2], 2% of 3112 adolescents reported symptoms of CRS by questionnaires. When these adolescents were interviewed, the prevalence was 0.8% calculated by symptoms criteria and 0.3% by endoscopic criteria. When a prevalence was calculated by using the diagnosis by physicians and procedure codes for medical encounters from national survey databases, the prevalence of CRS was lower than the prevalence calculated by questionnaires in both children and adults. The prevalence of adult CRS was only 2% when the ICD-9 codes from the diagnosis by physicians were used [19]. Sidell et al. [20] reported a prevalence of children with CRS at 4% by using the Medical Expenditure Panel Survey. Likewise, Gilani and Shin [21] assessed patient's doctor visits from national survey databases and identified that 2.1% of the visits were diagnosed with pediatric CRS. Children in the age group of 5 to 15-year-old were the most affected.

Nasal endoscopy is required to assess the prevalence of CRS with nasal polyps (CRSwNP) in epidemiologic studies. Johansson et al. [22] estimated a 2.7% prevalence of adult nasal polyps by endoscopy in a Swedish population. Min et al. [23] also used nasal endoscopy from a nationwide survey in Korea and estimated a prevalence of adult CRSwNP at 0.5%. CRSwNP is uncommon in children. The average age of onset was around 42 years old [24].

The impact of CRS on quality of life (QOL), particularly physical and psychosocial functioning domains, was assessed in children along with their parents. Children with CRS had severely impaired general health, especially in the physical domain. The physical impairments may be related to missing classes, impairments of concentration in school, sleep quality, and physical and emotional health. Body pain and physical limitations were higher in children with CRS than children with asthma, attention deficit hyperactivity disorder, juvenile rheumatoid arthritis, and epilepsy [25]. QOL is also impaired in adult CRS [26].

Causes and Mechanisms of Action

The Ostiomeatal Complex Occlusion

CRS is a heterogeneous chronic inflammatory disease with various causes and mechanisms of action with internal and external factors. In adults, the ostiomeatal complex occlusion is associated with the pathogenesis of rhinosinusitis. Anatomical obstruction of this functional unit affects the ventilation and drainage of the sinuses and results in chronic inflammation of the nose and paranasal sinuses [27]. In children, there are anatomical variations that causing ostiomeatal complex occlusion. The Agger nasi cell is the most common anatomical variation [28, 29], followed by septal deviation, Haller cell, concha bullosa, paradoxical middle turbinate, and Onodi cell. In contrast to the adults, the ostiomeatal complex occlusion in the pediatric age group is not associated with the extent and severity of CRS. Haruna et al. [30] assessed CT scans of 95 children and did not find any relationship between the presence of concha bullosa and pediatric rhinosinusitis. Al-Qudah [28] studied anatomical variations from CT scans of 65 children with CRS and failed to show an association between the presence of anatomical variation and the extent of rhinosinusitis. Likewise, Kim et al. [29] showed no relationship between rhinosinusitis and anatomical variations in 113 children with CRS. Instead, the most common anatomical obstruction of the pediatric population is hypertrophic adenoid causing a bottle-neck obstruction [30, 31].

Underlying Inflammatory Mechanisms

Inflammatory patterns of adult CRS, CRSwNP and CRSsNP, and pediatric CRS are different. In adults, patients with CRSsNP mainly manifest with type 1 response which cause an increase in the amount of transforming growth factor (TGF)- β , interleukin (IL)-2, and IL-10. Patients with CRSwNP show a predominance of type 2 inflammation [2, 32] with an increase of innate lymphoid cells (ILC2), Th2 lymphocytes, goblet cells, mast cells, and eosinophils, resulting in an increased production of IL-4, IL-13, IL-5, and specific immunoglobulin E (IgE) to staphylococcal

enterotoxins [13]. Tissue eosinophilia is closely related to CRSwNP severity. In addition, patients with eosinophilic polyps are significantly associated with squamous metaplasia and tissue remodeling [33]. Tissue eosinophilia is however uncommon in pediatric CRS patients, having increased tissue lymphocytes, CD8+, MPO+, and CD68+ cells in the epithelium, and more CD20+, kappa+, lambda+, MPO+, and CD68+ cells (representing increased number of neutrophils, macrophages, B lymphocytes, and plasma cells) in the submucosa [34]. Epithelium and basement membrane thickening were not found in pediatric patients.

Allergic Rhinitis

Allergic rhinitis is still a current controversial issue for both pediatric and adult CRS. Allergic inflammation of the nasal mucosa causes nasal congestion and impairs mucociliary function which decreases the clearance of proinflammatory agents. Hamizan et al. [35] assessed allergy tests of 120 patients with adult CRS. The results showed an association between inhalant allergen sensitization and a specific group of patients who had soft tissue thickening of the central portion of the nose and paranasal sinuses and spared the sinus roof or lateral wall. Tantimongkolsuk et al. [36] assessed allergy tests of 100 pediatric patients with CRS and reported a high prevalence of positive inhalant allergen sensitization of 53.6%. Likewise, Anamika et al. [37•] reported a prevalence of 52.7% for allergic rhinitis among pediatric CRS patients. In contrast, two large series by Leo et al. [38] and Sedaghat et al. [39] showed that the prevalence of atopy in pediatric CRS (27–29%) was equivalent to the general pediatric population. In addition, a prevalence of CRS was not different among allergic (61%) and non-allergic (64%) children [40]. However, the presence of allergic rhinitis is not correlated with the severity of CRS [41]. Increased allergen sensitization associated with impact of QOL has been also found in CRS with nasal polyps [42, 43].

Immunodeficiency

CRS may be the presenting symptom for primary immunodeficiencies which affect the humoral or the cellular immune system [44]. The immune system in children is not fully developed. Evidence of humoral immune dysfunction among pediatric CRS patients includes low IgG and its subclasses, low IgA, and poor response to pneumococcal vaccine. Baek et al. [45] assessed 16 children with either CRS or recurrent rhinosinusitis. Nine patients had immune dysfunction including IgG subclasses deficiency (4 patients) and poor response to a pneumococcal vaccine (5 patients). Likewise, Shapiro et al. [46] identified 34 of 61 pediatric patients with refractory CRS that had abnormal results on immune studies. When the prevalence of humoral immunodeficiency was compared

between the children and adult CRS, Vanlerberghe et al. [47] found no significant difference between the adults and children. The prevalence was 22% of 307 patients with refractory rhinosinusitis. Ramesh et al. [48] treated six pediatric patients with refractory CRS with intravenous IgG for 1 year. There were improvements after the treatment such as a decrease in duration of antibiotic treatment, a reduction in episodes of rhinosinusitis, and improvements in radiographic findings.

Cystic Fibrosis

Cystic fibrosis (CF) is an autosomal recessive disease characterized by thick viscous secretions in the respiratory tract, nasal polyps, recurrent respiratory infections, gastrointestinal abnormalities, and poor weight gain. *P. aeruginosa* and *S. aureus* are the most common microorganisms which affect the nose and paranasal sinuses [49]. Diagnosis should be confirmed by abnormally elevated sweat chloride levels and an abnormality in the CF transmembrane conductance regulator (CFTR) gene or protein [50]. Computed tomography shows an expansion of the paranasal sinuses (pseudomucocele of the maxillary sinuses) and hypo-development of the frontal and sphenoidal sinuses without evidence of bone erosion. Physicians should have a high index of suspicion for CF when treating pediatric patients with CRSwNP [2].

Primary Ciliary Dyskinesia

Primary ciliary dyskinesia (PCD) is an autosomal recessive disease. Patients with PCD have defects in ciliary beating with impaired mucociliary clearance. Clinical presentations are recurrent infections of the paranasal sinuses and the middle ears, situs inversus totalis (50%), situs ambiguous (12%), and infertility (50%) [51, 52]. Physical examinations of the respiratory tract show purulent nasal discharge, nasal polyps (18–33%) with decreased pulmonary function. Fifty percent of patients with PCD have Kartagener's syndrome which is a triad of rhinosinusitis, chronic bronchitis with bronchiectasis, and situs inversus [52]. Diagnosis should be confirmed by a lower nasal nitric oxide level, prolonged mucociliary transit times by the saccharin test, a lack of the outer dynein arms in cilia on electron microscopy, or a combined lack of both inner and outer dynein arms and genetic testing [53].

Contributing factors of pediatric and adult chronic rhinosinusitis are summarized in Table 1.

Clinical Presentations and Diagnosis

The European Position Paper on Rhinosinusitis and Nasal Polyps 2020 [2] defined rhinosinusitis as the presence of two or more out of four characteristic symptoms. The four symptoms criteria for adult and pediatric rhinosinusitis are slightly different. The criteria for adults are nasal blockage, nasal

Table 1 Contributing factors of pediatric and adult chronic rhinosinusitis

Contributive factor	Pediatric CRS ^a	Adult CRS ^a
Frequent viral URTIs ^b	+	ND
Small sinus ostia	+	ND
Anatomic sinus abnormalities	±	±
Immaturity of the humoral immune system	+	ND
Biofilm formation in sinus tissue	+	+
Enlarged adenoidal pads harboring biofilm	+	ND
Allergy	+	+
Defects in mucociliary clearance	±	±

– no or not present; ± controversial data; + yes or present; *ND* no data, *CRS* chronic rhinosinusitis, *CRSsNP* chronic rhinosinusitis without polyps, *CRSwNP* chronic rhinosinusitis with polyps, *N-ERD* nonsteroidal anti-inflammatory drug–exacerbated respiratory disease

^a Chronic rhinosinusitis

^b Upper respiratory tract infections

Fig. 1 Stepwise treatment algorithm in pediatric and adult chronic rhinosinusitis

<i>Stepwise treatment algorithm in pediatric versus adult chronic rhinosinusitis</i>	
<i>Pediatric</i>	<i>Adult</i>
STEP 1: First line medications	
- Intranasal corticosteroids - Nasal saline irrigation - Antibiotics for CRS with acute exacerbation	- Intranasal corticosteroids - Nasal saline irrigation - Antibiotics for CRS with acute exacerbation
STEP 2: Second line medications	
- Increased doses of Intranasal corticosteroids - Short course of systemic corticosteroids (optional)	- Increased doses of Intranasal corticosteroids - Long-term low-dose macrolides (for CRSsNP) - Short course of systemic corticosteroids (for CRSwNP) - Doxycycline (optional for CRSwNP) - Biologic agents (optional for refractory CRSwNP) - Aspirin desensitization (for N-ERD)
STEP 3: Surgery	
- Adenoidectomy ± middle meatal irrigation - Endoscopic surgery if adenoidectomy failure	- Endoscopic sinus surgery
STEP 4: After Surgery	
- Nasal saline irrigation - Intranasal corticosteroids	- Nasal saline irrigation - Intranasal corticosteroids - Consider long-term low-dose macrolides (for CRSsNP) - Consider biologic agents (for refractory CRSwNP) - Consider Aspirin desensitization (for N-ERD)

discharge, facial pain/pressure, and reduction of smell. The reduction of smell is replaced by cough in children [3•]. This is supported by a study which assessed clinical characteristics of pediatric CRS by Poachanukoon et al. [54]. They found that the most common complaints were cough (45%) and rhinorrhea (37%) and the most common presenting symptoms were rhinorrhea (96%) and cough (88%). Productive cough was more common (75%) and mostly occurred at night (71%). In small children, cough is commonly followed by vomiting. Periorbital pain and sleep apnea were less common. The sense of smell could not be assessed in 30% of the children especially children under 5 years old. For those who could be evaluated, smell dysfunction was found in 3%. Only a few numbers of pediatric CRS patients presented with nasal polyps. Children presenting with nasal polyps carry a substantially increased risk of underlying cystic fibrosis; therefore, investigations for CF diagnosis should be assessed in these children. Pediatric CRS is difficult to diagnose in clinical practice because most children present with more nonspecific and subtle symptoms than adults. Moreover, physical examinations may be unremarkable or difficult to perform nasal endoscopy because most children cannot tolerate the procedure.

In contrast, the most prominent symptoms in adult rhinosinusitis are hyposmia (79%) or anosmia [5, 55], followed by postnasal discharge (76%), nasal obstruction (72%), and discolored nasal discharge (64%) [56]. About half of the adult with CRS have facial pain and pressure (47%), and cough (55%). Symptom-based definition of CRS according to the EPOS criteria [2] has moderate reliability which may require further investigations such as nasal endoscopy and computed tomography. A prospective observational study by Ferguson et al. [56] assessed 125 adult patients presenting with symptoms suggesting CRS. Sixty percent of the patients had abnormal computed tomography. In the same way, Tomassen et al. [57] assessed the data from the GA2LEN European survey and found that 62% of the subjects having CRS symptoms had positive nasal endoscopy.

The diagnosis of CRS is primarily based on clinical manifestations. The diagnostic criteria in both children and adults are the presence of rhinosinusitis symptoms that last longer than 12 weeks in association with endoscopic or imaging signs. However, nasal endoscopy is not tolerable in most children and the sinus radiographs are insensitive, causing both false positive and false negative results. Additionally, the sinus radiographs are technically difficult when children are uncooperative subsequently causing incorrect positioning. A computed tomography is necessary only for presurgical evaluation [58].

Management of Rhinosinusitis

Medical therapy is the mainstay of management of both adult and pediatric CRS. The most common medications are antibiotics, intranasal corticosteroids, and nasal saline irrigation.

Although the medications for all age groups are similar, physicians should be aware that the adult and pediatric CRS are different in the pathogenesis, inflammatory pattern, and comorbidities. Surgery is considered when the patients do not respond to medications (Fig. 1). Endoscopic sinus surgery is suggested for adult patients but should be only considered in the pediatric CRS after failure of adenoidectomy.

Antibiotics

Antibiotics are commonly used in both pediatric and adult CRS. However, the duration of antibiotic treatment is varied depending on indications. Short-term and long-term uses of antibiotics are given with different aims such as for anti-infectious or anti-inflammatory purpose. CRS is a multifactorial inflammatory disorder rather than a persistent infection. In general, a short-term antibiotic treatment, defined as a treatment duration of 3 weeks or less, is aimed for the treatment of pathogenic infections. Thus, a short-term antibiotic should be prescribed for an acute exacerbation of CRS [59]. However, several randomized controlled trials did not show clinical benefits of a short-term antibiotic treatment in both adult and pediatric CRS [2]. One randomized controlled trial by Sabino et al. [60] studied 33 adult patients with an acute exacerbation of CRS. The patients received either amoxicillin/clavulanate or placebo added to mometasone furoate and nasal saline irrigation for 2 weeks. Both groups had similar clinical improvements in symptoms, QOL, and nasal endoscopy findings despite antibiotics susceptibility. Another randomized controlled trial by Otten et al. [61] studied 75 children with CRS between the ages of 2 and 12 who received either a 1-week course of 20 mg/kg/day cefaclor or placebo after an antral wash out. After 6 weeks, there was no difference in the numbers of patients with improved radiographic findings. The role of intravenous antibiotics in routine pediatric CRS is unclear [3•]. A retrospective study by Adappa et al. [62] showed that intravenous antibiotics reduced the rate of adenoidectomy in some children with refractory CRS.

Long-term low-dose macrolides have immune-modulating properties that modulate neutrophilic action by suppressing pro-inflammatory cytokines, such as interleukin (IL)-8 and tumor necrosis factor-alpha (TNF- α). In addition, they alter mucus rheological properties and promote effective mucociliary clearance [63•]. Ten randomized controlled trials assessed the effects of long-term low-dose macrolides for treating adult CRS and reported mixed results. A recent meta-analysis together with subgroup analyses by Seresirikachorn et al. [63•] showed benefits of a long-term macrolide in patients with CRSsNP using half dosage for 24 weeks. While there is evidence supporting the use of the long-term low-dose macrolides in adult CRS, the evidence in pediatric CRS is inconclusive. Iino et al. [64] conducted a clinical trial giving a low-dose clarithromycin to children with CRS and/or otitis media with

effusion for at least 8 weeks and reported a 63% success rate. However, this study did not compare the success rate between the treatment group and the control group. Another clinical trial assessed the effects of long-term antibiotics in pediatric CRS which included amoxicillin/clavulanic acid and second or third generation of cephalosporin for 12 weeks [65]. The long-term antibiotics in this study were aimed for bacteriologic eradication but there was no control group in the study. Thus, beneficial effects of long-term antibiotics could not be concluded. Doxycycline has dual antimicrobial and anti-inflammatory properties which impact CRSwNP treatments. The EPOS recommends doxycycline as a treatment option for patients with moderate CRSwNP [13]. A clinical trial by Van Zele et al. [66] demonstrated the effects of doxycycline on reducing polyp size and patient symptoms.

In summary, bacteriologic eradication properties of short-term antibiotics are not yet recommended for treating both adult and pediatric CRS. However, short-term antibiotics are suggested for CRS with acute exacerbation. The immunomodulating properties of long-term low-dose macrolides are effective for adult CRSsNP but their benefits are not yet evident for adult CRSwNP and pediatric CRS.

Corticosteroids

Although chronic inflammatory pattern in the CRS is heterogeneous, corticosteroids are effective anti-inflammatory agents for all CRS subtypes. Beneficial effects of intranasal corticosteroids on nasal symptoms and QOL improvement have been revealed by a systematic review and meta-analysis [67]. For adult CRSwNP, intranasal corticosteroids decrease the polyps size and reduce the recurrence of polyps after endoscopic sinus surgery [68]. They are safe and well tolerated. For pediatric CRS, only one randomized controlled trial assessed the safety of intranasal corticosteroids [69]. There is no evidence that supports the efficacy of intranasal steroids in pediatric CRS. Therefore, the recommendation of intranasal corticosteroids for treating pediatric CRS is mainly based on studies performed in adults [3••].

Due to the potent anti-inflammatory properties, a short course of systemic corticosteroid can be used for treating severe adult CRSwNP and pediatric CRSsNP patients [2]. In adults, there are 5 double-blind, randomized, placebo-controlled trials assessing the effects of short course oral corticosteroid for 7–20 days in patients with CRSwNP. Oral corticosteroids significantly reduced total symptom scores and nasal polyp scores. There are no trials evaluating the effects on patients with CRSsNP. In children, one randomized controlled trial by Ozturk et al. [70] studied 45 pediatric CRS patients receiving either oral methylprednisolone with a tapering schedule for 30 days or placebo added to amoxicillin/clavulanate. The patients receiving oral methylprednisolone had greater improvements on total symptoms scores, nasal

obstruction, postnasal discharge, cough, and computed tomography. Although beneficial effects were shown, severe adverse effects can occur and outweigh advantages of therapeutic value in the long term for routinely treating patients with CRS [71].

In summary, corticosteroids are the mainstay of medical treatment due to the recognition of inflammation etiology of both pediatric and adult CRS [2, 59]. Intranasal corticosteroids are effective on nasal symptoms, QOL improvement, and polyp size reduction. Systemic corticosteroids can be used as an option for a short-term treatment in severe CRSwNP.

Nasal Saline Treatment

Nasal saline treatment aims for mechanical clearance of thick mucus and inflammation mediators and improving mucociliary function. Taccariello et al. [72] assessed nasal saline irrigation and sea water spray versus no saline treatment in adult CRSsNP patients and demonstrated that the saline group had significant improvements in the quality of life and endoscopic findings. To date, there are ten randomized controlled trials evaluating the effects of nasal saline treatment for adult patients with CRSsNP but none for CRSwNP. The recommendations of nasal saline treatment for CRSwNP relied on those studies of CRSsNP and are based on the effective clearance by normal saline treatment. As for pediatric CRS, there are three randomized controlled trials showing benefits of saline treatment in both the sole modality and adjunction treatments. Although there are randomized controlled trials comparing saline treatment with hypertonic saline [73], hypochlorous acid [74], and gentamicin irrigation [75], there is no well-conducted study which compares saline with no saline treatments.

In summary, nasal saline treatment is suggested for both adult and pediatric CRS for effective clearance of thick nasal secretion [2, 3••, 59].

Adenoidectomy

Adenoids are acknowledged as a bacterial biofilm reservoir. Hypertrophic adenoids can cause an obstruction of the nasal discharge drainage. Therefore, adenoidectomy becomes the first-line surgical treatment for pediatric refractory CRS patients. Bettadahalli et al. [76] reported an improvement in QOL in 88% of children with refractory CRS after adenoidectomy. A meta-analysis by Brietzke et al. [77] pooled data from 8 studies and showed an overall success rate of 69%. The previously failed adenoidectomy required subsequent endoscopic sinus surgery. These patients were associated with asthma or age less than 7 years [78]. Maxillary sinus antral wash out together with adenoidectomy had higher success rate (88%) compared with adenoidectomy alone (61%). Maxillary sinus wash at the time of adenoidectomy is suggested for severe CRS patients with a high CT score greater than 6 [79].

Endoscopic Sinus Surgery

Endoscopic sinus surgery is recommended for adult CRS patients who did not respond to maximal medical therapy [13]. For patients with CRSsNP, the surgery is aimed to correct the ostiomeatal complex occlusion and revive normal physiology of paranasal sinuses [27]. In contrast, patients with CRSwNP who have thick eosinophilic mucin require surgical interventions to deliver topical medications throughout the entire cavity and remove eosinophilic hypersecretion [67, 80]. A meta-analysis by Soler et al. [81•] pooled data from 40 cohort studies and found that all studies consistently reported a significant improvement in quality of life. There have been more concerns regarding the success and safety of endoscopic sinus surgery for children than adults. There are reports supporting endoscopic sinus surgery for managing pediatric refractory CRS patients who did not respond to medical treatments. Children who received an endoscopic sinus surgery had greater improvements in nasal obstruction and rhinorrhea compared with medical treatment. The parents' satisfaction was higher in the surgical treatment group [82]. The success rate of endoscopic sinus surgery (77%) was higher than adenoidectomy (47%) [83]. Asthma was found as an independent predictor that endoscopic sinus surgery was significantly better than adenoidectomy [83]. Two meta-analyses reported the success rate of endoscopic sinus surgery between 71 and 100% [84, 85]. Bothwell et al. [86] performed quantitative and qualitative analyses and showed no statistical significance in facial growth between the 46 children who underwent endoscopic sinus surgery and 21 children who did not.

Other Therapies

Biologic agents such as omalizumab (anti-IgE), mepolizumab (anti-IL-5), and dupilumab (anti-IL-4R α) have shown efficacy in patients with severe CRSwNP refractory to intranasal corticosteroids [87–91]. At present, dupilumab is the only biologic drug approved by FDA and EMA to treat patients with severe CRSwNP. Aspirin desensitization improves nasal symptoms in patients with NSAID-exacerbated respiratory disease who have difficult-to-treat CRSwNP and asthma. It is well tolerated in most patients [92, 93].

Conclusions

Pediatric and adult chronic rhinosinusitis are two diseases with similarities but also with differences in their anatomy, epidemiology, causes, and mechanisms of action, diagnosis, and treatment. The anatomy of pneumatized adult paranasal sinuses is different from developing pediatric paranasal sinuses and the adenoids. While ostiomeatal complex occlusion is acknowledged as a principal cause of poor ventilation and

drainage of adult paranasal sinuses, it does not have a profound effect on pediatric rhinosinusitis. Instead, adenoids play a key role in pediatric rhinosinusitis as they are bacteria and biofilms reservoirs which cause chronic refractory rhinosinusitis regardless of adenoid size. The epidemiology is slightly different. The prevalence of CRS in children (5–15%) is lower than adults (11–12.8%). Causes and mechanisms of action should be considered cautiously in individual case. Comorbidities such as immunodeficiency, cystic fibrosis, primary ciliary dyskinesia, and allergy should be considered in pediatric rhinosinusitis that is persistent, rapidly relapses, or do not respond to treatments. Underlying inflammatory mechanisms of these two entities are different. Adult patients with CRSsNP mainly manifest with a type 1 inflammatory response while adult patients with CRSwNP manifest with a type 2 inflammatory response. In contrast, pediatric patients with CRS have greater numbers of neutrophils and macrophages, being tissue eosinophilia uncommon. The diagnosis of CRS is more difficult in children. Nasal endoscopy is not tolerable in most children and the sinus radiographs are insensitive. Intranasal corticosteroids and nasal saline treatment are the first-line medical treatment for both pediatric and adult rhinosinusitis. Endoscopic sinus surgery is suggested for adult patients who do not respond to medications, mainly refractory to intranasal corticosteroids but should be reserved in children until the failure of adenoidectomy. At the time of adenoidectomy, maxillary sinus antral wash out should be considered and performed at the same time for pediatric CRS patients with high severity categorized by computed tomography.

Compliance with Ethical Standards

Conflict of Interest Dr. Snidvongs has served on speakers' bureau for Merck Sharp Dolme, GSK, and Menarini. The other authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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