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PEDIATRIC ALLERGY AND IMMUNOLOGY (W DOLEN, SECTION EDITOR)

Chronic Rhinosinusitis in Children: Pathophysiology, Evaluation, and Medical Management

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Abstract

Purpose of Review Pediatric chronic rhinosinusitis (CRS) is a common disorder that carries significant morbidity. The diagnosis requires sinus symptoms that persist despite standard medical therapy greater than 3 months. Viral infections, allergies, and anatomic differences in children lead to chronic obstruction of the osteomeatal complex.

Recent Findings Chronic rhinosinusitis as a diagnosis is a conglomeration of multiple phenotypes and endotypes. As such, the diagnosis and management are complex. New survey studies provide some consensus on prevalence and management of this disease in children.

Summary In this review, we highlight the differential diagnosis of pediatric CRS, including non-eosinophilic/infectious variants, eosinophilic variants with and without nasal polyps, allergic fungal sinusitis, aspirin-exacerbated respiratory disease, primary immunodeficiency, and disorders of mucociliary clearance. Further, we detail treatment options that should be considered. Finally, we feature emerging potential treatment options of CRS, including anti-immunoglobulin E, interleukin-5, and interleukin-4 receptor alpha subunit.

Keywords Pediatric chronic rhinosinusitis · Osteomeatal complex · Nasal polyps · Treatment of pediatric chronic rhinosinusitis · Mucociliary clearance · Monoclonal antibodies

Introduction

Rhinosinusitis is a common disorder involving inflammation of the sinus and nasal mucosa. Typically, rhinosinusitis is classified according to the duration of symptoms: acute (less than 1 month), subacute (1 to 3 months), or chronic (greater than 3 months) [1]. When a diagnosis of acute rhinosinusitis is considered, adult guidelines suggest the presence of two major criteria (facial pain, facial pressure, facial congestion, hyposmia or anosmia, nasal congestion, nasal discharge, purulence or discolored postnasal discharge, or fever) or one major and two minor criteria (halitosis, dental pain, fatigue, cough, ear pain, ear pressure, or ear fullness) [2]. Similar guidelines have been suggested for children with acute sinus disease [3].

The diagnostic criteria for chronic rhinosinusitis (CRS) in children include persistence of the above symptoms of acute rhinosinusitis for greater than 3 months despite standard medical management, including antibiotics, steroids, saline nasal rinses, and nasal sprays. According to the most recent clinical

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consensus statement, at least two of the following should be present to diagnose CRS: nasal obstruction, purulent rhinorrhea, cough, facial pressure or pain, purulent drainage, endoscopic or CT scan findings consistent with the diagnosis, mucosal edema, or nasal polyposis [4••].

Importantly, pediatric CRS carries a major financial and healthcare resource burden due to its prevalence in the population. In a recent study of children, the authors note between 3.7–7.5 million visits per year for CRS in the USA [5••]. In children 12 years old or younger, $1.8 billion was spent on the treatment of sinusitis in just 1 year [6]. Many of these costs lie in determining the underlying cause of the disorder and the indicated treatment. Due to the complex nature of the etiology and pathophysiology of this disease in children, physicians must consider multiple diagnoses before determining a treatment plan. This review will focus on the pathophysiology, differential diagnosis, evaluation, and medical management of children with CRS.

Pathophysiology of Pediatric Chronic Rhinosinusitis

The sinuses are air-filled spaces within the bones of the face that are lined with respiratory epithelium, including mucus producing goblet cells and pseudostratified ciliated columnar epithelium. The cilia present in the sinuses assist with clearance of secretions. The osteomeatal complex (OMC) is the channel that connects the majority of sinuses (frontal, anterior ethmoids, and maxillary) to the middle meatus and provides both an entrance and exit point to the sinuses from the nasal cavity. Obstruction of the OMC is often the starting point for sinus disease in the pediatric population, as blockage leads to negative pressure in the sinuses, stimulating mucus production and retention in the sinus cavities which may lead to infections [7].

Development of Sinuses in Children

"Normal" sinus anatomy, as defined in adults, is not present at birth, as the sinus cavities will continue to develop and pneumatize into teenage years. Ethmoid and maxillary sinuses are present at birth and complete growth by age ten, while sphenoid sinuses pneumatize by 9 months of age and complete growth is achieved by age 12–14 years. Frontal sinuses develop from anterior ethmoid air cells and are present from age 7 to 8 years but do not complete development until around age 19 [1, 4••, 6]. Therefore, children over the age of 13 should be considered as having mature sinuses and can be treated much like an adult with similar disease processes. Children under the age of 13 are managed differently because of the immature development of the sinuses [4••].

Anatomic Differences in Children

Anatomic differences in children may be blamed for the development of CRS. Some have suggested that the smaller openings, or ostia, of the sinuses in children predispose them to increased risk of the development of CRS. However, quantitative studies have not been performed to assess this risk. Other evidence suggests the presence of anatomic defects that might affect the ostia (Haller cells, paradoxical curvature of the middle turbinate, etc.) do not predispose individuals to CRS [8–10].

Alternatively, several studies have shown that enlarged adenoids can play a role in the development of CRS in children [11–15]. One study compared children with CRS to those with obstructive sleep apnea and showed that those with CRS had comparatively larger adenoids. It has been suggested that larger adenoids can obstruct sinonasal passageways and become a reservoir for microbes [16, 17]. These findings have been used to support the role of adenoidectomy for early treatment of children with CRS [18, 19].

Cellular Infiltrate in Children with CRS

In adults and children over the age of 13 with CRS, the diagnosis and treatment of the disease hinges on the presence or absence of both eosinophils and nasal polyps (NP) [20–22]. In children younger than 13, there is conflicting evidence regarding the cellular phenotype of sinus disease, specifically the predominance of either neutrophilic or eosinophilic inflammation. In two studies comparing adult and pediatric CRS, neutrophilic inflammation was more prevalent in children with CRS as compared to adult CRS, where, at least in US populations, eosinophilic inflammation dominated [21, 23, 24]. These studies also found increased levels of submucosal lymphocytes, thinner and more intact epithelium, thinner basement membranes, and less mucous glands in the children [23, 24]. However, in another study by Baroody et al., the authors noted eosinophilic inflammation in children with refractory CRS, despite appropriate medical management [25]. The obvious correlation with this finding might have been allergy and asthma; however, statistical significance was not reached for this association. Most studies of children with CRS have shown a lower prevalence of nasal polyp tissue when compared to adults [23] with few exceptions—those pediatric patients with cystic fibrosis, allergic fungal sinusitis (AFS), and aspirin-exacerbated respiratory disease (AERD) [26–29].

The Role of Viral Infections in the Generation of CRS in Children

Numerous predisposing factors serve as possible triggers for the development of CRS in children. The sheer number of

viral infections experienced by children is an obvious culprit. In general, children average 3–8 viral infections each year, which subjects them to an increased risk of the development of acute bacterial sinusitis [8]. The role of these viral infections in the inception of CRS has not been extensively studied to date. However, one can imagine that multiple viral and bacterial infections lead to mucosal edema and the production and retention of mucus, setting up a vicious cycle of sinus disease via obstruction of the ostia, impaired mucociliary clearance, stasis of secretions, and diminished aeration of the sinuses (Fig. 1). This cycle cannot be understated as a potential risk for the development of CRS.

The Role of Allergy in the Generation of CRS in Children

In children and adults, there is conflicting information regarding the relevance of allergic sensitization in the development of CRS. While some studies show an association, others have shown no significant association at all [4••]. A large series of 4044 pediatric patients with CRS found that allergic rhinitis was the most common comorbidity within the population [30]. Another study by the same group reported that patients with allergic rhinitis who developed subsequent CRS did not have more severe allergic rhinitis, negating the idea of an "allergic dose-response" leading to CRS [31]. Based on current consensus, however, allergic sensitization is believed to play a role in the development of CRS, especially in older children [4••, 32]. When one considers the role of the OMC in the generation of CRS, it is clear that IgE-mediated mast cell degranulation can lead to mucosal edema of the nasal passages, and the presence of eosinophils in the nose of subjects with allergic rhinitis can impair mucociliary clearance (Fig. 1) [33–35]. Therefore, it is the opinion of the authors that allergen sensitization should be considered for all pediatric patients who present with CRS.

Differential Diagnosis of Pediatric CRS

When considering the differential diagnosis of CRS in children, it is important to understand the underlying mechanisms. For this review, we will focus on the following mechanisms: non-eosinophilic/infectious causes, eosinophilic causes with and without NP, primary immune deficiency (PID), and disorders of mucociliary clearance. Histopathology, underlying comorbidities, and laboratory data can help to distinguish these subtypes. It is important to recognize the signs and symptoms associated with certain subtypes as these should drive the evaluation and management of patients. Other possible etiologies for pediatric CRS are listed in Table 1.

Non-eosinophilic/Infectious CRS in Children

Non-eosinophilic/infectious CRS is the usual presentation for children with persistent sinus disease. As stated above, much of pediatric CRS is defined by neutrophilic or lymphocytic predominance. While studies have not shown evidence of smaller ostia causing CRS, there is good evidence that larger adenoids may lead to the generation of the non-eosinophilic/infectious variant [11–15]. Biofilm formation on the mucosal surfaces of the adenoids is a common and persistent problem that must be addressed when considering this variant of CRS

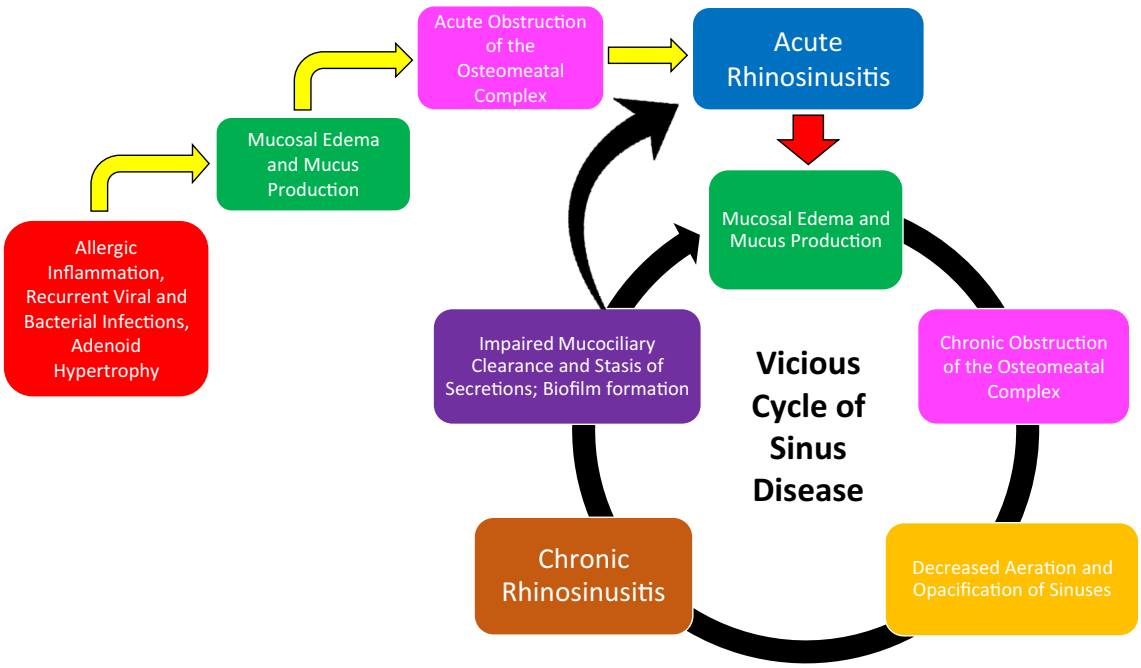

Fig. 1 The vicious cycle of sinus disease

Table 1 Possible etiologies of pediatric CRS

Possible etiologies of pediatric CRS
Anatomical differences
Mucosal edema (allergic/viral rhinitis)
Non-allergic rhinitis
Unattended foreign bodies (including iatrogenic, i.e., nasotracheal tube, prolonged ventilation)
Immune deficiency
Cystic fibrosis
Gastroesophageal reflux
Nasal tumors
Smoking
Environmental pollution
Sarcoidosis
Granulomatosis with polyangiitis
Significant dental disease
Primary ciliary dyskinesia syndrome

[8, 11, 36, 37]. These frequent infections can lead to CRS in children, especially with chronic blockade of the OMC.

Eosinophilic CRS with and without NP in Children

In adults, eosinophilic CRS with and without NP commonly associates with disorders such as asthma and allergic rhinitis; as the Baroody et al. study has shown, children with refractory sinusitis will also have eosinophilic inflammation [1, 25]. Diseases that recruit eosinophils to the mucosal tissue do so through the generation of the "eosinophilopoeitin" and eosinophil chemoattractant, interleukin (IL)-5 along with other T-helper (Th)2-biasing cytokines (IL-33, IL-25, thymic stromal lymphopoietin, and prostaglandin D2) [38–40], leading to allergic sensitization and immunoglobulin (Ig) E, the allergic antibody. In a 2014 study, uncomplicated pediatric CRS patients were found to be sensitized to indoor allergens in 62.9% (mostly dust mite) and outdoor allergens in 47.1% of cases [30]. Studies support that more than 50% of individuals with allergic rhinitis will have clinical or radiographic evidence of CRS, and a diagnosis of CRS is associated with allergic sensitization in 25–58% of cases [41, 42]. These findings can complicate the diagnosis and treatment of pediatric CRS and must be considered.

Allergic Fungal Sinusitis in Children

Another eosinophilic sinus process that can present with NP in older children with more mature sinuses is allergic fungal sinusitis (AFS). According to the literature, AFS is found in 5–10% of adults requiring surgery for CRS [7, 43, 44]. AFS is not an invasive fungal disease; rather, it is a type I hypersensitivity response to fungal epitopes, leading to eosinophilic inflammation, and very thick, "peanut butter consistency," eosinophilic mucin. Unlike many other forms of sinus disease in children, it commonly presents with NP. Children with AFS can develop proptosis and facial distortion in addition to NP. Imaging studies typically show unilateral sinus opacification with nonerosive sinus expansion in children [6, 26, 32]. The unilateral findings on CT are different from adults, who usually suffer from bilateral sinus disease in the setting of AFS [6, 45]. The disease is more common in humid environments, including the southeast and south central USA. The most common fungal pathogens associated with AFS include Bipolaris (most common), Aspergillus, Alternaria, Drechslera, Curvularia, and Exserohilum species [43].

Aspirin-Exacerbated Respiratory Disease in Children

Aspirin-exacerbated respiratory disease (AERD) is an eosinophilic CRS with NP that can rarely present in children. Classically diagnosed with Samter's triad, a syndrome of asthma, NP, and aspirin and other cox-1 inhibitors hypersensitivity [46, 47], this complex of symptoms typically presents between the teenage years and the 40s, with some patients as young as 7 years [28•, 46]. In fact, Tuttle et al. report that 8 out of 227 patients in their AERD patient registries reported the onset of NP before the age of 18 [28•]. Patients with AERD have intermittent sinusitis early in the disease process that typically evolves into a severe, persistent, chronic disease with NP [48]. The NP are intensely eosinophilic, and most patients with AERD have anosmia [48, 49]. Symptoms occur 30–120 min after aspirin exposure and include increased rhinorrhea, acute nasal congestion, ocular erythema, chest tightness, and bronchoconstriction. However, because of the risk of Reye's syndrome during febrile episodes, aspirin is not a generally recommended therapy in children. Therefore, it is also important to remember that other cox-1 inhibitors can cause similar issues. A study in adults done by Berges-Gimeno involving patients with AERD observed the NSAIDs that were most commonly noted to cause respiratory symptoms were aspirin (80%) trailed by ibuprofen (41%) [50].

Primary Immunodeficiency Syndromes and Sinus Disease in Children

Primary immunodeficiency (PID) syndromes, especially those related to humoral immunity, should be considered in children with frequent and persistent sinus infections [51, 52]. The vast majority of patients with humoral immune deficiencies present with additional infections besides sinusitis, especially pneumonias. However, some clinicians recommend a limited work-up for antibody-mediated immunodeficiency in the setting of multiple and frequent sinus and ear infections.

Recent research in adults has found that patients with humoral immune deficiencies and frequent infections have low or absent IgE [53]. The authors show the total serum IgE is below the limit of detection in 75.6% of these patients, which is an uncommon finding in the general population (3.3% of children and adults in the Lawrence study). Therefore, in the pediatric patient with frequent sinus infections for which allergic sensitization is a consideration, a low or absent total IgE should trigger consideration for evaluating PID.

Cystic Fibrosis, Ciliary Dysmotility Disorders, and Sinusitis in Children

Disorders causing impaired ciliary motility can lead to CRS in children. Cystic fibrosis (CF) is the most common disorder encountered in these patients, and it is highly associated with CRS with NP. In fact, the prevalence of CRS in the CF population is nearly 100% [54–58]. Because CF is rare, though, its overall contribution to the number of CRS cases is low [1, 6]. Physicians treating children with polyps and sinus disease should have a high index of suspicion for CF, particularly in the context of poor weight gain, respiratory disease, and gastrointestinal abnormalities.

Kartagener's syndrome, or primary ciliary dyskinesia (PCD), is another disorder of impaired mucociliary clearance. PCD is an autosomal recessive disorder causing inefficient and unsynchronized movement of the cilia. It is associated with frequent sinus and ear infections, situs inversis totalis (50% of those diagnosed), heterotaxy or situs ambiguus (12% of those diagnosed), and infertility (50% of males diagnosed) [59]. Depending on the study, acute and/or CRS were present at the time of diagnosis of PCD in older children 11–71% of the time [60–62].

Evaluation of Pediatric CRS

The medical evaluation of a pediatric patient with CRS must take into account the diverse etiologies that exist for the disease. A thorough and complete history plays an important role, as this provides much of the groundwork for establishing the diagnosis [1]. Elucidation of symptoms and their longevity provides clues regarding the etiology and course of treatment. A thorough evaluation of the numbers of infections, incidence of antibiotic use, and nutritional status is important. Asthma, both its presence and control, must be considered, and determination of exposure to NSAIDs is critical. Finally, physicians should ask about the patient's ability to smell and taste food as anosmia and dysgeusia can be a sign of NP.

Physical examination plays an important role in the evaluation as well and generally reveals rhinorrhea, nasal turbinate swelling and edema, and erythematous nasal mucosa. Signs of allergic sensitization may also be present, including allergic shiners, Dennie's lines, and the allergic salute (a crease along the top of the nose).

If allergic rhinitis is suspected in conjunction with CRS, allergy testing can provide additional insight. It is essential to test for aeroallergens, both perennial and seasonal, as this can provide targeted therapies to improve patient symptoms [1]. Evidence shows that patients with sinusitis have a higher incidence of positive skin prick testing, which supports allergic involvement in CRS [32].

Imaging has been a long-standing part of the diagnostic approach to sinus disease, and it continues to be included in establishing a CRS diagnosis. Plain radiographs are not recommended as sensitivity and specificity are limited [1, 4••, 6]. Ultrasound imaging has the benefit of less radiation exposure in pediatric patients. However, it is difficult to see mucosal thickening of the sinuses, and there is low sensitivity and specificity for CRS. Therefore, ultrasound is not a recommended study for this disease.

Non-contrasted computed tomography (CT) scan, with coronal, sagittal, and axial views, is the imaging modality of choice for uncomplicated CRS refractory to medical treatment [4••]. Specific recommendations regarding the diagnosis of rhinosinusitis with this modality exist [6]. These include complete or partial opacification of the sinuses, air-fluid levels, and thickening of the mucous membrane 4–6 mm [1]. CT has superior resolution of both bone and soft tissue and also provides information regarding altered anatomy that might require surgical intervention.

If a sinus mass or intracranial/orbital complications (proptosis, opthalmoplegia, decreased visual fields, etc.) are suspected, magnetic resonance imaging (MRI) demonstrates superior soft tissue imaging [6, 63–65]. While the lack of radiation exposure makes MRI an enticing choice for diagnosis of CRS, MRI as a single test lacks the bone detail that is often required when considering surgical interventions [63].

The timing for obtaining imaging is an important aspect of care. In a recent survey of pediatric otolaryngologists, 80% stated they would use CT scan in establishing diagnosis only if symptoms persisted with appropriate medical therapy [66••]. Some of these experts also felt that adenoidectomy should be performed before CT scan [67••]. Radiation exposure in sensitive areas (i.e., eyes, brain, etc.) is an important consideration in the pediatric population, and therefore, all options should be considered prior to CT imaging.

In a compliant subject, nasal endoscopy can prove useful in evaluation of CRS in children. Endoscopic evaluation in this disease will show posterior pharyngeal drainage, edema, or purulent discharge beyond the nasal vestibule [1, 4••]. Further, this diagnostic tool can be used to diagnose adenoiditis and adenoid hyperplasia or hypertrophy, NP, mucosal edema, and septal deviation. In a recent survey study, 48% of otolaryngologists reported they always or almost always use nasal endoscopy to establish a diagnosis of CRS in

children; 21% of these experts stated they usually use endoscopy to make a diagnosis [66••]. Endoscopy can provide useful information and help confirm pediatric CRS diagnosis as well as provide direct cultures for further infection work-up and consideration of treatment.

If the history supports the diagnosis, the patient does not respond to proper medical management, or if there is presence of NP in a pediatric patient, additional testing should be performed. Such testing would include sweat chloride and genetic testing for CF, nasal and bronchial biopsy with genetic testing for PCD, and appropriate testing for allergic fungal sinusitis (AFS) and aspirin-exacerbated respiratory disease (AERD). These diagnoses require high index of suspicion. For instance, in PCD, ~ 50% of patients who have the disease may not have a genetic abnormality to support the diagnosis [68]. Therefore, biopsy and evaluation with electron microscopy should be used before or after culture of epithelial cells, which is the gold standard in PCD diagnosis [68]. In certain laboratories, a nasal nitric oxide can be performed, which will be low in patients with PCD. In AFS, patients will have positive allergy tests for a myriad of fungi, with Aspergillus, Bipolaris, and Alternaria being the most common organisms encountered. These patients will also have high levels of total IgE, and nasal endoscopy will show thick eosinophilic mucin. The diagnosis of AERD can be ascertained via history if exposure to aspirin has occurred. However, in the absence of exposure, a pediatric patient with asthma and NP without another unifying diagnosis will require provocation challenge to aspirin [28•]. Recently, adult studies have shown that urinary leukotriene E4 can be used to identify patients with aspirin intolerant asthma. This test has yet to be studied in the pediatric population; however, it is a promising diagnostic for future management of AERD in children [69•].

Medical and Surgical Management of Pediatric CRS

The initial management of pediatric CRS is medical, with goals that include reducing inflammation, improving drainage, and eradicating pathogens [32]. To do this, a variety of therapies are needed, including antibiotics, nasal irrigation, topical and consideration for oral steroids, and allergen immunotherapy in the proper context. Early consideration for surgical adenoidectomy can improve outcomes as well [11–15]. The crux for treatment of this disease in children is proper "sinus hygiene." Children frequently do not blow their nose well and commonly do not use sanitary techniques. They are also more prone to illness, and, as mentioned in this manuscript, any obstruction of the OMC is a set-up for the generation of CRS.

Unlike adults with CRS [34, 70], long courses of oral antibiotics targeting the pathogens routinely found in the nasal cavity of patients with rhinosinusitis is first line in children, especially with the initial diagnosis. Empiric antibiotics are typically prescribed to common pathogens. In children, the most common bacterial pathogens include Streptococcus pneumonia, Hemophilus influenzae, Moraxella catarrhalis, and beta-hemolytic Streptococcus pyogenes [71•, 72, 73]. Culture-directed antibiotic therapy should be considered when empiric antibiotics have failed [71•].

High-dose amoxicillin (90 mg/kg) is a good first-line oral agent for empiric therapy in pediatric CRS, while clindamycin provides an alternative for patient's allergic to penicillin or when concern for MRSA infection exists [71•]. Consideration of the combination of antibiotics and oral steroids is important with studies showing decreased symptoms and sinus CT scores in patients receiving both classes of medications compared to those receiving antibiotics alone, especially in acute rhinosinusitis and early CRS. There were few adverse effects from this combination in short bursts, and complete recovery occurred more often in the group receiving both classes [8, 74].

The duration of antibiotic treatment is a debated topic. Some studies have shown that 20 days of antibiotic therapy is adequate for treatment of rhinosinusitis while 10 days was inadequate. Other studies recommend primary therapy with antibiotics for 3–6 weeks [1, 4••, 6, 71•]. In recent surveys, consensus amongst experts was impossible to obtain regarding length of treatment with 56% recommending treatment for 15–21 days, 27% for 14 or less days, and 17% for more than 21 days [66••].

Nasal saline irrigation is a widely used therapy for treatment of CRS [4••, 66••] that is effective and well tolerated with little risk for side effects. The combination of sinus rinses and topical steroids can be beneficial because the rinses will remove debris and mucus, providing direct access for the topical steroids to the nasal and sinus mucosa. Together, this therapy has proven to decrease frequency of sinus surgeries and has improved quality of life in patients with CRS [75]. While the addition of steroids to nasal saline irrigation is beneficial, studies of adding antibiotics to nasal rinses have shown little to no statistical benefit [34]. The exception, in adults, has been mupirocin in post-operative patients with culture positive staphylococcus infections [76, 77].

Intranasal steroids can be used alone or in combination (as above) with other therapies in the treatment of pediatric CRS. They are usually included in the initial medical management [66••]. Intranasal steroid sprays have been beneficial in combination with oral antibiotics in pediatric CRS as they decrease the amount of mucosal inflammation visualized and also improve symptoms, such as cough and postnasal drainage [6, 18, 78]. Topical steroids also provide quicker resolution of symptoms in CRS [8, 75]. The rationale for treatment with topical steroids is particularly relevant when considering patients with asthma or NP with eosinophilia of sinus tissues. However, an argument can also be made for use of topical steroids in non-allergic disease through their effects to decrease inflammation

and mucosal edema, leading to more open ostia, and thus improving sinus drainage.

There are numerous opinions on the role of oral steroids in treatment for CRS, and some have found them useful for maximum benefit in patients who need to undergo surgery [67••]. For example, treatment of allergic fungal CRS warrants removal of polyps, fungus, and inflamed tissue through sinus surgery, and oral steroids are commonly used postoperatively, as the risk of recurrence of this disease is high without treatment [6, 32]. However, chronic treatment with oral steroids has significant side effects, and they should be used judiciously and in the proper context, particularly in the pediatric patient.

Children with defined allergies should be counseled to avoid their allergic triggers. Allergen immunotherapy (IT) is another potential treatment modality for patients with defined environmental allergies. Treatment with high-dose maintenance IT has been shown to decrease medication needs and improve symptoms [79]. Current recommendations suggest that 3–5 years of IT is sufficient to improve symptoms, leading to tolerance to the allergens and increased quality of life even upon stopping the therapy [79]. In allergic CRS, IT is associated with diminished turbinate hypertrophy, decreased closure of the middle meatus after surgery, and less synechiae formation [80, 81].

Potential Therapies "On the Horizon" for Pediatric CRS

While there is a dearth of literature and research evaluating biomarkers for non-allergic triggers of sinus disease, the future for treatment of allergic CRS is bright with possibilities. Eosinophilic CRS with and without NP can have increased total and specific IgE and increased expression of IL-4, IL-5, and IL-13, as well as increased numbers of mast cells, eosinophils, and basophils [22, 82, 83]. There are many of these inflammatory mediators that are now targets for tailored therapeutic interventions, with testing occurring in adult patients with CRS. These targets include IgE (omalizumab), IL-5 (mepolizumab and reslizumab), and IL-4 receptor subunit alpha (dupilumab). Importantly, there are no trials in children with CRS using these medications to date.

Omalizumab is an IgG1 monoclonal antibody that binds to free IgE in the blood. It is currently approved in the USA and in Europe for the treatment of moderate to severe allergic asthma for adults and children beginning at age 6. Early evidence of the relevance of IgE in CRS with NP to symptoms and severity of disease made it an inviting target for intervention. In an adult study of 24 individuals with CRS with NP and comorbid asthma, omalizumab significantly decreased NP burden, improved CT scores, and improved nasal symptoms in those with and without allergic sensitization [84••]. This study led to clinical trials (now in phase 3) for use of this medication to treat CRS with NP (ClinicalTrials.gov identifier: NCT03280550). These trials also have shown a significant reduction nasal polyp burden, supporting the use of this monoclonal in this population.

Mepolizumab, an anti-IL-5 antibody approved down to 12 years of age, has been studied with some effect in adults with CRS with NP. One study has shown mepolizumab given in 2 intravenous injections of 750 mg improved NP scores in patients with NP refractory to topical steroids compared to placebo (60% in contrast to 10%, respectively) [85••]. In this study, improvement was also noted in symptoms (such as postnasal drip and sense of smell), radiographic severity, blood eosinophils, and IL-5R levels. In 2017, a randomized double-blind control study of adults with severe bilateral NP treated with topical steroids showed that adding on mepolizumab decreased the need for revision surgery at 25 weeks compared to placebo (30 vs. 10% reductions, respectively) [86•]. Phase 3 clinical trials are currently underway, using mepolizumab as add-on therapy to treat CRS with NP (ClinicalTrials.gov identifier: NCT03085797). Reslizumab, another anti-IL-5 antibody, has been studied in patients with poorly controlled eosinophilic asthma. Interestingly, the subgroup of patients with poorly controlled eosinophilic asthma and NP had improved quality of life scores as detected by the Asthma Control Questionnaire, while the larger group had more modest improvements [87]. Reslizumab is only approved for use in adults. More studies are needed to determine the effect size for treatment with anti-IL-5 drugs, especially in children.

Dupilumab is a monoclonal antibody that targets the IL-4 receptor alpha subunit and is approved for the treatment of atopic dermatitis in adults, 18 and older. Both IL-4 and IL-13 share the alpha subunit of the IL-4 receptor, and the blockade of this receptor provides a two-prong defense against the generation of type 2 inflammation, leading to lower serum IgE and decreased nasal eosinophils in current studies [82]. In a proof of concept trial, 60 adult patients with CRS and NP treated with dupilumab and mometasone furoate nasal spray for 16 weeks were studied. Many of the treatment group showed improvements in NP scores compared to placebo (70% compared to 20%, respectively). Further, symptoms scores, sinus opacification on CT scan, and CT scores (Lund-McKay) were also improved in the treatment group [88••].

There are many unanswered questions regarding the role of monoclonal antibody treatment in CRS, especially when considering pediatric populations. To date, there are no studies to determine the superiority of one monoclonal antibody over another for CRS. Given the expense of these medications, further research should focus on biomarkers that will provide the best clinical outcomes for specific patients seen in clinic for specific endotypes of sinus disease. Translating these findings into pediatric therapies is even more challenging, as studies of monoclonal antibody treatment in children with CRS have yet to be performed. Treatment protocols for interval and dosage as well as safety studies must be established in this

population before any recommendations can be made regarding CRS.

Conclusion

Pediatric CRS is a disease with huge clinical impact, constituting both a large economic and healthcare resource burden. With numerous etiologies contributing to pediatric CRS, there are a myriad of treatment options to consider. Antibiotics, adenoidectomy, intranasal steroids, nasal saline irrigation, topical steroids, and endoscopic sinus surgery, in some cases, are all mainstays of therapy. Future treatment options for eosinophilic processes include monoclonal antibodies to IgE, IL-5, and IL-4 receptor alpha subunit. However, definitive and age-appropriate studies are needed to find the safest and most effective therapies for the resolution of CRS in pediatric patients that improve both symptoms and quality of life.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

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- • Of importance
- •• Of major importance

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