Do Adult Forms of Chronic Rhinosinusitis Exist in Children and Adolescents?

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Abstract: Pediatric chronic sinusitis is currently designated as pediatric chronic rhinosinusitis. In most pediatric cases, sinusitis is considered as infectious. In the adult literature, a wider repertoire of chronic rhinosinusitis conditions is recognized. In this review, the adult forms of chronic rhinosinusitis are used as a framework for identifying and defining the potential spectrum of pediatric chronic rhinosinusitis that exists beyond the most recognized condition, pediatric infectious chronic rhinosinusitis.

Keywords: pediatric; children; adolescent; chronic sinusitis; chronic rhinosinusitis; nasal polyps; eosinophilic mucin chronic rhinosinusitis; Samter's triad

1. Introduction

Chronic rhinosinusitis (CRS) in adults is not uncommon and is often classified as CRS with or without polyps [1]. A recent extensive International Consensus Statement [2] and a theme issue of the Clinical Commentary Reviews [3] have provided insight into the pathophysiology, clinical presentation, and treatment of adult CRS. However, little to no comment is made about any equivalent disease(s) in the pediatric population. This review outlines what is known about pediatric CRS and uses the framework of the more established adult CRS conditions as a basis for determining where adult–pediatric CRS equivalencies (might) occur.

1.1. Definitions of Adult Chronic Rhinosinusitis

Based on the International Consensus Statement on Rhinosinusitis [2] and the Clinical Commentary Reviews [3], adult CRS can be divided into these different categories:

A. Chronic rhinosinusitis without nasal polyps
B. Chronic rhinosinusitis with polyps
C. (Infectious) Chronic rhinosinusitis
D. Aspirin or nonsteroidal drug-exacerbated chronic rhinosinusitis (AERD)
E. Eosinophilic mucin rhinosinusitis (EMRS)

Deliberately excluded in this review is fungal rhinosinusitis (AFRS), based on its rarity and its accepted presence in children. Also excluded is pediatric CRS associated with cystic fibrosis (CF), primary ciliary dyskinesia (PCD), and primary immunodeficiency disorders (PID), but each of these other circumstances is discussed in the Clinical Commentary Reviews [3]. The above-listed adult categories (A–E) have a greater frequency and are, by large, stand-alone conditions.

Information on pediatric CRS, extracted from the International Consensus Statement [2], suggests that CRS is considered exclusively as an infectious form, and is further defined below. A brief mention is made of the presence of nasal polyps in children, and a further discussion of pediatric CF, PCD, and immunodeficiency round out the International Consensus discussion [2].

The collection of individual articles in Clinical Commentary Reviews [3] provides only a marginal expansion of the potential pediatric expression of any of the adult phenotypes. Individual manuscripts on the theme issue include findings that the presence of polyps raises the specter of CF [4,5] but CRS without polyps raises no pediatric discussion [6]. The authors of the manuscripts about infectious CRS and AERD provided no pediatric perspective [7,8], but children are briefly mentioned in a section of other phenotypes [5].

The Clinical Commentary Review mentions the term "eosinophilic (mucin) CRS" in the context of allergic fungal rhinosinusitis [9]. The broad topic of eosinophilic mucin is almost always linked to allergic fungal sinusitis, although it appears to have some support as a separate entity [10]. The "eosinophilic mucin CRS" term is also used in the International Consensus Statement, all in the context of allergic fungal sinusitis [2]. Limited literature exists for a non-allergic fungal sinusitis (non-AFS) form of eosinophilic mucin rhinosinusitis [10].

In summary, the listed definitions of adult CRS in both the International Consensus Statement [2] and Clinical Commentary Reviews [3] have minimal pediatric comment other than it being a chronic infectious process.

Until recently, numerous publications on pediatric chronic sinus disease have focused almost solely on the infectious nature of the condition. Two contemporary articles have presented an integrative approach to the discussion of pediatric chronic rhinosinusitis [11,12]. These two articles have provided brief discussions on additional phenotypes of pediatric CRS beyond its infectious nature.

To further expand the perspective on pediatric CRS, this review uses a systematic approach to expand the classification of potential pediatric CRS entities, using the framework of the adult processes of CRS as a guide.

1.2. Potential Definitions of Pediatric Chronic Rhinosinusitis

A.　　Pediatric (infectious) chronic rhinosinusitis
B.　　Aspirin or nonsteroidal drug-exacerbated pediatric CRS
C.　　Pediatric CRS with polyps
D.　　Pediatric CRS without polyps
E.　　Pediatric eosinophilic mucin CRS (EMRS)
F.　　Other
G.　　Recognized but not discussed

A.　Pediatric (infectious) chronic rhinosinusitis

Pediatric chronic sinusitis has morphed, descriptively, to the term chronic pediatric rhinosinusitis [13]. A more accurate term would actually be pediatric chronic infectious rhinosinusitis. This author has published an extensive updated review on pediatric (infectious) CRS [14]. A Clinical Consensus Statement on pediatric chronic rhinosinusitis by otolaryngologists was published in 2014 [13]. The pediatric infectious CRS summary in The International Consensus Statement [2] largely mirrors the Clinical Consensus Statement on pediatric CRS [13].

Chronic infectious rhinosinusitis in children has reasonably defined time periods and symptoms (acute, subacute, chronic), although the route from the normal sinus to chronic rhinosinusitis is not well understood. The topic of pediatric infectious CRS has been recently extensively reviewed [14]. In brief, there is a good consensus as to the standards for diagnosis, the selection of a first-round antibiotic, and length of treatment, but the therapy for refractory patients and determining the presence of refractoriness is not well defined [12]. Areas of future research include the microbiome of pediatric chronic rhinosinusitis, imaging specificity, alternative antibiotic selection, ancillary therapy, and optimal surgical therapy [11,12,14]. Recent detailed discussions on pediatric CRS was presented by Hamilos and included proposals for the potential route from acute sinusitis to the more chronic state [11,12].

B.　Aspirin or nonsteroidal drug-exacerbated pediatric CRS (AERD)

Aspirin or nonsteroidal-drug exacerbated CRS was discussed in the Clinical Commentary Review. The specific manuscript on the topic makes no mention of the occurrence in pediatrics [8]. The definition of hypersensitivity responses to nonsteroidal anti-inflammatory drugs was provided in a position paper in 2013 [15]. No specificity to a pediatric expression of aspirin or nonsteroidal drug-exacerbated respiratory disease was provided in that publication [15].

The pediatric presentation of asthma, nasal polyps (with CRS), and aspirin (ASA) or nonsteroidal anti-inflammatory drug (NSAID) allergy (Samter's triad) is not common and has minimal literature reference. A case report from 2013 details one child [16]. An otolaryngology tertiary referral center reported in 2013 on 28 children with nasal polyps, of which three had aspirin sensitivity and two were reported as having had an aspirin desensitization [17]. Of the two case reports, one child did not have defined asthma and one had mild asthma. Both underwent functional endoscopic sinus surgery. Neither publication referenced previous pediatric literature on Samter's triad [16,17]. An up-to-date 2017 literature review simply stated that children and adolescents are rarely affected [18].

Two published reports on aspirin-exacerbated respiratory disease (aspirin-induced asthma) were reported in the United States at a single site [19], and in Europe in 16 clinical centers [20]. The single American site, at Scripps Clinic in San Diego, examined the natural history of 300 subjects, all of who had a positive aspirin challenge [19]. The age of onset was 34 ± 12 years, thus indicating pediatric age in a percent of subjects; the youngest studied subject was 17 years old. In the European study, of the 500 study subjects with positive aspirin challenges, the ages of onset of rhinitis, asthma, and polyps were 29.7 ± 12.5, 31.9 ± 13.5, and 35.2 ± 12.1, respectively [20], again showing a pediatric onset of Samter's triad clinical symptoms.

A recent clinical commentary in 2016 presented three children with AERD. Several other publications with limited pediatric AERD inclusion were referenced in this report [21].

Both NSAID-associated CRS and Samter's triad is exceedingly rare in children and adolescents, but do exist. No collections of exclusively pediatric cases from one or collaborative centers are available. Limited information suggests a similar presentation in children as in adults, and therapy is likely similar to adults.

C.　Pediatric CRS with polyps (pediatric CRSwNP)

The 3rd edition of the textbook Pediatric Allergy mentions in the allergic rhinitis chapter that nasal polyps are frequent in cystic fibrosis but not in pediatric allergic rhinitis [22]. The chapter on sinusitis makes no mention of nasal polyps [23].

The previously mentioned otolaryngology referral center publication on Samter's triad actually mentioned a total of 28 children with nasal polyposis over a 6-year period [17]. The three children with aspirin sensitivity were discussed in detail. No further details on the other children with CRSwNP were presented.

A South Korean publication stratified their CRS with nasal polyposis subjects by age. Twenty pediatric subjects with CRS and polyps were discussed. The surgical procedure and outcome was the focus of the manuscript [24].

Another Korean otolaryngology group selected pediatric patients with protracted sinus infection [25]. Children with a multitude of complicating factors including CF, immunodeficiency, aspirin-allergy, and antrochoanal polyps were excluded. Any "suspicious" polypoid tissue at surgery was examined histologically. Overall, 64% of the children with CRS who went to surgery had sinonasal polyposis proven histologically.

An Israeli study covering pediatric endoscopic sinus surgery due to nasal polyps from 2000 to 2010 was published in 2012 [26]. Thirty-one subjects, 8–18 years, met their criteria. Thirteen had an antrochoanal polyp, 16 had chronic sinusitis with nasal polyposis, and 3 had a mucocele. One child had previously undiagnosed CF. They further stated that chronic sinusitis with

polyps is predominately seen in adults, and they speculated on whether it is the same disease process in children. They suggest that literature on pediatric CRSwNP in otherwise healthy children is absent.

A French study in 1997 reported on 14 children with nasal polyposis alone and 5 children with asthma and polyposis [27]. Children with CF were discussed separately. No comment was made of accompanying CRS in the non-CF children, but the surgical description suggests that sinus pathology was present.

A German study on functional endoscopic sinus surgery in children and adolescents with chronic rhinosinusitis was published in 2009; the study population was from a referral center between 1995 and 2004 [28]. Of the 115 children, 59 subjects had CRS without polyps and 45 cases had CRS with polyps (including 6 with CF). No results were presented on histological changes in any of the subjects, and the report focused on the surgical aspects of the disease.

A quality of life outcome study was reported in children with chronic rhinosinusitis with nasal polyps undergoing functional endoscopic sinus surgery (FESS) [29]. Published in 2013, the authors stated that although FESS is relatively successful, children with CRSwNP should undergo maximum medical therapy prior to surgery, and that data on this population is scarce.

CRS with polyps in adults is a complex immunological process with a strong emphasis on type 2 immunity, including interleukin-5 (IL-5), interleukin-13 (IL-13), eotaxin-2, and eosinophilia [30]. Similar information is lacking in children. An older study on eosinophilia in sinus tissue of children with chronic sinusitis has been published [31]. Children with chronic sinusitis with asthma ($n = 13$), without asthma ($n = 11$), and with CF ($n = 10$) were reported. Sinus tissue was histologically examined and compared to sinus tissue from sphenoid sinuses in six controls. In general, all three disease groups had higher eosinophils in tissue compared to the sphenoid sinus tissue, and the non-asthma children had the lowest among the disease groups. The degree of allergy between the disease groups did not influence the eosinophilia in the diseased sinus mucosa.

An older study of pediatric nasal polyps reported on 120 cases: 24 children had unilateral and 22 children had bilateral polyps, and the other cases were from CF or with antrochoanal polyps only [32]. The tissue of the polyp was uniformly reported as normal respiratory mucosa. Cellular infiltrates within the polyp were acute and chronic inflammatory cells, but eosinophilia was rarely found. The presence of concomitant CRS appears to have been present in the non-CF, non-antrochoanal patients, but was not well defined.

Other reports on the prevalence of nasal polyps in pediatric sinus surgery have ranged from 7% to 18.8% [33–35]. Tissue from pediatric nasal polyps might mimic an adult eosinophilic state or, less commonly, neutrophilia.

In summary, CRSwNP is rare in children and adolescents, with some evidence for eosinophilia within the extracted sinus tissue. Its separate pediatric existence without allergy, without a bacterial infectious component, and without CF or ciliary dyskinesia co-morbidity is not well defined. Any future reports in children and adolescents with CRSwNP should examine the immunological constitutionality of the sinus tissue, the cellular composition of the polyp, and bacteriological presence, including the spectrum of the microbiome. Since surgery is potentially performed on these children/adolescents, studies of this type could be performed.

D.   Pediatric chronic rhinosinusitis without polyps (pediatric CRSsNP)

A condition of adult CRS without polyps appears to exist [6]. However, its presence as a distinct pediatric entity is non-existent in the literature. Any population of pediatric CRS without polyps, if clinically viable, must exclude infectious CRS, allergic rhinitis, nasal polyps, aspirin-exacerbated respiratory disease (ARED), CF, immunodeficiency, AFRS, and eosinophilic mucin CRS.

Hamilos proposed a scenario where persistent pediatric CRS might evolve into a complex condition, reflecting a potential for a CRSsNP status; however, he further proposed a "maladaptive-eosinophilic" state in a minority of children [11,12].

It is possible to speculate that a pediatric infectious CRS situation could, after a long duration, morph into a microbiomically (microbiologically) altered, neutrophilic-driven CRS. If true, it is also possible that at some point antibiotics cannot resolve the condition. These children may, in effect, drive surgically managed pediatric infectious CRS (recalcitrant) [14].

The adult condition of CRSsNP gathers no clinical correlation in children in virtually all historical publications. The true potential form of a pediatric non-polyp CRS that correlates with either a purely neutrophilic end-stage or with an eventually or separate eosinophilic end-stage needs further investigation.

E.　Pediatric eosinophilic mucin CRS (EMRS)

Separate from an entity associated with allergic fungal sinusitis, literature evidence has been summarized for a pediatric eosinophilic mucin CRS condition; although all were adolescents and of limited number compared to adults [10]. Another publication termed this entity as "AFS-like syndrome" [36]. In that report, a pediatric patient was included [36].

Histological comparisons between adult and pediatric CRS

Another way to potentially divide pediatric and adult CRS forms, other than by definitional standards, is to examine the histopathology of surgical tissue. Two studies have approached the differentiation in this way, and one older study has examined mucosal histology in older children with chronic (rhino)sinusitis as compared to normal adults. The 1995 publication compared the sinus tissue from 24 non-CF children with 6 normal adult sphenoidal tissue samples [31]. The mean age was 7 (range 3–16 years). A publication in 2004 reported on 19 children with ages 1.4 to 8 years and adult CRS controls [37], which was further extended in the same children in 2009 using immunopathology [38]. A 2011 publication examined sinus mucosa from 16 CRS children with mean age 11.6 (range 7–16) and 29 adult CRS controls [33]. Table 1 attempts to compare and contrast the findings, although methodologies between the three studies are not comparable (per se). The re-analysis [38] of the children in the 2004 study [37] stands alone and shows that pediatric CRS is less eosinophilic than adult CRS controls and more skewed based on cellularity from excessive microbiological stimulation.

Table 1. Comparison of published histological studies of chronic rhinosinusitis (CRS) in children.

		Eosinophils	Lymphocytes	Suggested Phenotype in Children
1995 [31] *	Pediatric CRS no asthma	Present	ND	
	Pediatric CRS asthma	Present **	ND	
	Adult normal controls	0	ND	
2004 [37] *	Pediatric CRS	Low	High	Infectious CRS
	Adult CRS	High	Low	
2011 [33] *	Pediatric CRS	Low	Equal	Infectious CRS
	Adult CRS	High	Equal	

* The same articles were descriptively discussed in a report by Hamilos [11]. ** Present or elevated.

F.　Other minor classifications of chronic rhinosinusitis

Publications are available that define a condition termed eosinophilic chronic rhinosinusitis [39–41]. In essence, it is made up of a collection of other more recognized CRS conditions, including CRS with polyps, allergic fungal sinusitis, aspirin or non-steroidal drug-exacerbated chronic rhinosinusitis, and eosinophilic mucin CRS. Each of these has been previously and separately discussed for a pediatric presence.

G.   Other recognized—or not reviewed—pediatric CRS phenotypes

1.   CRS associated with adenoid hypertrophy [42]
2.   CRS with anatomical abnormalities [43]
3.   CRS with ciliary motility defects
4.   CRS with immunodeficiency
5.   CRS with cystic fibrosis

CRS with adenoid hypertrophy/adenoiditis may be a co-morbid factor of chronic infectious pediatric rhinosinusitis, but with an exaggerated adenoid dysfunction due to chronic nasal dysbiosis [42]. This was further discussed by Hamilos [11].

Anatomical abnormalities, although uncommon in children, may also allow for the development of pediatric infectious rhinosinusitis, although the role of anatomical contributions in CRS has been downplayed [43].

The entities of CRS with ciliary motility defects, CRS with immunodeficiency, and CRS with cystic fibrosis have been intentionally excluded from this review.

Surgical Approach to Pediatric CRS

Surgical therapy for pediatric CRS can include children with recalcitrant pediatric infectious CRS or for other forms of pediatric CRS. These could include aspirin or nonsteroidal drug-exacerbated pediatric CRS, pediatric CRS with polyps, and eosinophilic mucin CRS (an uncommonly used classification). The surgical approach for any of these separate etiologies may overlap. The Consensus Surgical Review does not differentiate between different surgical approaches, unless polyps are present [13].

2. Summary

Pediatric CRS is not an uncommon clinical diagnosis but it is vastly under-represented in the literature with any phenotypic subtypes. CRS in the vast majority of children, especially pre-school age, likely starts as viral rhinosinusitis that, without resolution, develops into pediatric infectious CRS [11,12,14]. The natural history of pediatric infectious CRS is unknown, and some small percentage will require surgical intervention. Polyp growth in infectious CRS is rare.

Older children and adolescents appear to have a bigger repertoire of beginnings of their CRS. Undoubtedly, ARED can start in later childhood, with or without asthma. True CRSwNP without aspirin or NSAID allergy rarely occurs. Whether this is type 2 cytokine-driven, as in adults, needs further investigation. CRSsNP has no pediatric correlates in the literature; however, pediatric infectious CRS could morph into this condition if left untreated for an extended period (speculative).

Recently, a sophisticated immunological cluster analysis of the adult rhinosinusitis phenotypes with polyps and CRS phenotypes without polyps has been published [44]. Defining the phenotypes of adult CRS obviously has important mechanistic implications, and only further highlights the divide between adult disease and the continued under-emphasis of pediatric CRS. Establishing clinical patterns of CRS in pediatrics could provide a pathway to define these conditions using similar complex methodologies.

To our knowledge, this is the first review to attempt to systematically categorize pediatric CRS into definable conditions based on the current literature. Using an adult-based system may prove, ultimately, to be incorrect; however, enough evidence exists to support a number of adult–pediatric CRS equivalencies. Using the general term pediatric CRS limits the background by which each child reaches the level of medical care and investigation. Unfortunately, the ability to investigate a group of like-presenting children using more invasive means may always be limited by ethical and regulatory constraints. Until a time when less invasive biomarkers become available to investigate pediatric CRS, literature using broad terminology will continue to provide only a limited picture of a chronic pediatric condition.

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