

Fifty Years of Chronic Rhinosinusitis in Children: The Accepted, the Unknown, and Thoughts for the Future

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Chronic sinusitis is an often-used term in both lay and medical circumstances. In children, it has significant but largely undefined healthcare costs. Chronic rhinosinusitis (CRS) in children has well demarcated time periods and symptoms, although the actual pathway from normal sinus to CRS is not well understood. There is reasonable consensus as to the standards for diagnosis, the selection of a first-round antibiotic, and length of treatment. However, no recent prospective studies of antibiotics are available. Areas of continued speculation include the following: the microbiome of pediatric CRS, the best use of standard imaging, alternative antibiotic selection, ancillary therapy, and treatment of refractory CRS. In addition, older adolescents can present with a more adult-oriented CRS with or without polyps, suggesting a broader spectrum of disease than is commonly recognized. An accounting of the accepted elements of pediatric rhinosinusitis, as well as areas for future research, is emphasized in this review and, where appropriate, suggestions for potential investigations are offered.

Medical History of Chronic Rhinosinusitis: A Look to the Future

A 1933 TREATISE on pediatric sinusitis in the *Journal of Pediatrics*, second volume, serves as a bellwether for all future discussions of pediatric sinus anatomy and disease.¹ Contained in the article is a detailed description of the anatomy of sinuses in children, originally published by Davis in 1918.²

A 1949 individual physician's report of his treatment protocol for chronic sinusitis in children contains statements about causative factors, symptoms, and diagnosis that have a direct link to any child with the disease in this decade. A significant deviation occurs, however, in the treatment protocol used by the author.³ The author reports satisfactory results with X-ray radiation and Proetz displacement and irrigation with penicillin in saline. The author's comment, "the modern trend in treatment leans away from the radical methods of treatment in vogue some twenty-five years ago," points to long-term medical recognition and treatment regimens for the disease.

A detailed search over the past 50 years shows an incredible number of published articles on the topic of pediatric rhinosinusitis, with many mixing details of acute and chronic rhinosinusitis (CRS). Vast numbers of articles summarizing diagnosis, symptoms, or treatment are available (partial reviews), but a significant number provide a comprehensive

review. Consensus reports on pediatric CRS are available and serve as a substitute for classic systematic reviews. Any endeavor to detail a summary of all the partial reviews of pediatric rhinosinusitis would be monumental and has not been attempted.

Prospective studies of antibiotics for pediatric CRS, in contrast to the number of partial or comprehensive review articles, are scant. No meta-analysis of antibiotics but a few of the surgical techniques in children are published. Looking over the past 50 years, progress in pediatric CRS, in large part, consists of rereviews of clinical presentation, minimal advancement of antibiotic therapy, controversy over radiological support, and no all-encompassing surgical procedure. Recent advancements have occurred in microbiological research. In this review, the knowledge base for this disease over the past half-century (1966–2016) is discussed, perspectives are provided, and suggestions for future study offered.

Background of the Normal Homeostatic Sinus

Anatomy and development of the sinuses

The paranasal sinuses start developing in the embryo as outgrowths from the nasal cavity.⁴ Ethmoid and maxillary sinuses are present at birth and slowly grow in size; sphenoid and frontal sinuses appear later and are well developed by the age of 7–10. Sinuses have continued growth up until

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puberty. The paranasal sinuses surround the nasal cavity and communicate with it through small ostia (2–6 mm in diameter), which allow for the slow exchange of air between the sinuses and the nasal cavity.⁴

The normal sinus environment

Role of nitric oxide. Nitric oxide (NO) is a gas with antimicrobial and vasodilatory effects found in high concentrations in the nasal passageway and sinuses.⁴ It is produced by NO synthase in healthy sinus epithelium. High levels can act as a defense against infections, while reduced production may lead to increased susceptibility to sinus infections.⁴

Sinus microbiome. Recent studies have shown that the nasal cavity, middle meatus, and sinus mucosa in healthy adults have a rich microbiome consisting of multiple organisms.^{5–7} Past studies asserting that the sinuses were sterile is thus incorrect. The finding that NO levels are elevated in healthy sinuses would suggest that the sinus microbiome survives in the presence of high NO.⁴

Microorganisms beyond what is considered the normal microbiome may colonize the nasal cavity, especially in children. Single or multiple colonized bacteria may be present, most commonly in a biofilm environment.

The role of a potentially altered microbiome and its role in the development of pediatric rhinosinusitis is a fertile area for research, including serial evaluation before and after antibiotic therapy. Serial measures of nasal NO might provide support of clinical status after antibiotic therapy.

Ciliary function and fluid production. The sinuses and nasal cavity benefit from normal serous fluid flow, mucus production, and mucociliary clearance. Ciliary activity could possibly be altered by nasal microbial biofilm presence, although this is not known. Ciliary dysfunction is present with CRS.

Innate and adaptive immunity. The developing pediatric immune system offers surveillance and functionality, as new infections are encountered and an immune response generated, including secretory IgA. Local innate immunity provides additional benefit.

Sinusitis Definitions in Children

Acute rhinosinusitis

Viral-initiated upper respiratory tract complaints, generally with a fever that is almost exclusively clinically defined as a new illness in a patient with no prior concerns, generally resolved by 14 days. This acute viral condition is termed as acute viral rhinosinusitis.

Subacute rhinosinusitis

Less clinically defined symptoms but a new acute viral process not resolved in 21 days.

Chronic rhinosinusitis

Based on an 8–12-week period of persistent disease often with less obvious clinical symptomatology.^{8,9} Depending on the clinical circumstance, the presentation may be rhinosinusitis, (chronic) sinusitis, or rarely (chronic) rhinitis; possibly with chronic adenoiditis as an accompaniment.

Recurrent rhinosinusitis

Multiple episodes with apparent clinical resolution between episodes.

Refractory rhinosinusitis

Presumably the same CRS that has not resolved after reasonable therapy; also termed recalcitrant.

Chronic rhinosinusitis

Almost exclusively an adult process,⁸ with a recent description of its various immunological forms¹⁰; this process is extremely uncommon in children.

Epidemiology: Prevalence and Incidence of Chronic Sinusitis

The epidemiological aspect of CRS is a commonly overlooked topic in current comprehensive reviews. Virtually, no specific studies of this matter in the past 50 years exist, although several recent reviews provide data, in part, extrapolating from adult reports.^{11–14}

Likely, only a small percentage of acute rhinosinusitis diagnoses become chronic. It is highly probable, however, that the direct and indirect costs for diagnosing and treating children with CRS are substantial.

Prospective studies using children in different daycare environments could provide perspective, as a similar study by Wald et al.¹⁵ was valuable for determining frequency of viral illnesses and otitis media rates. However, the lack of consistent diagnostic criteria and lack of noninvasive test procedures would make for a difficult study design.

Predisposition to CRS in Children

Given the normal homeostasis of the sinuses, as discussed above, the development of chronic sinusitis in a child must require overwhelming factors to occur. Some of the possible comorbidities are suggested here and/or have been mentioned in previous comprehensive reviews.^{11,14,16–19}

Daycare

In the setting of modern childcare, daycare has become a standard in many families. In this regard, preschool children are exposed to various nonfamily members allowing for free exchange of viral infections and potentially, nasal bacterial carriage burdens. Based upon the groundbreaking studies of Wald et al., daycare children may have 6–10 infections yearly, often compressed into a 4–6-month season.¹⁵ A seminal adult study of rhinovirus nasal infection and CT scan changes points to the relative ease with which a viral nasal infection can change the sinus radiological appearance.²⁰ In this study, a rhinovirus infection caused a change in the CT of the sinuses that lasted about 2 weeks.

Equally interesting would be the chronology of the local sinus mucosal changes that occur after a viral rhinitis. A murine model of chronic (rhino) sinusitis showed a disrupted sinus histology 4 weeks after a single bacterial inoculation, with surgical sinus ostial obstruction.²¹

A study of the nasal microbiome before and after starting daycare (or school) might have value.

Common comorbidities

There are other conditions that have been demonstrated to potentially impact the development of CRS. In a child who has recurrent CRS, these following conditions should strongly be considered as important comorbidities: anatomical abnormalities, allergic rhinitis, obesity, passive smoke exposure, and laryngopharyngeal reflux.^{11,14,16–19}

Chronic disease comorbidities

Other chronic disease states are well recognized as having a component of chronic sinusitis.^{11,14,16–19} It is interesting that major changes in mucociliary clearance and significant aberrant microbiological biofilming (cystic fibrosis), or radical reduction in ciliary motion (immotile ciliary syndrome), or absent or markedly diminished immunological function (immune deficiency syndromes) all have sinus manifestations. Equally, this points out the importance of these multiple components as necessary to maintain sinus homeostasis in normal children.

Microbiology

There is a report of microbiological involvement in pediatric CRS in the publication of Uhr et al. from 1933, and the authors referred to additional unreferenced studies in 1930 and 1921.¹ The microbiology of pediatric CRS resurfaced in a 1981 article by Brooks.²² His report detailed 41 pediatric subjects with sinus symptoms for 3 weeks or more. In 1988, Otten and Grote reported on 141 pediatric subjects with purulent rhinorrhea for 3 months or more.²³ In 1989, Tinkelman and Silk detailed bacterial cultures in 35 of 116 children with symptoms for 30 days or more.²⁴ Muntz and Lusk, in 1991, reported 105 children after 2 antibiotics, with cultures done at surgery.²⁵ In 1991, Orobello studied children undergoing surgery with 12 weeks of symptoms.²⁶ In 1994, Otten et al. published a follow-up in 79 children.²⁷ These studies, with comments, were summarized in a review of the microbiology of chronic sinusitis in children in 1997 by Wald.²⁸ Her closing statement was “The failure to respond to multiple antibiotics.... the process causing the chronic symptoms is not caused by bacterial agents.” Reviews on pediatric CRS by Wald in 1992 and 1995 covered microbiological evidence and antimicrobial coverage without additional conditional remarks.^{9,18} A review of the role of bacteria in adult and pediatric chronic sinusitis was reported by Brooks in 2005.²⁹ This review provided an extensive summary of all pediatric microbiology studies to that point. Three organisms dominated the culture results as follows: *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. A current summary of microbiology of chronic pediatric rhinosinusitis was presented in a 2015 consensus report. The report states that microbiology has not altered in the past 3 decades, although there has been a rise in *Staphylococcus aureus* and anaerobic bacteria.³⁰

The New Microbiology: Microbiome, Biofilms, and Colonization

Studies in adults using nonculture-based molecular diagnostics have clearly demonstrated the presence of a healthy microbiome and that the microbiome is different in adult patients with chronic sinusitis.³¹ What is currently lacking is any

similar information in the pediatric population. The timeline of nasal and sinus microbiome development from newborn through adulthood is also unknown. It is also unknown if early daycare exposure permanently alters microbiome expression or whether an altered microbiological presence, with biofilm development, is of a temporary or of a more permanent nature. Surprisingly, colonization with pathological bacteria (i.e., *S. pneumoniae*) appears not to result in a local nasal problem, as isolated chronic (or even acute) bacterial rhinitis (in children) is exceedingly rare. It is possible, however, that a chronic altered microbiological presence (colonization with biofilming) more easily allows for sinusitis to develop.

In the earlier periods of CRS, the sinuses may harbor an altered microbiological presence similar to what is seen in otitis media in children as follows: *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*, possibly by extension from previously colonized nasal cavities.²⁹ If true, this may allow for adequate treatment if temporally recognized. When chronic sinusitis goes unrecognized for an extended period of time, the organisms likely become polymicrobial, at least in adults.^{29,30,32} Treatment at this point may prove more difficult.

Thus, to actually develop CRS, there must be disruption of the potentially static microbiome colonization interaction, possibly by viral infection, serious disrupted sinus hygiene processes, and/or yet other underappreciated factors, all leading to a dysbiotic state in the nose, sinuses, and (likely) lymphatic tissue (adenoid).

Presenting Symptoms

Accurate descriptions of symptoms of chronic pediatric sinusitis existed in articles from 1933 to 1949.^{1,2} No additional studies have emerged in the past 50 years (1966–2016) to enhance the clinical diagnosis. Surprisingly, a 2014 comprehensive review states “this condition is often overlooked in pediatric practice.”¹¹

In a child who has an underlying CRS, complaints of nocturnal cough, nasal congestion, and parental comments of “(s)he keeps a cold” might surface. In older children, weeks to months following an upper respiratory infection, complaints of daytime cough, nocturnal cough, cough with exercise, nasal congestion, sleep disturbance, and/or mouth breathing should alert a clinician to consider a CRS diagnosis.^{8,11}

An overlooked comorbidity is the fact that children of any age, who have had unrecognized CRS for an extended period of time, will likely have had additional clinical phenomena occur, including Eustachian tube dysfunction, adenoidal hypertrophy with/without snoring, and conceivably, even ancillary surgical approaches, including adenoidectomy and/or tympanostomy with tube placement.¹¹ These downstream processes greatly enhance medical costs.

It is very conceivable that a large pediatric otolaryngology group could assess the comorbidity of CRS in children undergoing selected pediatric otolaryngology procedures such as tympanostomy tube insertion and/or adenoidectomy.

Finally, in the author’s experience, there exist a small number of older adolescents who will present with a similar clinical picture to adults with CRS with or without polyps and with or without NSAID allergy.

This pediatric-age “adult-like” process is under-recognized and the true incidence is unknown. Furthermore, CRS in adults has distinct immunological variants.¹⁰ Data of this sort are totally lacking in adolescents.

Examination Findings

Examination findings might include the following: presence of purulent, thick mucus, excessive serous drainage and/or erythema of the nasal mucosa, possibly with enlarged turbinates.³³ Other findings are posterior nasal drainage (often demonstrated on slight gag with a tongue blade), posterior oropharyngeal *cobblestoning*, and, less commonly, halitosis. These findings would suggest, by definition, a pediatric CRS. It is not unusual to find minimal intranasal changes, implying a process more confined to the sinuses.

Radiological imaging

Just as there have been few prospective studies of antibiotics in pediatric CRS (see *Treatment* section), equally rare are studies using serial sinus imaging procedures. At the earliest period of the past 50 years, a retrospective review of 100 children with insidious nasal symptoms, cough, and otitis media was diagnosed with sinusitis.³⁴ Ninety-six percent had involvement of the maxillary sinuses, with ethmoiditis at 37% and frontal or sphenoid 14%. Contrast this report to the range of recent review and consensus-based recommendations as follows: from “sinus radiographs are discouraged,”¹¹ to “plain x-rays have no role in the diagnosis of pediatric CRS,”³⁰ and to “plain x-rays or CT scan is not recommended (unless surgery is considered).”⁸ In essence, the pendulum has swung from using the tools

available and allowing it to assist with diagnosis to being reticent to considering standard high-definition or nonhigh-definition imaging, and apparently, referring to a surgical decision and radiological evaluation those children who are refractory to empirical treatment.

A single older study stands alone as a serial radiologically assisted study of the effect of different antibiotics used in a double-blinded manner.³⁵ Eighty-four children were assigned to 4 arms, 3 antibiotics, and 1 assignment of an antihistamine–decongestant. At each follow-up, a repeat Waters’ view of the sinus helped to guide the subsequent step of therapy.

Based on this study, which has never been repeated, one obvious deficiency about pediatric CRS persists in that the medical community supports a definition of pediatric rhinosinusitis as a condition that has existed for a minimum of 12 weeks, and it is illogical that there is little consensus to prove the condition has gone after using empirical antibiotic therapy, which is being recommended for an arbitrary period of time.

Furthermore, since there is no standard for assessing total resolution of CRS if an infection occurs, it is likely (although never studied) that recurrent chronic sinusitis is actually the resurgence of nonresolved CRS.

What remains totally unknown is the natural history of chronic pediatric rhinosinusitis. For example, assuming the underlying dysbiotic microbial process has resolved after 3 weeks of antibiotic therapy, how long does it take for the

TABLE 1. ANTIBIOTIC RECOMMENDATIONS IN COMPREHENSIVE REVIEWS AND CONSENSUS REPORTS ON PEDIATRIC CHRONIC RHINOSINUSITIS

References	Study type	Recommendation	Critical comment
37	Review	Based on nasal culture	
17	Consensus	2–4 weeks Amoxicillin	First consensus, variable antibiotics and course time, with nasal cultures and possible switch
18	Review		Multiple options discussed
9	Review	A-CP	Other options mentioned
38 ^a	Review		“Antibiotics cannot be currently considered effective in chronic sinusitis.” Largely adult data
16	Review	A-CP	Other options discussed
14	Review		No clear recommendation
12	Review		Not specific about acute versus chronic. Amoxicillin first line, A-CP second line
29	Review	A-CP	21 days. Other options suggested
39	Review		21 days. No clear recommendation
40	Review		Conceptual, no recommendations
13	Review		No antibiotics unless “chronic with frequent exacerbations,” no specific recommendation
41	Review		No studies supporting specific antibiotic or duration
42	Review	A-CP	
43	Review	A-CP	With an acute exacerbation of CRS, 3–4 weeks
44	Review		Broad-spectrum beta-lactam oral antibiotic
8	Consensus		“Might be a place for longer term antibiotics” third EPOS
45	Review	A-CP	
46	Review		Long-term antibiotics, 3–6 weeks
47	Consensus		20 days, no specific antibiotic
11	Review		3–6 weeks, options discussed
48	Review		Extensive review of nose and paranasal disease in children.
30	Consensus		No antibiotic recommendation, but long term Extensive references. No specific recommendation

^aReviews that have scant pediatric data.

A-CP, amoxicillin–clavulanate potassium; CRS, chronic rhinosinusitis.

accompanying inflammatory process to resolve on radiological evaluation? The management of chronic pediatric rhinosinusitis would be greatly enhanced with limited (number and views imaged) serial investigative radiological support of the usual clinically based decision of symptom resolution only.

Treatment of chronic rhinosinusitis

Two older studies stand out as attempts to address pediatric CRS with antibiotics without a surgical arm. In 1982, Rachelefsky et al. published their report of 84 children with maxillary sinusitis and allergy treated in a double-blinded manner with amoxicillin, erythromycin, trimethoprim-sulfamethoxazole, or antihistamine-decongestant combination.³⁵ Amoxicillin or trimethoprim-sulfamethoxazole provided good radiological and clinical response. In 1991, Brook and Yocum retrospectively reported on 40 children with pediatric CRS treated with clindamycin ($n=15$), amoxicillin or ampicillin ($n=16$), erythromycin ($n=6$), or cefaclor ($n=3$) antimicrobial therapy.³⁶ Clindamycin was most successful (less antibiotic changes and less surgical outcome) and erythromycin least successful. These 2 studies stand alone in the past 50 years as multiarm antibiotic studies for pediatric CRS.

Subsequently, partial reviews, comprehensive reviews, and consensus reports started recommending various antibiotics, although amoxicillin-clavulanate potassium has majority support. Table 1 details the Reviews and Consensus reports of antibiotic recommendations over the past 50 years.

The recommendation for Augmentin, however, ignores the frequent concern for adverse reactions to penicillin products. Additional treatment options, which are presented in reviews (Table 1), include cefuroxime, cefpodoxime, cefdinir, clindamycin, and trimethoprim-sulfamethoxazole. Currently, there is no consensus for antibiotic dosing/duration recommendations for these alternative antibiotics for CRS in children. Referral for penicillin testing would be of benefit for antibiotic choice.

What is definitively needed in an investigatory way is to determine alternative antibiotics for penicillin-allergic children and what second-tier antibiotic is a consideration if an initial choice was not clinically successful. As mentioned previously, regardless of choice of antibiotic, the critical issue that remains is the appropriate method to assess resolution of disease concomitantly with the cessation of therapy.

A previous study by Gwaltney et al. followed the radiological course of acute sinusitis.²⁰ A similar study using judicious serial limited cut CT scans in pediatric chronic sinusitis patients after antibiotic therapy would provide extremely beneficial information. Caution must remain for radiation exposure.

Surgical Intervention

The literature available on surgical treatment for pediatric CRS, recalcitrant CRS, or nonmedical therapy-responsive pediatric CRS is truly staggering, both in duration of time procedures reported and for the number of actual publications. There have been few comprehensive systematic reviews of these multiple surgical procedural approaches within the past 50 years, although specific pediatric-directed procedural reviews and a meta-analysis report are available.⁴⁹⁻⁵¹

Considering the monumental scope of cataloging all the possible outcomes of sinus surgery for pediatric CRS, it seems reasonable to cite the consensus reports published, with a summary of their review of surgical options. The evolution of these guidelines through 2013 was reported.⁵²

The initial pediatric CRS consensus report was published in 1998, based on a panel convened in 1996.¹⁷ The methods used to compile the published surgical options they reviewed and discussed are not stated. References for the discussed techniques were provided. Techniques discussed included the following: adenoidectomy (provisional approval); antral lavage (provisional); and endoscopic sinus surgery (ESS) (positive). The panel divided ESS indications into absolute and possible. Chronic pediatric rhinosinusitis was a possible indication. They also stated that sinus surgery for CRS was indicated for a "small fraction of all children."

The EPOS (European Position Papers on Rhinosinusitis and Polyps) published reports in 2005, 2007, and 2012. The 2012 position paper stated surgical management is an option for those children who fail "maximal medical care."

Surgical options included adenoidectomy with or without antral washing and functional endoscopic surgery.⁸ No preference was provided.

A clinical consensus statement on pediatric CRS was published in 2014.⁴⁷ A rigorous survey methodology for panel opinion was used. Consensus opinions about adenoidectomy and ESS, balloon sinuplasty, and turbinateplasty were provided. Statements of each consensus opinion were either in agreement of effectiveness or not in agreement. For adenoidectomy (adenoiditis may coexist), consensus was reached for effectiveness for younger children (up to 6 years) and less agreement for older children. No consensus for tonsillectomy. For ESS, consensus was reached for performing a CT before ESS surgery and doing ESS when medical management or adenoidectomy has failed. Both balloon sinuplasty and turbinateplasty failed to reach consensus support. Extensive discussions and references were detailed.

A 2015 international consensus statement on allergy and rhinology provided a 2-paragraph summary of the known surgical options for pediatric CRS, stating they are age and anatomy dependent.³⁰ Balloon sinuplasty was considered too new for comment.

Small case reports have been published showing success with balloon sinuplasty in children alone or compared to ESS or adenoidectomy.⁵³⁻⁵⁵

Ancillary Therapy

There is clinical evidence to suggest that ancillary therapy combined with antibiotics may be of value in the treatment of pediatric chronic sinusitis. These include the following: nasal steroid sprays, nasal saline washes or sprays, oral mucolytics, and oral corticosteroids. In support of oral corticosteroids, a study examining their effectiveness in the management of acute sinusitis has been published.⁵⁶ A recent *ex vivo* study reported a role for corticosteroids in modifying biofilm formation by pathological organisms in adults with CRS.⁵⁷ A prospective study of ostiomeatal complex obstruction, in a limited uncontrolled number of children, showed oral corticosteroids had the best benefit compared to antibiotics or nasal corticosteroids.⁵⁸ Furthermore, a prospective study of antibiotic with or without methylprednisolone showed the oral steroid to be of a significant additive benefit in outcome

and CT scan improvement.⁵⁹ These findings echo the comments of Wald in 1997.²⁸

Following intensive antibiotic utilization to resolve CRS, a potential role for probiotics to repopulate the nasal cavity and sinuses with a nonpathological microbiome could be studied in pediatric chronic sinusitis. A study of supplementing younger children with recurrent infections using probiotics was successful.⁶⁰ The hypothesis that probiotics could play a role in diminishing pneumococcal disease by modifying pneumococcal carriage was presented in an opinion article.⁶¹ An animal model of sinusitis has shown that inoculation of a probiotic can ameliorate the inflammatory response due to sinus inoculation of pathogen bacteria.⁶² An additional strategy, not to the author's knowledge yet investigated, is to add unconjugated pneumococcal vaccine (Pneumovax) to the vaccine regimen for selected children with a pattern of recurrent upper respiratory tract infections, including recurrent CRS.

Conclusion

Pediatric CRS is an oversimplified but an extensively reviewed disease, with largely circumstantial guidelines without supportive research.

It is clear there is an abundant need for additional research, specifically focusing on treatment, radiological/technical support, total direct and indirect costs, and the influence of CRS on ancillary comorbidities.

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