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Diagnosing and Managing Chronic Pediatric Rhinosinusitis: Still More Questions than Answers!

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Abstract

Pediatric chronic sinusitis is a well-recognized medical condition. There has been an evolution in its terminology, now termed pediatric chronic rhinosinusitis. In actuality, pediatric infectious chronic rhinosinusitis is a more complete term. There is however, continuing diagnostic and treatment dilemmas. Using a case-based scenario, the questions that still remaining in the diagnosis and management of this condition are addressed and, when available, literature-based evidence is provided.

Keywords: *Pediatric Sinusitis, Pediatric Chronic Sinusitis, Pediatric Chronic Rhinosinusitis, microbiome.*

Background

Pediatric chronic (infectious) sinusitis has been renamed pediatric chronic (infectious) rhinosinusitis (CRS). The terminology change has, however, not further clarified the pathophysiology. The disease process has had a recent extensive review with a historical perspective[1], and a second recent publication provides a more complete examination of the comparison of adult and pediatric forms of the disease.[2] An previous perspective on pediatric chronic rhinosinusitis summarized controversial aspects of the disease elements to be discussed henceforth.[3]

Two additional reviews of pediatric chronic rhinosinusitis have been recently published[4-5] An International consensus report on phenotypes and endotypes of chronic rhinosinusitis reviews patho-physiology, but did not include children.[6] A review of CRS contrasted between adult and pediatric forms has been published.[2]

As long as immunological defects, anatomical abnormalities, ciliary dyskinesia or cystic fibrosis don't co-exist, the purely infectious form of pediatric rhinosinusitis is not uncommon, but still remains, largely, a clinical diagnosis.[1-5] The pediatric process is non-allergic, non-eosinophilic, and not related to adult CRS with or without polyps. [1-6] Allergic rhinitis could however, be a concomitant disease, and may play a role in its development, although the evidence is largely circumstantial.[7]

The complexity of the microbiological modification of the sinuses in pediatric CRS has been recently reviewed using a pediatric construct.[8,9] The concluding statement from the publication of Drago et al provides a reasonable perspective on the development of the disease in a child: "*The presence of a new acute pediatric rhinosinusitis where sinusitis developed in an anatomically sequestered cavity, an active/negative local microbiome and pathogen/s interaction (not necessarily endowed in a biofilm) can presumably lead to a rapid progression of the disease. Subsequently, without an appropriate antibiotic therapy and/or with continued lack of natural clearing of accumulated mucous, bio filmed or non-bio filmed pathogenic bacteria become entrapped, and after 8–12 weeks of incubation obtain sufficient bacterial overgrowth to result in a chronic rhinosinusitis. Most of all these processes involved in the acute "bacterially" infected sinus tract and in the development of a chronic rhinosinusitis are still not known.*"[9]

The objective for this manuscript is to take a clinical view of pediatric infectious CRS, and provide accepted, known, and under-recognized tenets of medical

therapy for this disease with the goal of providing a perspective for improved patient care and/or future research.

Illustrative Case

A 5 y. male presents to a specialty respiratory medicine clinic with a chronic cough and a frequent nocturnal cough with emesis. He had an uneventful pregnancy and delivery, born at 35 weeks with 2 days in the NICU. No asthma in either parent, no intrauterine or home smoke exposure. He had early gastroesophageal reflux, but his proton pump inhibitor medication had been discontinued before age 2. Before his 2nd birthday he was diagnosed as acute croup, with a subsequent recurrent "croupy" cough. About age 4 his diagnosis was modified to asthma (cough variant); and micro-particle beclomethasone dry powder inhaler was prescribed two times a day. His cough was not remarkably improved, and historically the albuterol was not beneficial. His inhaler technique was not optimal for either the controller or rescue medication.

Pertinent examination findings revealed generous intra-nasal mucoid to mucopurulent drainage. Ear examination revealed bilateral serous otitis media. The chest examination was negative. A chest x-ray was normal. His skin tests to relevant allergens were negative. His waters and lateral sinus x-ray showed opacified maxillary sinuses, with minimal adenoid hypertrophy.

Chronic Infectious Pediatric Rhinosinusitis: Clinical Presentation

What are the clinical clues that a pediatric chronic sinusitis is the potential diagnosis for pediatric chronic upper airway symptoms?

There is not one over-riding symptom for pediatric infectious CRS, so the provider must have a high index of suspicion based on the over-all clinical presentation. Nasal congestion, chronic cough, supine cough, rhinitis (anterior or posterior) and chronic sniffling all, or in part, might be noticeable in pediatric CRS.[1] Chronic cough has a long and (sometimes) complex differential diagnosis, especially when standard medical care for a non-upper airway clinical diagnosis (i.e. cough-variant asthma) fails to resolve the symptom. The intranasal examination of CRS has a markedly variable presentation; in no particular order: intranasal purulent material, intranasal mucoid material, posterior nasal drainage (mucoid or purulent), pharyngeal lymphatic studding (cobble-stoning), or even a normal examination. The pediatric nasal examination is an art, and nuanced findings are gained with experience. The ability of "sinus" material to end up thru sinus drainage portals and into the nose is the critical variable. The co-morbid status of nasal bio-filming could add to the burden of the material expressed into the nasal vault. When chronic cough/ sniffling is present, the assumption is the volume and viscosity of the material exceeds the muco-ciliary clearance ability. In the author's experience foul nasal odor is not an issue, and when found strongly suggests a foreign nasal body.

Interestingly, a review of pediatric CRS by Silivu-Dan in 2014 stated "this condition is often overlooked in pediatric practice".[10]

Chronic Infectious Pediatric Rhinosinusitis: Radiological Aspects

Does a standard sinus film add additional information to clinical findings?

A historical and interesting report of repeated (serial) sinus x-rays in "average healthy children" published in 1940 serves as a backdrop to the conversation about routine sinus films.[11] This study will never to be repeated due to radiation hazards and informed consent, so, despite its age, it deserves mention. A comprehensive verbal description of the results of 3051 sinus x-rays in 100 children ages 1-14 years includes the following statement: "it has been a continual shock to us for several years to observe the frequency with which completely opaque sinuses are seen in the roentgenograms in the absence of clinical signs of infection"

A 1986 editorial concerning imaging of the paranasal sinuses reviews data from 1940.[12]In a summary of the use of standard sinus films, the author states"at any age the finding of a clear sinus is reliable and makes significant sinus pathology unlikely." He further states "that until age 6 years, the presence of mucosal thickening or sinus opacification is a common finding observed in one-third to one-half of children."

An Expert panel on pediatric Imaging concluded in 2018, based on a literature review, that "the Water view reveals a sensitivity of 84.2% and specificity of 76.6% (32% false-negative and 49.2 false positive) for the detection of sinus disease as compared to CT".[13]

A 2016 survey of American Rhinology Society and American Society of Pediatric Otolaryngology members only discussed sinus CT results in their pediatric CRS management practice.[14]

The evolution of radiological utilization in pediatric CRS is obvious, based on the data presented form 1940 to 2018. However, room still remains for discussion of the topic:

- If the accepted definition of pediatric infectious CRS is the "presence" of disease for at least 8-12 weeks it seems logical to assume that modern radiological sensitivity can accurately assess a difference between a non-infected sinus and the prolonged disrupted sinus mucosal barrier that exists in a CRS child.
- The necessity of imaging the sinuses of asymptomatic children is unwarranted.
- If a clinical diagnosis of CRS is determined, and therapy is initiated, an abnormal Water view sinus x-ray could support the diagnosis but not determine the treatment plan.
- The use of the plain sinus x-ray becomes a practitioner preference, and clinical experience is the principal attribute, and all evidence is factored into the treatment decision.[4]

In the illustrated case the non-aerated maxillary sinuses supported the clinical impression.

[4]The decision to not do a sinus CT was deferred if a referral to otolaryngology was necessary.

Chronic Infectious Pediatric Rhinosinusitis: Antibiotic Treatment Aspects

Are there evidence-based studies for antibiotic therapy for pediatric CRS?

There have been no multi-arm antibiotic studies for pediatric CRS since 1991. An extensive review of all consensus reports was summarized for 1966-2016.[1] The majority concensus was for Augmentin, with a time-frame of up to 6 weeks. The following (Table 1) lists options for the first-line treatment for pediatric CRS; although studies are not available to support more than clinical experience.[1] In the case of a penicillin allergic patient, alternatives are empirical, and every effort should be directed to resolving the penicillin issue expediently, as recently reviewed.[15]

Table 1. *Antibiotic Options in Pediatric CRS*

Augmentin 45 mg/kg
Amoxicillin 90 mg/kg
Cefuroxime axetil (20-30 mg/kg, divided BID)
Cefdinar (14 mg/kg, divided BID)
Clindamycin (20-30 mg/kg, divided TID)

Chronic Infectious Pediatric Rhinosinusitis: Ancillary Treat Aspects

What additional therapy could assist with resolution of pediatric CRS?

There appears to be an evolving support for using oral steroids concomitantly in pediatrics CRS.[1,4,16]Since the goal is to "resolve" a microbiologically-dictated inflammatory process in a sequestered cavity[9], the addition of a systemic anti-inflammatory has distinct possibilities. The sole pediatric double-blind protocol to date used oral steroids for 15 days with Augmentin vs Augmentin alone. [16]

Nasal saline rinse has been supported;[4] and could be supplemented with nasal steroids either as early or added therapy after oral steroids.[1, 4]A short course of dexamethasone ophthalmic drops (0.1%) might substitute as nasal steroids, although dose and duration has not been studied. Supplementing with intranasal Ciprofloxin otic drops might be a theoretical option, but pediatric studies are not available.Intranasal antibiotics used in a sinus rinse, such as Mupirocin, could be an option, although no data exists for infectious pediatric CRS.[17]

Probiotics are occasionally prescribed as adjunctive to gastrointestinal bacterial stabilization with oral antibiotics. Their role to orally re-populate the nasal and sinus microbiome is speculative. A probiotic nasal rinse has been released, but not studied in children. Empirically it has a potential place in prevention.

Chronic Infectious Pediatric Rhinosinusitis: Follow-Up Planning

Almost nothing is published on this topic. The exception would be the extensive otolaryngology literature that emphasizes the surgical role in "resolving" pediatric infectious CRS, which has been

summarized.[1] In regards to medical management at follow-up it has been previously stated: "*In that the medical community supports a definition of pediatric rhinosinusitis as a condition that has existed for a minimum of 12 weeks, it is illogical that there is little consensus to prove the condition is gone after using empirical antibiotic therapy which is being recommended for an arbitrary period of time.*"[1]

A true chronic pediatric infectious rhinosinusitis with appropriate antibiotic therapy for a reasonably extended period of time will have several outcomes at 4-6 weeks after therapy. *What are these possibilities?*

- Minimal or no resolution clinically (or radiologically);
- Clinical resolution, (but not radiological resolution);
- Clinical resolution, (and eventual radiological resolution);
- No radiological resolution with continued clinical resolution.

Unfortunately, there are no studies that have followed the natural history of a treated (or untreated) pediatric infectious CRS. Traditionally, the eventual outcome for an "unresolved" and "clinically active "CRS has been a surgical approach.[1, 18, 19] If, in fact, the CRS is not resolved, and clinically" inactive" what eventually happens is totally unknown; however, the suspicion is the symptoms will re-occur. Interesting, an older study by Racheflksy et al[20] suggested asthma has better outcomes when sinusitis is addressed**,** which indirectly suggests one- airway homeostasis can be achieved. The subject of asthma and sinusitis has been reviewed.[21]

Based on the empirically driven outcomes listed above, the follow-up of the illustrative case revealed:

Follow-up in one month revealed a largely resolved cough and total resolution of nocturnal cough and emesis. Mother stopped all asthma therapy due to improvement. Examination revealed improving serous otitisand a normal nasal examination, but bilateral expiratory wheezing. His pre-post albuterol pulmonary function test revealed a 14% improvement in the forced vital capacity at one second. His repeat sinus film showed persisting, near-complete, opacification. He was returned to bid micro-particle beclomethasone dry powderand oral Montelukast for asthma, and his sinus infection was treated with Augmentin plus Amoxicillin, each at 45 mg/kg, for 21 days, with an oral prednisone taper over 15 days. Due to the ascertainment of pediatric asthma, follow-up was planned. The on-going concern for his CRS remained.

If the child had prolonged (> 12 weeks) symptoms prior to the initial therapy, what period of time is allowable for their disease to completely remit?

To state the pediatric CRS outcome possibilities another way, once a 3month (or more) period of time has passed to result in a pediatric CRS the chance that the complex microbiologic milieu that has occurred (pediatric CRS) will spontaneously or gradually remit after only a 10 day course of an antibiotic seems unlikely. This, therefore, is the indirect argument for extended antibiotic therapy.

Chronic Infectious Pediatric Rhinosinusitis: Consultative Options

What are the several possible scenarios that might result in a consultation?

- The chronic symptoms dictate a referral to a respiratory specialist for the eventual diagnosis;
- There is evidence of a chronic sinusitis, which was partially treated, but with continued symptoms, and a surgical plan for the specific sinusitis diagnosis is required.

A child with a chronic cough and nasal congestion might be referred to a respiratory specialist, either an Allergist-Immunologist or a pediatric pulmonologist, who would diagnosis the CRS as a cause. Depending on the experience level of the provider and the proceeding therapy, the non-surgical specialist has options, although no major difference in antibiotic therapy choices truly exists (consensus only)[1], except for duration of therapy and the addition of adjunctive treatment. Follow-up with the specialist may entail several visits. Since the natural history of a treated, or even an untreated, pediatric infectious CRS is unknown, the child's symptoms, (with or without radiological support) will determine the outcome.

If a longer duration of symptoms, with partial or incomplete resolution of symptoms has occurred, the first referring physician may be an otolaryngologist. Surgical options may be presented, depending on the duration of symptoms. Multiple international surgical guidelines have been published, and all were referenced and reviewed in 2016[1]; and a summary of pediatric sinusitis surgical options was recently published .[19]

The 2nd follow-up of the illustrative case revealed:

At the end of the 3 weeks of dual antibiotic therapy, with minimal clinical symptoms throughout, the child and sister developed a viral illness, and the coughing with vomiting returned. The repeat pulmonary function on micro-particle beclomethasone dry powder was similar to the post-bronchodilator therapy test the previous month. The nasal examination was normal but the serous otitis remained. Serum immunoglobulins were normal. Immunological tests showed 1/14 pneumococcal antibodies titers in a protective range. The tetanus and diphtheria titers were protective. The sinus x-ray was not repeated. A PPSV23 (Pneumovax) vaccine was administered. A week later he was diagnosed with acute otitis media by his primary care provider, and treated with Cefdinir 14 mg/kg, divided bid x 10 days. His mother reported improvement per a phone conversation.

Time from Start to Resolution of a Chronic Rhinosinusitis

Using a time-honored definition that a chronic rhinosinusitis must have existed for 8-12 or more weeks at the point of diagnosis[18], there are no natural history studies that provide guidance to when a CRS disappears. Andfrustratingly, there are no definitions of a time-frame of "near" or total asymptomatic status to reassurance parents. Older children and adolescents might have a better opportunity to allow clinical decision making, but younger children with viral illnesses and day care experiences will have intermittent nasal conditions that might reduce clinical resolution assuredness. An older study of rhinovirus infection in adults did show a CT sinus abnormality can occur but clears within 2-3 weeks.[22]

Long-Term Prophylacticantibiotic Options for Treatment

A unknown and not medically addressed possibility to consider in pediatric CRS is that the microbiome in a long-term involved sinus is altered permanently. Similar findings occur in adult CRS.[8]If the microbiome is altered then re-occurrence of CRS or low grade persistence of CRS may be possible. The only indirect evidence of long-term persistence is the literature supporting a surgical approach to the disease.[1,18,19]. The potential for long term microbiome disruption raises the possibility that using macrolides for both their anti-infective and anti-inflammatory potentials.[23] There are, however, no controlled or open label studies in adults or children.

Long term azithromycin has been used in severe asthma, but macrolide resistance occurs.[24-25] In general, macrolides are not used in first-line pediatric CRS therapy, but their use as a suppressive approach might be a consideration in very selected cases. However, no studies are available in pediatric CRS to categorically support this approach, and using other antibiotics as prophylaxis are not recommended due to the development of resistance. In addition, studies have not shown isolation of *Chlamydiapneumoniae* or *Mycoplasmapneumoniae* DNA in sinus aspirates of adults with sinusitis.[26]

Modern microbiome identifications studies of extracted sinus tissue in children has potential for break throughs in understanding CRS in children.[8,9]

Chronic Infectious Pediatric Rhino sinusitis: Preventative Options

Given a successful, especially non-surgical, outcome for a patient CRS patient, what arepotential preventative approaches to avoid a recurrence?

With no direct outcomes based evidence available, but with reasonable empiricism, the following suggestions can be considered: a smaller daycare experience or in home care, no tobacco smoke exposure, allergy management and nasal steroids, proper home humidification, and pneumococcal titers evaluation and vaccination.

Proper management of each successive viral illness, possibly including sinus rinse is suggested[4], and the role of Mupirocin or ciprofloxin as antibiotics rinses may have a place. Sinus rinse with Mupirocin added to the lavage has been suggested in adult CRS,[17] but could be adapted to older children and adolescents.

The continuation of a new infectious rhinitis beyond 14 days suggests a 10-14 day course of antibiotics, as the key is not letting a new infection lead to the same prolonged CRS experience (assuming the original CRS was resolved).

Long-term re-alignment of the sinus microbiome is a (the) potential goal. A sinus rinse, Probiorinse ™, with Lactococcus lactis W136 nasal and sinus probiotic, is available without current FDA approval. No pediatric data is available. Oral probiotics and Vitamin D_3 supplementation for microbiome and immune homeostasis could be considered.[27-29]

At 3rd follow-up, he had finished Amoxicillin and was not coughing, but had resumption of nasal congestion.

His examination showed improved serous otitis (resolved); but mucoid intranasal drainage. A repeat x-ray was not done. His immunity was scheduled for a post- vaccination re-check, with pneumococcal titers, diphtheria titer and hemophilus influenza b titer. He was placed on Azithromycin Monday, Wednesday and Fridays at 5 mg/kg, and scheduled for a CT and ENT visit a month later.

Current Status for Assessing Resolution of a Pediatric Infectious CRS

Given a satisfactory completion of a single or subsequent course of antibiotics what parameters can be used to assess successful resolution of a pediatric CRS?

Currently, there are no definite methods for assessing total resolution of a child who had adequate treatment for a pediatric CRS. Some arguments has been raised here, and elsewhere, that a proper radiological procedure might demonstrate complete sinus clearing. [1,3, 12] which would be reassuring. In the absence or hesitation to utilize imaging, only good clinical judgement remains. This approach would necessitate extended temporal lack of the major (and minor) presenting complaints (See **Clinical Presentation),** along with resolution of visible co-morbidities (serous otitis, intranasal mucoid (or purulent) material), and when asthma is a co-morbidity, improved symptoms and control. The missing element in the clinical method is the definitive "proof" that the infectious CRS is gone and it won't, over-time, return or that a "recurrent" CRS is truly not a continuationof the "old" CRS, or the process is left as a persistence of an altered microbiome.[8,9]

Summary

A recent overview of this topic is available.[30] Pediatric infectious CRS continues to be a vexing problem, likely under-recognized in the primary care setting, and assuredly under-treated, and often perplexing to both allergists and otolaryngology specialists for a final solution. We offer here medical perspectives to the disease, but agree on the necessity of additional studies, although the limitation of blinded pediatric study protocols is appreciated.

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