Pediatric Chronic Rhinosinusitis: The Old, the New, and the Reasonable

CME EDUCATIONAL OBJECTIVES

1. Provide a working definition of pediatric chronic rhinosinusitis and differentiate this condition from that in adults.

2. Discuss the pathophysiology of chronic rhinosinusitis in children highlighting the role of inflammation and biofilms.

3. Determine the common comorbidities found with chronic rhinosinusitis in children and address treatment options for this condition.

C hronic rhinosinusitis (CRS), has a significant effect on a child’s quality of life. CRS may aggravate comorbid diseases and is often refractory to treatment.\(^1,2\) It is more frequently diagnosed in between the 4 and 7 years, whereas acute rhinosinusitis usually affects 1- to 5-year-old children.

The exact incidence of pediatric bacterial sinusitis is unknown. However, it may be inferred indirectly from the frequency of six to eight upper respiratory infections (URI) that children have every year, with 5% to 13% of these infections becoming acute bacterial rhinosinusitis. In adults, only 2% of viral URI become CRS. Similar information in children is not available.

A survey estimates the prevalence of CRS in the general adult population to

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be 2.7% to 6.6%, with an increase with age. This condition is often overlooked in pediatric practice, which may lead to lack of adequate management.

**DIFFICULTIES OF DIAGNOSIS**

Variations in the definition of CRS reflect our poor understanding of the exact nature of this condition.

Although its inflammatory nature is increasingly recognized as the main characteristic, the role of bacterial involvement, as well as that of the initiating events of host susceptibility and environmental factors in the pathogenesis of the condition, remain unknown.

There has been some consensus on a working definition of CRS: a multifactorial inflammatory disorder involving the nasal mucosa and paranasal sinuses, with symptoms persisting for more than 12 weeks. Similar to the adult form, diagnosis requires identification of two major, or one major and two minor, clinical criteria (see Table 1). At least one objective finding on physical exam or on CT scan needs to be added.

Accurate diagnosis of pediatric CRS is difficult because children present with more nonspecific, subtle symptoms than adults. Physical exam may be unremarkable or difficult to carry out optimally if the patient will not tolerate nasal endoscopy and because imaging procedures in this age group are generally discouraged.

Because children have frequent URIs and are prone to allergic rhinitis, both diseases with similar symptoms to CRS, it is hard to tell where one pathology ends and the other begins. Suspicions of CRS in children may be decreased by the occasional belief that paranasal sinuses are not yet developed in the small child.

**ANATOMY AND PATHOPHYSIOLOGY**

The paranasal sinuses are air-filled cavities in the bones of the head that communicate with the nasal passage through tubular openings (ostia). They are lined with a ciliated epithelium that sweeps mucus toward the ostia. The maxillary and ethmoid sinuses are the most commonly involved in young children’s sinusitis and are present at birth. Their complete pneumatization is reached at about 12 years. Sphenoid sinuses begin to develop at 3 years, and frontal sinuses begin to appear at 7 years. Pneumatization of these sinuses is completed in mid- to late adolescence. The frontal sinuses may remain underdeveloped in 15% of the population, while the sphenoid sinus is hypoplastic in 26% of the population. The prevalence of sinusitis increases after 6 to 8 years, marking the addition of the frontal sinuses as another site that can be affected by rhinosinusitis.

**KEEPING SINUSES HEALTHY**

Normal function of the sinuses requires that the ostia remain patent, the mucociliary function is normal, and the systemic and local immunity responses are appropriate. When all of these work well, sinuses generally remain sterile and transient, low-density bacterial contamination is dealt with effectively.

**THE ORIGINS OF DISEASE**

Defective mucociliary clearance, obstructed sinus drainage, or a large microbial threat close to the sinuses may act individually or in combination to lead to the development of CRS.

Ostium patency is affected by mucosal inflammation of any type or by mechanical obstruction. The mucosa in the nasopharynx and overlying adenoids and tonsils may harbor bacterial aggregates of more than 10^4 CFU/mL, constituting the source of infection for adjacent sinuses.

Blocked mucus drainage through the sinus ostia decreases oxygenation and lowers the pH inside the sinuses. These local conditions facilitate bacterial growth. Once purulent secretions form, they further contribute to the decrease of oxygenation in the sinuses.

CRS, however, does not result simply from obstruction to sinus drainage and exposure to microorganisms. The nasal epithelium mounts an inappropri-
THE ROLE OF INFLAMMATION

Mucosal biopsy samples of CRS show intense inflammation with eosinophils, neutrophils, and lymphocytes, as well as T-cell-produced cytokines and chemokines, in response to allergens, irritants, such as ozone or cigarette smoke, or exposure to bacterial superantigens.

Regardless of the inciting factor, the elevation in cellular constituents in CRS points to a vigorous immune response. The effects of the released mediators are vasodilatation, increased mucus secretion, plasma extravasation, neurogenic inflammation, and mast cell-nerve interactions. The resulting inflammation leads to local changes that favor the development of infection, as previously described. Inflammation and infection engage in a cycle that may explain in part the protracted nature of CRS.

Samples of sinus mucosa from young children (1 to 8 years) with CRS show a lymphocytic infiltrate unlike in adults, in whom eosinophils and neutrophils prevail. The eosinophilic remodeling with thickened basement membrane and submucosal gland hyperplasia seen in adults is not present in young children with CRS. These morphologic changes become apparent only in older children, suggesting that there may be a progression of sinus tissue damage from the very young to the adult type of CRS. Early diagnosis and treatment may prevent the long-lasting changes typical for CRS.

ELEMENTS OF INFECTION

CRS used to be thought of essentially as an infection of the sinuses. Paralleling the recognition of its inflammatory nature, there is increasing doubt about the role of infection in CRS. This may be partly caused by difficulty identifying any pathogens on cultures of nasopharyngeal secretions, and the less-than-optimal effect of antibiotics that, in the absence of culture and sensitivity guidance, are used empirically. Even when positive cultures are obtained, contamination with colonizing bacteria is often suspected.

From a more integrated perspective, numerous factors contribute to CRS, including infection, because it causes inflammation. The lack of success in treating CRS with antimicrobials is explained by the fact that CRS is generally managed as a planktonic (free-floating) bacterial infection. However, ample evidence shows biofilm to be present in surgically removed sinus mucosa from patients with CRS.

BIOFILM IN INFECTION

A bacterial biofilm consists of complex colonies of microbial cells that live within a self-produced polysaccharide matrix and are strongly adherent to surfaces, such as respiratory mucosa. Microorganisms cross-talk, a process called “quorum sensing.” Within biofilms, bacterial gene expression is different from in the planktonic state and metabolic requirements are reduced. These adaptations render the biofilm bacteria more resistant to antibiotics and to killing by immune factors. The reservoirs of biofilm for sinuses are the adenoids, tonsils, and nasopharyngeal mucosa.

Biofilm pathogen identification requires research-based networks. Antibiotics best suited to treat biofilms may need different characteristics than those effective against free-floating bacteria. Biofilms associated with CRS are typically polymicrobial, commonly including Staphylococcus aureus, Pseudomonas aeruginosa, Streptococcus pneumoniae, coagulase-negative Staphylococci, Moraxella catarrhalis, Haemophilus influenzae, anaerobes, and even fungi.

CLINICAL FEATURES

The usual symptoms of CRS in adult sand the most common presenting symptoms in children listed in Table 2.
these complications may be delayed because symptoms continue to resemble those of sinusitis.\textsuperscript{14,15}

**PREDISPOSING FACTORS/COMORBIDITIES**

It is not clear whether host factors (systemic and local) and environmental conditions that affect CRS induce the disease or share a common pathway of pathogenesis with it. Following is a listing of these factors.

**Environmental Factors**

Viral URI is the most common predisposing factor for bacterial sinusitis. Attendance in day care facilities triples the incidence of URI.\textsuperscript{3,16} Viral rhinosinusitis causes nasal obstruction and abnormal mucociliary activity.\textsuperscript{3} Symptoms that persist for weeks and months after a viral respiratory infection should raise consideration for an ongoing CRS. Increased exposure to bacteria or fungi heightens the risk of superimposed secondary infections.

Environmental exposure to tobacco smoke inhibits mucociliary clearance and epithelial regeneration. Noxious inhalants, such as ozone, chlorine, and other pollutants, present as small particulate matter may irritate the nose and sinuses.\textsuperscript{3,17} Systemic host factors may cause or worsen CRS.

**Allergic Rhinitis**

Allergic inflammation alters the sinonasal physiology with regards to mucociliary clearance and patency of the ostia. Late-phase allergic inflammation may contribute to CRS development.

Immunotherapy for allergic rhinitis was shown to help in CRS.\textsuperscript{5} However, it is still controversial whether allergy plays an important role. Overlapping symptoms make it difficult to differentiate between the two conditions.

In some studies, the prevalence of sensitization to aeroallergens in CRS patients is about the same as in the general pediatric population, whereas other studies show a higher prevalence of atopy in patients with CRS compared with the general population. Allergic-type inflammation (elevated IgE, presence of IL-4) can be found even in the non-allergic CRS patients.\textsuperscript{4,18}

**Local Allergic Rhinitis**

Some studies have not shown a significant association with local allergic rhinitis because some patients have local nasal allergy without positive skin tests or serum IgE elevation. These patients meet the clinical criteria for perennial or seasonal allergic rhinitis. Positive nasal allergen provocation tests may prove the correlation.

In some studies, nasal provocation tests to dust mite allergen were positive in 54\% of patients thought to have idiopathic rhinitis. Nasal provocation tests were positive to seasonal allergens in 62.5\% of patients with rhinitis and negative skin tests. It appears that local B cells in the nasal mucosa can become sensitized and produce specific IgE that binds to local mast cells.\textsuperscript{19}

**Nonallergic Rhinitis**

From 17\% to 52\% of CRS is associated with nonallergic rhinitis, which has a 5\% to 10\% prevalence in the general population. Rhinitis triggered by allergic and non-allergic factors is considered mixed rhinitis.\textsuperscript{5}

**Allergic Fungal Rhinitis**

The role of fungi in the pathogenesis of CRS is unclear. Fungi are present in the air at all times and can be found in the normal nose. Allergic fungal rhinosinusitis (AFRS) is a noninvasive form of CRS, caused by a hypersensitive reaction to the inhaled fungi. This is the most common form of fungal CRS in children.\textsuperscript{20}

All children with AFRS are atopic, and almost all have nasal polyps. In children with unilateral asymmetrical nasal polyps, facial abnormalities, or proptosis, AFRS should be considered.\textsuperscript{21}
Asthma

Asthma occurs in frequent association with rhinitis — 80% of children and adolescents with asthma have rhinosinusitis, and 40% of children with CRS have asthma. Asthma and CRS can amplify each other, and they show correlating severity. Treatment of CRS often improves bronchial hyperreactivity. It is not clear how exactly the two conditions interact.

Cough is often thought to be a symptom of asthma. However, in one-third of patients with a nocturnal cough, it is not asthma but CRS that causes the symptom. Chronic cough is a prominent symptom of CRS in children. The widely embraced concept of cough-variant asthma may decrease the likelihood that pediatricians will make the diagnosis of CRS.5,21,22

Immunodeficiency

Immunologic incompetence or immaturity may contribute to the pathophysiology of CRS in children. CRS, usually without polyps, is the most common complication of common variable immunodeficiency (75%).23,24 Immunocompromise secondary to chemotherapy in children is associated with an increased incidence of CRS and invasive fungal sinusitis in these patients.1

Immunodeficiency is usually suspected when a patient has recurrent pulmonary infections and otitis media in addition to chronic rhinosinusitis, or when CRS is poorly responsive to usual therapy.20

Otitis Media with Effusion

Otitis media is often a presenting symptom of chronic rhinosinusitis. In one study, radiologic abnormalities in keeping with CRS were found in patients with otitis media refractory to treatment in half of the patients 10 to 20 years and in almost 80% of the 4- to 9-year-old children.25

Because the middle ear has an anatomic and functional connection with the nasopharynx through the eustachian tube, the middle ear cavity is also a paranasal sinus. Nasal mucosal inflammation may cause obstruction of this “sinus” ostia, (ie, the eustachian tube opening), leading to its dysfunction. Consequently, the middle ear pressure is impaired and fluid accumulates.21

Gastrointestinal Issues

Gastroesophageal reflux disease (GERD) is related to CRS in some pediatric patients, but its association with respiratory disease and remains in doubt.1 Gastroesophageal reflux is a physiological phenomenon at 3 to 4 months and naturally decreases thereafter, but it is still present in 20% of infants. Pharyngeal reflux is documented in half of these children.26

On the other hand, studies have shown that esophageal reflux occurs in 63% of chronic rhinosinusitis patients and in only 5% of the general population. Nasopharyngeal reflux was demonstrable in one-third of children in the CRS group. Treatment of GERD resulted in significantly improved sinus symptomatology for most patients, even when nasopharyngeal reflux was not demonstrated.27

In another study, therapy of coexisting GERD in children with refractory chronic rhinosinusitis often obviated the need for sinus surgery.21,28 The clinical diagnosis of GERD is difficult because children rarely complain of typical symptoms of heartburn, sour eruptions, or regurgitation. They commonly have less specific manifestations, such as nausea and decreased appetite.27

Reflux of gastric acid into the pharynx and nasopharynx can cause sinus ostial inflammation, impaired mucociliary clearance, and, consequently, sinusitis.29

Cystic Fibrosis

Cystic fibrosis (CF) is an autosomal recessive disease caused by a gene mutation that leads to formation of thick viscous secretions favoring infections in the respiratory tract. P. aeruginosa and S. aureus are the microorganisms most frequently cultured from the sinuses.24

Nasal polyps are generally rare in children, but 5% to 86% of CF children have nasal polyps. Even in the absence of symptoms, most CF patients have chronic sinus inflammation. The prevalence of CRS is increased even in heterozygotes when compared with normal populations. CF should be considered in children with nasal polyps or with CRS appearing at an early age.5,24

LOCAL HOST-RELATED FACTORS

Primary ciliary dyskinesia is a rare genetic disease in which the sinonasal cilia are reduced in number and have abnormal morphology and function. All these predispose to infection. Biopsies to evaluate the morphology of cilia are difficult to interpret.14 Interestingly, nasal polyps do not develop in primary ciliary dyskinesia, despite mucus stasis and inflammation.30

Mucociliary dysfunction may also occur secondarily to infection. The morphology of cilia may become abnormal in the context of CRS itself, contributing to the self-perpetuating nature of the disease. Loss of ciliated epithelial cells occurs in rhinitis medicamentosa induced by topical decongestants, explaining the delay in a return to normalcy of the sinonasal mucosa even after discontinuation of the vasoconstrictor drugs.31

Anatomic abnormalities that cause nasal obstruction may be conducive to unilateral or bilateral sinusitis. Septal dislocation caused by birth trauma, unilateral choanal atresia, nasal fractures, foreign body in the nose, septal deviation, or concha bullosa (middle turbinate aerated from the ethmoids) can cause blockage. Dental infections may spread into the sinuses, causing odontogenic sinusitis.8

A family history of asthma or inhalant allergies appears to be a risk factor for the development of pediatric CRS.14,23
CHALLENGES IN DIAGNOSIS

The history should elicit information regarding specific symptoms and pattern of symptoms to assess exacerbations and complications, precipitating factors, existing comorbid conditions, environmental exposure, personal and family medical history of atopy, and response to therapy. A particular challenge for the pediatrician is to differentiate true CRS from frequent URI, or perennial allergic rhinitis with overlapping manifestations.

A handheld otoscope or a head lamp with nasal speculum are usually appropriate for a nasal examination to look for purulent discharge, swelling, and other mucosal changes. Nasal endoscopy may be difficult in young children because it requires cooperation. In older children, it may be satisfactorily carried out after a topical decongestant and a local anesthetic spray.

Transillumination of sinuses is not reliable in children. It may be useful only if complete opacification is present.

IMAGING

Sinus X-rays are discouraged, except for exceptional circumstances. Sinus X-rays are non-specific and insensitive, with many false positive and false negative results. Only the Caldwell and Waters views are helpful in children younger than 4 years; lateral views may be added for older than 4 years. Sinus X-rays are technically difficult if the child is uncooperative and or if positioning is incorrect.

A computerized tomography (CT) scan is not necessary for the diagnosis. It is the imaging modality of choice only in presurgical cases. The radiation doses delivered are higher than plain X-ray, and thus are a concern for children. The American Academy of Pediatric Section on Radiology states that “pediatric health care professionals’ role is to decide when CT is necessary and to discuss the risk with the patient and family.”

Some specialists believe that sinus CT scan is reasonable if a child has failed to respond to 3 weeks of antibiotic therapy and CRS is suspected. Contrast media is not generally needed, unless complications are suspected. CT scan should be done urgently in propptosis, impaired eye movement, or vision because of orbital complications; CT scan should be done emergently if an intracranial spread of sinusitis is suspected (severe headache, vomiting, altered sensorium).

Magnetic resonance imaging (MRI) is generally not practical because of its high cost and sedation requirements. It can differentiate between sinus secretions and mucosal thickening, between inflammation and malignancy, and is very useful in chronic fungal sinusitis.

PATHOGEN IDENTIFICATION

Bacterial recovery is not recommended when deciding on management. Empiric treatment may be started once the clinical diagnosis of CRS is made. Nasal and postnasal cultures are not reliable. Maxillary sinus puncture is the gold standard to retrieve relevant microorganisms; a drawback is that it reflects only the pathology in the maxillary sinus.

It is an invasive and uncomfortable procedure, performed only by otorhinolaryngologists. To correctly identify pathogens in biofilm tissue, the sample requires tests used only in research. Fungal cultures are never required in children, because their form of fungal CRS is not invasive.

COMORBID CONDITIONS

When allergies or asthma are suspected, a full work-up by an allergist is indicated, which may include an environmental assessment, skin tests, nasal provocation tests, and pulmonary function tests as deemed necessary. When immunodeficiency is suspected, immunoglobulins and lymphocytes should be assessed.

Investigations for GERD involve pH esophageal monitoring, if symptoms suggest this condition. For CF, a sweat chloride test should be done.

To diagnose mucociliary dyskinesia, a mucosal biopsy may be done.

MEDICAL OR SURGICAL TREATMENT

Treatment of CRS in children has medical and surgical components. Initial therapy should be medical, except where obvious anatomic obstruction requires surgical relief.

Medical treatment should address both the inflammatory and infectious components. CRS is now recognized as a multifactorial inflammatory disorder rather than a mere persistent bacterial infection. Nonetheless, sinus drainage is impaired in all forms of CRS, leading to secondary bacterial infections. Typically, relatively long-term courses of antibiotics are needed to treat acute relapses of CRS, based on experience in adults.

Antibiotics are given over 3 to 4 weeks, rarely longer, until the patient is symptom-free for 7 to 14 days. Short-term courses are inadequate. The antimicrobial agent covers a polymicrobial infection with aerobic and anaerobic bacteria.

These are shielded by the biofilm structure, exhibit certain resistance patterns, and produce beta-lactamase. Taking these issues into consideration allows effective empiric use of antimicrobials, despite the lack of reliable culture/susceptibility results in most cases. In the future, polymerase chain reaction testing on biofilm tissue may lead to more accurate identification of pathogens to guide therapy.

Studies have showed amoxicillin-clavulanic acid or cefuroxime axetil provide good first-line treatment. Macrolides, with anti-inflammatory effects in addition to their antibacterial activity, may be better than other classes of antibiotics in treating biofilm infection.
Treatment data are mostly derived from adult studies and can only be extrapolated to pediatric CRS.11

Clindamycin, the “newer” quinolones (levofloxacin, moxifloxacin), and cephalosporins other than first generation have all been used successfully.

For methicillin-resistant Staphylococcus aureus, a clindamycin and sulfamethoxazole-trimethoprim combination was reported to be effective.6 The effectiveness of topical antibiotics and antifungals has not been proven.4 Antifungals are not recommended because there is no evidence of effectiveness.21

Nasal steroid sprays are being widely used to decrease inflammation from CRS, based mostly on anecdotal evidence. However, a recent literature review has confirmed that they provide a modest benefit. Some preparations have been reported to reduce linear growth, at least temporarily.

Mometasone furoate is the only intranasal corticosteroid approved for patients older than 2 years. This drug has no long-term effect on growth or the pituitary axis. Fluticasone propionate is approved for those older than 4 years.6

Oral corticosteroids are probably safe and effective when given in short bursts for severe symptoms of CRS; repeated or prolonged use significantly enhances the risk of side effects.33

Adjuvant therapies in children include oral antihistamine if allergy is present. In the absence of allergies, antihistamines are not used to treat bacterial sinusitis because they can thicken and dry secretions.

Saline nasal washes help remove crusts, infective agents, and inflammatory mediators, liquefy secretions, act as a mild vasoconstrictor on nasal blood flow, and provide symptomatic relief. They show consistent evidence of benefit and are recommended as adjunct in the therapy of CRS.5,32 Nasal saline washes at concentration of isotonic saline (0.9%) or hypertonic saline are commercially available or can be home-made. Instructions for preparation and use of a common regimen of an isotonic nasal saline solutions are presented in Table 2 (see page 215).

Oral mucolytics, such as guaifenesin, may benefit symptoms of CRS. Proven to be an effective expectorant, its use remains empiric in CRS. It has no side effects, and it is recommended for symptomatic relief.4 Antileukotrienes have no proven efficacy in CRS.21

Preventing and treating comorbid conditions include antireflux therapy in GERD,12,24 environmental control for allergens, smoke, and pollutants exposure.21 Antibiotic-associated diarrhea occurs in 11% to 31% of children treated with antibiotics.

The potential role of probiotics in reducing the risk of this complication has been studied with increasing interest. While inconclusive results exist, some studies and meta-analyses of trials found evidence that probiotics given during antibiotic use, either as single agents (ie, Lactobacillus) or as yogurt containing active bacterial culture, decreased significantly the incidence of diarrhea in these children. They are safe to be used except in patients with a compromised integrity of the barrier of the intestine, those with short gut syndrome, the immunocompromised, and patients with central venous catheter. A large proportion of recently surveyed gastroenterologists confirmed they recommend probiotics in selected patients taking antibiotics.34-37

SURGICAL TREATMENT

Surgery is rarely indicated and should be considered as a last resort in the pediatric population.5 Adenoidectomy is the first-line surgical step to remove the reservoir of biofilm for chronic sinus infection. Functional endoscopic sinus surgery (FESS) can be done to enlarge natural ostia and to correct anatomic deformities bearing an effect on CRS. It may be considered when there is no improvement with maximal medical therapy, in failed adenoidectomy, in CF, ciliary dyskinesia, patients with immunodeficiency and allergic fungal sinusitis. There are concerns of hindering midface growth in children undergoing this procedure, with conflicting data.24

WHEN TO REFER A PATIENT WITH CRS

Specialist consultation should be sought when:

- The allergic or immunologic basis of a case of CRS needs to be clarified;
- There is refractoriness to appropriate treatment;
- There are frequent exacerbations that will severely affect the child’s quality of life and performance;
- There are opportunistic infections, symptoms and signs suggestive of CRS complications; or
- Comorbid factors need further assessment (ie, GERD).

SUMMARY

Pediatric CRS may present with subtle, nonspecific symptoms, not always matching the criteria of diagnosis established for adults. It is a multifactorial disease and it requires a comprehensive and sometimes a multidisciplinary approach. As a biofilm infection, CRS needs therapy that takes this fact into consideration. Use of probiotics in conjunction with antibiotics in selected patients may reduce the risk of antibiotic-associated diarrhea.

Our understanding of the role of predisposing/comorbid factors is evolving. The concept of local rhinitis may change the thinking about the involvement of allergy in CRS. Appropriate work-up should take into consideration these factors as clinically indicated.

Histopathologic data may indicate that there is progression in the severity of tissue damage over time and that early diagnosis and treatment may prevent this progression.
REFERENCES


