

Problem-based learning discussion: Medical treatment of pediatric chronic rhinosinusitis

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ABSTRACT

*This problem-based learning case focused on the approach to evaluation and management of a 5-year old girl who was “always sick” with sinus infections. The discussion unfolds in a “real life” scenario, i.e., based on information available to the clinician initially and after the acquisition of laboratory data, and, ultimately, after sinus surgery. Emphasis is placed on the differential diagnosis of the patient’s symptoms, discussion of the initial management strategy for chronic rhinosinusitis (CRS), evolution from acute rhinosinusitis to CRS, the prevalence of and differential diagnosis of nasal polyps in children, treatment considerations specific for CRS with nasal polyps, the significance of *Pseudomonas aeruginosa* sinus infection, the significance of an abnormal sweat chloride test in a young child with nasal polyposis, special considerations in children with CRS who have cystic fibrosis, treatment considerations after endoscopic sinus surgery, and, finally, prognostic factors that impact the outcomes of endoscopic sinus surgery. This problem-based learning case highlights many facets of managing refractory CRS in children.*

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[The Facilitator Presents the History]

Christy S. was a 5-year-old girl, who presented to the physician’s office accompanied by her mother, with the chief concern that, “She is always sick.” Her mother narrated that she had been sick with respiratory infections since she started preschool this fall; she has had greenish yellow nasal mucus associated with a severe cough and fevers up to as high as 102.5°F, in association with either an ear infection or a sinus infection every 2–3 weeks for the past 5 months. Each time she was sick, she had been seen a different pediatric nurse practitioner or pediatrician at the big clinic in town. Her mother reported that, although some of the providers waited for 2 weeks before they prescribed an antibiotic, “Others prescribed it right away, generally for 10 days.” Within several days, Christy’s colored mucus, cough, and fever usually subsided. Most recently, a different pediatric nurse practitioner reviewed her chart and said that she might just have the same infection that was “not getting totally better” and prescribed her a 3-week course of amoxicillin–clavulanic acid, along with fluticasone nasal spray once a day. However, although her symptoms initially improved, within 1 week off the antibiotic, her nasal congestion and purulent secretions returned, at which time the pediatric nurse practitioner put her back on amoxicillin–clavulanic acid for another 3 weeks and said, “Christy needs to get a sinus computed tomography (CT) near the end of her 3-week course and needs to see either an allergist or an otolaryngologist to determine if anything more can be done.”

Before developing the constant nasal symptoms this fall, Christy had experienced intermittent nasal congestion for over a year. Previously, her mother had tried several over-the-counter cold remedies for Christy and daily cetirizine for several months without benefit. Her mother also noted that, when Christy experienced worsening nasal symptoms, it also flared her asthma and required the use of an albuterol inhaler up to every 4 hours for a few days.

At approximately the age of 2 years, Christy was diagnosed as having Asperger syndrome and had always been extremely difficult to adequately examine, especially her eyes, ears, and nose. However,

she had had normal growth and development otherwise and was in Kindergarten this fall but had not attended preschool.

Her review of systems was noncontributory. Her medical history was notable for no emergency department visits or hospitalizations. Christy experienced intermittent coughing and wheezing episodes since infancy, but she had only needed a few courses of oral steroids in her first 2 years of life; none in the past 3 years. She had no drug allergies. Her environmental history was notable for the fact that she lived with her mother, father, and 8-year-old brother in a 10-year-old home, in a suburban neighborhood, with 5-year-old carpeting and a 3-year-old cat that would get on her bed. Christy was not exposed to cigarette smoke. She slept on a 3-year-old mattress, with a synthetic polyester pillow and quite a few stuffed animals on her bed. Her family history was significant only for her mother having hay fever each spring and fall.

On physical examination, Christy is a well-appearing white female child in no acute distress, until you attempt to examine her. She had to be restrained by several of your staff and her mother while you attempted her examination. Her vital signs revealed a normal respiratory rate of 18 breaths per minute, heart rate of 100 beats per minute, and height and weight in the 50th percentile. Examination of her eyes revealed bilateral infraorbital edema; her tympanic membranes were dull bilaterally, without a light reflex and decreased mobility bilaterally as best as can be determined. Examination of her nose revealed pale and edematous mucosa, with scant yellow rhinorrhea on the right. Examination of her throat revealed a somewhat erythematous pharynx, with a cobblestoned appearance, but no post-nasal drainage as you got a glimpse of her pharynx. Her chest was clear while screaming. The rest of the examination was normal.

[The Facilitator Asks: “What is your impression?”]

The Initial Clinical Impression. In learning Christy’s history, my diagnostic impression before obtaining a sinus CT was that she had either chronic rhinosinusitis (CRS) or recurrent acute rhinosinusitis (RS). Certainly, she could also have underlying perennial allergic rhinitis as a contributing factor to RS, but perennial allergic rhinitis would not account for her febrile episodes and prompt response to antibiotics. The major distinguishing feature between CRS and recurrent acute RS is that patients with recurrent acute RS have episodic rather than continuous symptoms, are healthy between episodes, and have no evidence of chronic disease on sinus CT.¹

There was discussion in some of the breakout groups about whether a sinus CT should be done before initiating medical treatment. Expert panel reports are equivocal on this point. It is universally agreed that objective evidence of sinus disease is needed to

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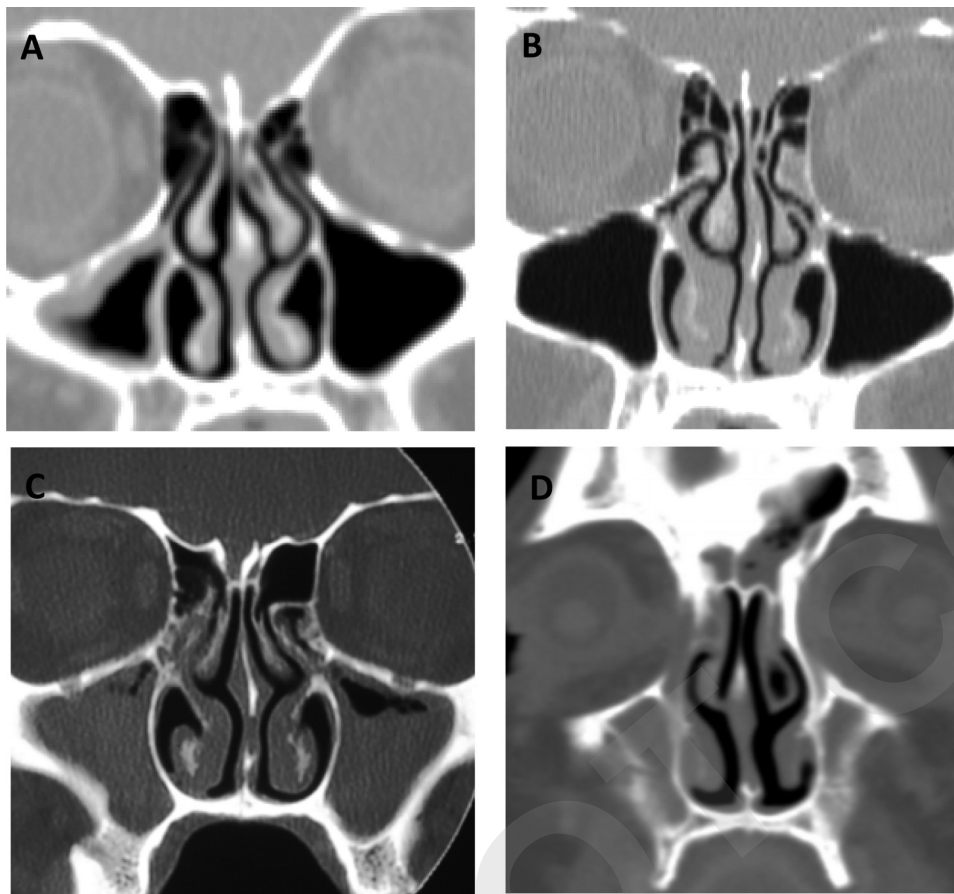


Figure 1. Examples of sinus ostial obstruction that may cause chronic rhinosinusitis. (A) Soft-tissue obstruction of the right maxillary sinus infundibulum, with associated mucosal thickening in the right maxillary sinus. (B) Isolated opacification of one left anterior ethmoid cell. (C) Bilateral soft-tissue obstruction of the maxillary infundibula, with associated near-complete opacification of both maxillary sinuses. There is associated soft-tissue thickening overlying both uncinate processes. (D) Obstruction of the left frontal recess, with associated partial opacification of the left frontal sinus, with bubbly appearing fluid present. Note: The frontal sinuses are not developed in the images shown in (A), (B) or (C).

establish the diagnosis of CRS. However, although nasal endoscopy is acknowledged as an acceptable means of documentation, in a primary care office, nasal endoscopy is not always available. An alternative would be to make a presumptive diagnosis of CRS and initiate medical treatment, thereby reserving the sinus CT for patients whose symptoms fail to resolve with this treatment. However, there are potential drawbacks to this approach. A sinus CT can be highly valuable to establish the diagnosis of CRS and guide appropriate treatment. A child may present with symptoms of nasal congestion and chronic mucoid drainage (with or without nasal purulence) of >12 weeks' duration, which thereby fulfilled symptomatic criteria for CRS, but have only allergic rhinitis with a negative sinus CT. In such a case, embarking on a course of intensive medical treatment (as discussed later) for CRS would be unwarranted and expose the patient to unnecessary treatment. However, in this case, the presence of nasal purulence and response to antibiotics, with rapid recurrence of symptoms after cessation of antibiotic treatment, were highly suggestive of CRS.

Expert guidance reports acknowledged that initiating medical treatment before obtaining a sinus CT is a reasonable approach. A guidance document was also recently published that addressed appropriate use of sinus CTs in children. This document states that a sinus CT is indicated in pediatric patients with CRS when medical management and/or adenoidectomy have failed to control symptoms.²

How Is Normal Sinus Function Maintained? Maintaining sinus function requires five essential elements: patent sinus ostia, adequate mucociliary clearance, normal systemic immunity, local innate immunity, and protection of the sinus mucosal barrier.³ In most cases, the development of CRS without NP is due to persistent sinus ostial blockage, which sets the stage for persistent sinus infection. This may

involve partial or complete blockage of one or both ostiomeatal units, but, alternatively, it may involve any sinus, even an isolated ethmoid sinus blockage. A few examples of sinus ostial blockage seen in CRS are provided in Fig. 1. It should be noted that the ethmoid and maxillary sinuses are typically pneumatized at birth, but pneumatization of the sphenoid and frontal sinuses begins at 9 months and 5 years, respectively.⁴⁻⁶ In less-common instances, CRS may arise without sinus ostial blockage, as in the case of occult odontogenic rhinosinusitis.

Evolution from Acute RS to CRS. CRS that arises from sinus ostial blockage evolves in stages, with different pathologic processes, different bacteriology, and different forms of medical treatment that apply in each stage. The earliest stage of CRS evolves from antecedent acute RS with sinus ostial blockage as depicted in Figure 2. Experts use the term "subacute sinusitis" to denote the transition period from acute RS to CRS, but there is debate as to whether to define the time frame of subacute RS as 4–8 weeks⁷ or 4–12 weeks.¹ This distinction is arbitrary. The best data on subacute RS come from bacteriologic studies of patients who had symptoms from 30 to 120 days, which found that the organisms associated with subacute RS were the same as those involved in acute RS, with a predominance of *Streptococcus pneumoniae*, *Hemophilus influenzae*, and *Branhamella (Moraxella) catarrhalis* (the latter mainly being found in children).^{8,9} The most recent expert panel reports define acute RS as symptoms that last up to 4 weeks and CRS as having symptoms that last 12 weeks, which implies that patients with symptoms for 4–12 weeks have subacute RS.¹⁰

In the transition from subacute RS to CRS, the bacteriology transitions from acute RS bacterial pathogens to a greater prevalence of α -hemolytic streptococci, coagulase-negative *Staphylococcus*, and anaerobes.¹¹ The prevalence of anaerobes is likely under-

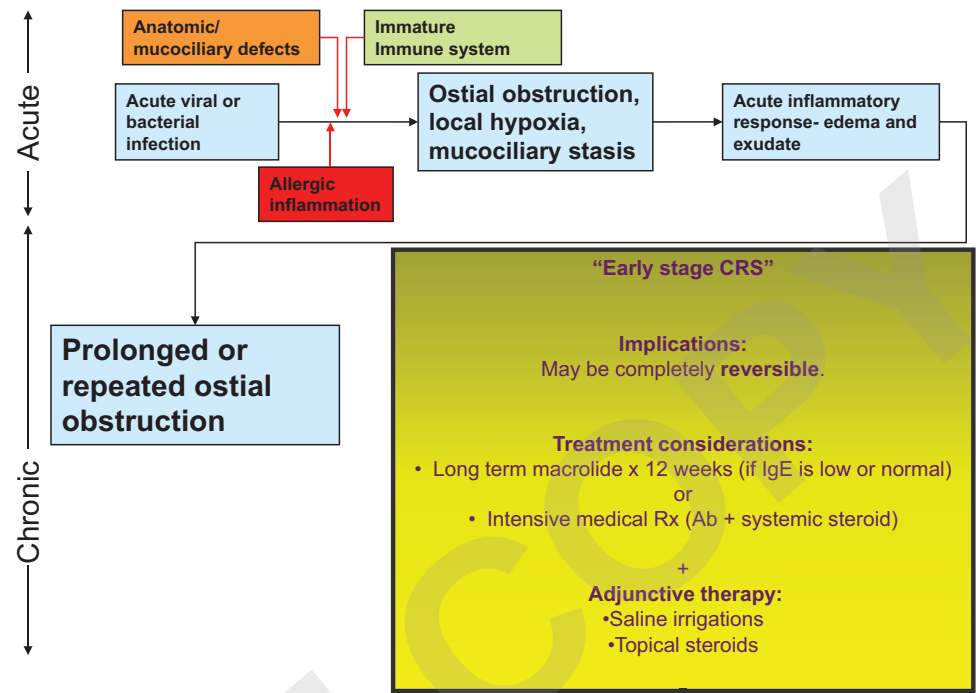


Figure 2. Uncomplicated "early" stage pediatric chronic rhinosinusitis (CRS).

estimated in many studies due to limitations in anaerobic sampling methods. As CRS becomes more persistent, the disease process becomes more complex, difficult to manage, and less likely to be reversible with medical treatment as depicted in Figure 3. In patients with CRS who are going to sinus surgery, studies have identified the presence of mucosal biofilm in 56.3%.¹² Furthermore, the presence of bacterial biofilm was found to be associated with more-severe preoperative disease and more-persistent disease after surgery.^{13–15} Several studies have pointed to the importance of adenoidal biofilm as a key factor in pediatric CRS, which represents an important difference from adult CRS. In the study by Cotichchia *et al.*,¹⁶ adenoidal biofilm area was found to cover, on average, 94.9% of the mucosal surface in CRS cases and only 1.9% of the mucosal surface in cases of adenoidal hypertrophy associated with obstructive sleep apnea.

[The Facilitator Asks: "What diagnostic testing would you consider in this case: Allergy testing? Sinus CT? Immune evaluation? Other?"]

My stepwise approach to pediatric CRS evaluation and management is outlined in Fig. 4. Initially, a preliminary diagnosis of CRS could be made based on the clinical history and physical examination, without the luxury of having objective documentation by sinus CT or nasal endoscopy. This preliminary diagnosis is sufficient to guide initial treatment. A presumptive guess is made as to which type of CRS is present, *viz.* either CRS without nasal polyps (NP) (the most common in children) or CRS with NPs (CRSwNP) (if NPs are seen on physical examination). Although allergic fungal RS (AFRS) would be difficult to suspect based solely on a history and physical examination, it could be considered more likely if the clinical history were that of unresolved CRS despite multiple rounds of antibiotics or if gross facial dysmorphism were present, possibly even in the absence of symptoms.¹ However, confirmation of a CRS subtype will require objective documentation, either by sinus CT, nasal endoscopy, or sinus surgery. Because evaluation for perennial allergy could have an impact on clinical care, I agreed that it should be done in this case.

[The Facilitator provides the following test results and asks: "How do you interpret this information?"]

"Allergy skin tests showed significant positive results by prick testing to both species of dust mites only. The immune evaluation was normal for the child's age. A sinus CT revealed pansinusitis with a unilateral NP in the right middle turbinate area (not visualized because of the "difficult examination")."

In our case, we are told that a sinus CT was performed and showed pansinusitis with a unilateral polyp in the right middle turbinate area. The abnormalities seen on sinus CT could be acute, chronic, acute superimposed on chronic, or unrelated to RS. Air-fluid levels are more indicative of acute disease, whereas mucosal thickening and partial or complete sinus opacification do not distinguish acute from chronic disease. In truth, a CT cannot definitively confirm that the soft tissue in the right middle meatus was a polyp. Furthermore, a unilateral polyp is not diagnostic of CRSwNP because polyps in CRSwNP are usually bilateral. Given that a sinus CT was done, certain features could have indicated AFRS, such as sinus opacification with hyperdensities, bony expansion, or bony erosion; however, because these were not present, the index of suspicion for AFRS was not high in this case. I shall discuss further the causes of NPs in children below.

When deciding on a treatment plan, we should also consider contributive factors in CRS and whether these warrant further evaluation. The main contributive factors are listed in Table 1 (reviewed in Hamilos³). In our case, it was discovered that Christy had dust-mite allergy. This is relevant because some but not all studies reported an increased prevalence of perennial allergy in association with CRS.^{17,18} Given that Christy was found to be allergic to dust mites, environmental control measures to minimize exposure to dust mites should be recommended. Because of the patient's frequent infections, an immune evaluation was also warranted. We were told that this evaluation was normal. In my opinion, this evaluation should include not only assessment of serum immunoglobulins but also assessment of the patient's immune response to vaccination. The report of a unilateral NP in the

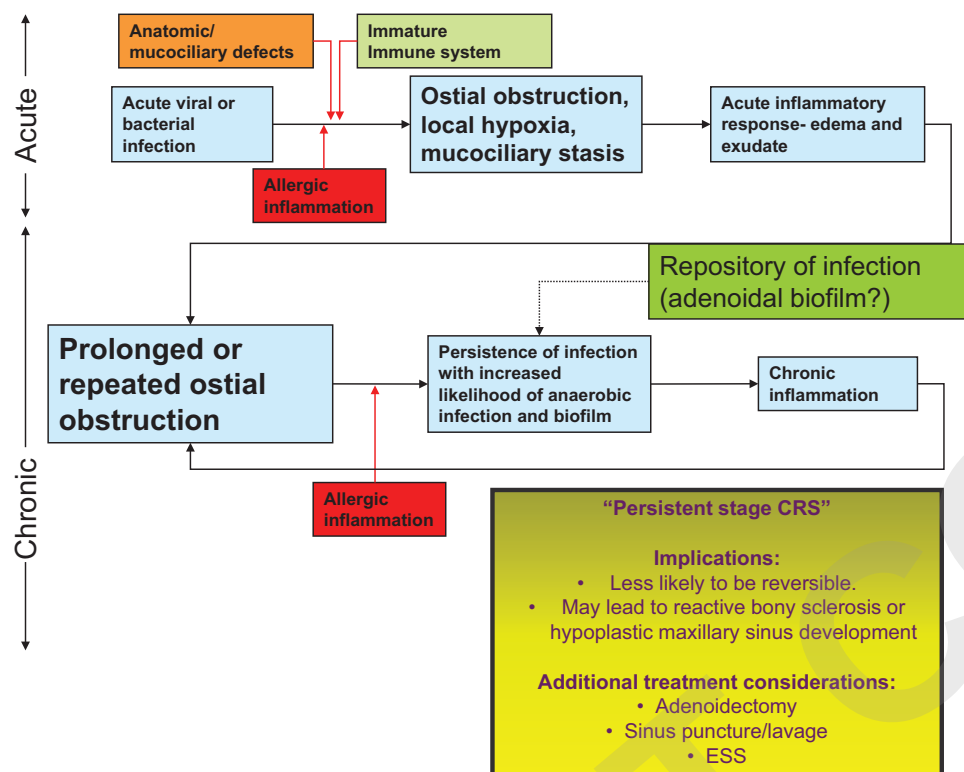


Figure 3. Persistent (“established”) stage of pediatric chronic rhinosinusitis (CRS).

sinus CT report identifies a finding that was not readily detectable on physical examination, perhaps due to the patient’s severe nasal congestion and/or her difficulty in cooperating for a physical examination. The presence of a NP impacts significantly on the subsequent discussion of this case.

How Common Are NPs in Children and What Is Their Underlying Cause? NPs are uncommon in children. Berger *et al.*¹⁹ reported a prevalence of NPs in 18.8% of patients who were going to surgery, all of whom were ages of >7 years. In two other surgical series, the prevalence was 7% and 8.9%.^{20,21} The differential diagnosis of NP in children includes antrochoanal polyps, rare tumors or cysts that arise from the sinuses or central nervous system; “idiopathic” or “adult-type” eosinophilic polyps; and less typical NPs. The less typical NPs include those characterized as “neutrophilic” and those associated with cystic fibrosis (CF) or primary ciliary dyskinesia (PCD). Antrochoanal polyps are usually unilateral and arise from a sinus and extrude into the nasal cavity.²²

Antrochoanal polyps cannot be distinguished from NP visually but have a different significance, which represents primarily a structural problem amenable to surgical removal. Rare tumors and cysts may likewise be difficult or impossible to distinguish from NPs. Suspicion for their presence would be raised if the sinus CT shows predominantly right-sided sinus disease, bony invasion, or expansion of the sinus mass beyond the sinus cavities into the orbit, central nervous system, or cutaneous tissue. CF NP are likewise not distinguishable from idiopathic non-CF NP. Suspicion for CF would be raised by the concurrent presence of chronic cough, chronic respiratory tract infection, digital clubbing, pancreatic insufficiency, chronic diarrhea, or poor growth or nutritional status. However, these comorbid features might not be present (see below). Although NPs are described as a feature of Kartagener syndrome, it is unclear from the literature at what age the NP typically develops, and pathologic studies of NP in Kartagener syndrome and PCD are lacking. Other clinical signs and symptoms that would raise suspicion for PCD include recurrent cough, neonatal respiratory distress, recurrent otitis, situs abnormalities, or a positive family history, none of which were present in this case.²³ There also is the rare Woakes syn-

drome, described in 1979, associated with infantile NPs, broadening of the nose, frontal sinus aplasia, bronchiectasis, and production of highly viscous mucus.²⁴

Even though NPs are uncommon in children relative to adults, they, nonetheless, can occur in the absence of other pathologic conditions. They are typically eosinophilic NPs and are emblematic of a late or “maladaptive” stage of CRS (Fig. 5), in which eosinophilic inflammation is the predominant feature. In adults, syndromes associated with NP can be further separated into idiopathic NP, eosinophilic mucin RS (EMRS), Samter triad, and AFRS. NPs in all of these conditions are histologically similar, with a preponderance of eosinophilic infiltration, and can only be distinguished by the presence or absence of other clinical or pathologic features. Although eosinophils and eosinophilic degranulation products are present in the mucus associated with idiopathic NP, the mucus is not otherwise striking.

In contrast, in EMRS, the mucus has a highly viscous, inspissated appearance, described as “allergic” or more precisely “eosinophilic” mucin.²⁵ This pattern is analogous to that described in AFRS. The key distinctions between EMRS and AFRS are that (1) in EMRS, the eosinophilic mucin is devoid of fungal hyphae and fungal allergy may or may not be present; and (2) in AFRS, fungal hyphae are present, and fungal allergy is always present.²⁶ Although fungal hyphae can be missed when using conventional fungal stains, many adult patients have eosinophilic mucin in the absence of fungal allergy and are more appropriately classified as having EMRS. Patients with EMRS are also more likely to have comorbid asthma than are patients with AFRS.²⁵ In my experience, EMRS cases outnumber AFRS cases 3 to 1 except in regions where AFRS is unusually prevalent, such as in the southeastern United States. EMRS has not been reported in children *per se*, but I have observed it in children as young as 8 years old. Aspirin triad or Samter triad is rarely described in children. However, some pediatric cases of aspirin or nonsteroidal anti-inflammatory drug intolerance are consistent with the Samter triad.²⁷ Finally, children who present with AFRS have typical eosinophilic NPs.

Key clinical and pathologic features that help distinguish the underlying syndromes associated with NP in children are summarized in

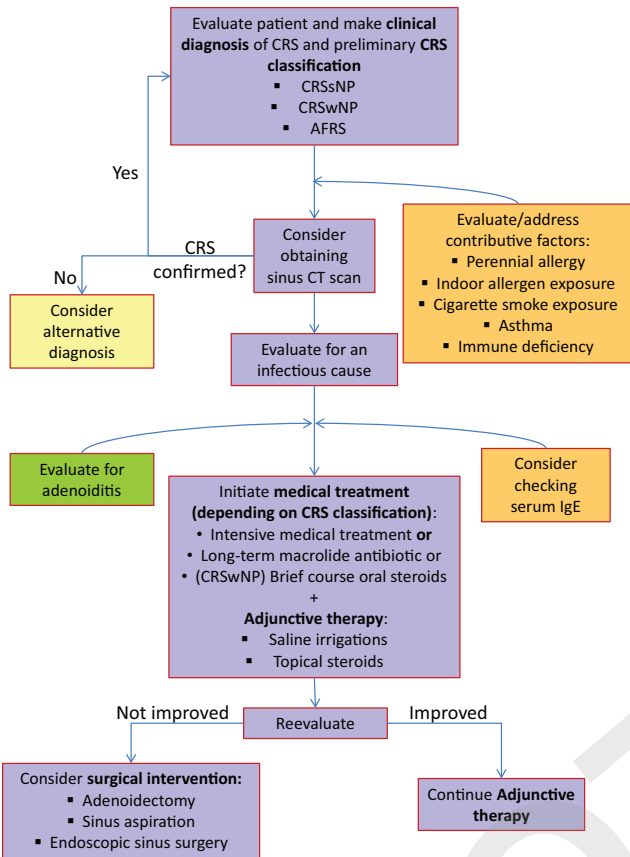


Figure 4. Stepwise approach to pediatric chronic rhinosinusitis (CRS) evaluation and management. (See text for discussion of each step.)

Table 1 Factors that may contribute to the development of pediatric chronic rhinosinusitis

Frequent viral upper respiratory tract infections
Small sinus ostia
Anatomic abnormalities in the sinuses
Immaturity or deficiency of the pediatric immune system
Enlarged adenoidal pads harboring bacteria that cause chronic rhinosinusitis
Defects in local innate immunity
Allergy
Secondhand cigarette smoke exposure
Impairment in mucociliary clearance (cystic fibrosis, immotile cilia syndrome)
Gastroesophageal reflux (in some cases)
Odontogenic sinusitis

Table 2. Age is an important factor. In the study by Berger *et al.*,¹⁹ none of the 16 children with NPs were <7 years old, and, in the study of 87 children with CRS by El Sharkawy *et al.*,²⁰ all 6 of the children with NP were ages >10 years. In contrast, in the study by Schwachman *et al.*,²⁸ 6.7% of 742 children with CF had NP, and NPs were noted in children with CF of all ages, with the youngest being 2.5 years old. Therefore, NPs that occur before the age of 6 years, as in our case, are highly suggestive of underlying CF. The presence of asthma increases the likelihood that NPs are eosinophilic and that the underlying condition is either CRSwNP, EMRS, AFRS, or Samter triad. The presence of aspirin or nonsteroidal anti-inflammatory drug intolerance suggests underlying Samter triad. The presence of sinus opacification with sinus CT hyper-

densities is suggestive of the presence of eosinophilic mucin, which is characteristic of either EMRS or AFRS. The presence of sinus opacification with hyperdensities and bony erosion is a constellation highly suggestive of AFRS. The presence of situs inversus is suggestive of underlying Kartagener syndrome. The presence of *Pseudomonas aeruginosa* sinus infection or *Burkholderia cepacia* infection in the sinuses or lungs is suggestive of underlying CF.²⁹ The presence of chronic lung infections or pancreatic insufficiency, likewise, is suggestive of underlying CF. The presence of neutrophilic predominant inflammation in the NP is suggestive of underlying CF or PCD.

In our case, an antrochoanal polyp would not fully explain the bilateral pansinusitis. The child has asthma, which increases the likelihood that her polyps could be idiopathic or associated with EMRS, AFRS, or Samter triad. The lack of hyperdensities on the sinus CT decreases the likelihood of EMRS or AFRS. Other features of Kartagener syndrome or PCD, such as situs inversus or recurrent lower respiratory tract infections are also lacking.

[The Facilitator Now Asks: “Please write down what your recommendations would be: Environmental control measures? Choices of therapy for rhinosinusitis? Antibiotic therapy (short term versus long term)? The indications versus risks of sinus and polyp surgery versus conservative medical therapy? Choices of therapy for her asthma? What additional tests might be considered? What about gastroesophageal reflux disease causing CRS?”]

Treatment Considerations at this Point. Most expert guidance documents are based on studies of adults with little discussion of pediatric CRS. Initial treatment, according to expert guidelines, depends on the presence or absence of NPs. There is very limited expert guidance for pediatric CRS. In the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS2012)³⁰ document, the initial treatment for CRS without NPs includes saline solution nasal irrigations and topical steroids. For children with moderate or severe symptoms, “long-term antibiotics” are to be “considered.” The only published studies of long-term antibiotic treatment involve the use of macrolides. The recommendation for use of macrolides in EPOS2012³⁰ is based on limited data from small randomized control trials that showed marginal clinical benefit.^{31,32} The rationale for this treatment is based on the putative anti-inflammatory properties of macrolides rather than their antibiotic activity, and studies of long-term macrolides have not included bacteriologic end points. Use of “low-dose” macrolides for extended periods of time is popular among some specialists in the United States but is not based on compelling evidence.^{33,34} EPOS2012³⁰ also reserves the recommendation for long-term macrolide antibiotics to patients with low or normal immunoglobulin E levels.

The recent RS practice parameter update report acknowledges that there is little evidence that supports use of antibiotics for CRS but acknowledges that antibiotics may be useful, including antibiotics combined with a short course of prednisone.¹⁰ Our group proposed the term “intensive medical treatment” as the initial treatment of CRS with an antibiotic for 4 weeks combined with 8–10 days of oral prednisone, given along with adjunctive saline solution nasal rinses and intranasal steroids, based on a retrospective study of 40 adult patients.³⁵ A similar treatment was shown in a randomized, placebo-controlled treatment trial to be beneficial in children with CRS and concomitant asthma by using amoxicillin-clavulanate (20 mg/kg twice daily for 14 days) in combination with deflazacort (1 mg/kg daily for 2 days, 0.5 mg/kg daily for 4 days, and 0.25 mg/kg daily for 4 days).³⁶ In contrast, there is good expert agreement that the initial treatment of CRSwNP should consist of a short course of prednisone, along with adjunctive treatment. Antibiotic treatment is not recommended unless there is evidence of concurrent infection. In our case, a unilateral polyp is present, but there also is evidence of unresolved infection justifying use of antibiotics.

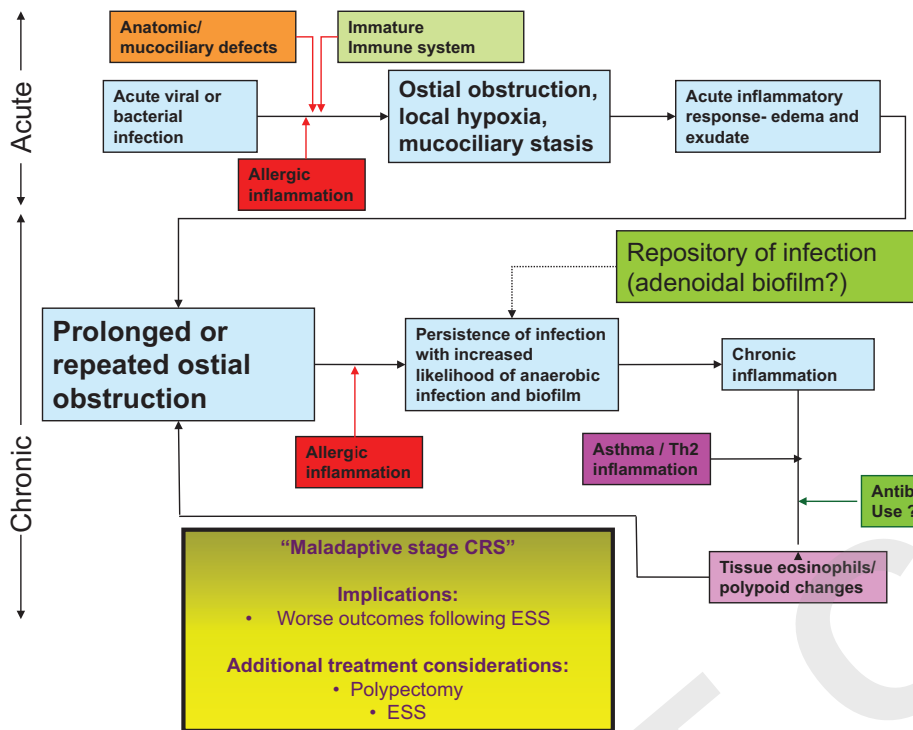


Figure 5. Late “maladaptive/eosinophilic” stage disease pediatric chronic rhinosinusitis (CRS).

The initial selection of an antibiotic regimen for CRS should ideally be culture directed. However, in clinical practice, this is often impractical. Cultures obtained from the middle meatus correlate well with maxillary sinus cultures if purulence is present.³⁷ However, in a 5-year-old child with autism-spectrum illness and a very congested nose, a middle meatus culture would be very difficult to obtain. Alternatives, *e.g.*, maxillary sinus puncture with culture and lavage, can be helpful both diagnostically and therapeutically.³⁸ If I had been asked to select an antibiotic empirically in this case, I would have been influenced by the recent use of amoxicillin-clavulanic acid and other antibiotics before that. One possible choice would have been clindamycin, based on an observational study.³⁹ Most experts avoid the use of fluoroquinolones in children due to concerns about tendinitis, tendon rupture, and emergence of fluoroquinolone-resistant pathogens.⁴⁰ In this case, I would have opted for “intensive medical management” before submitting our patient to ESS, and I would have preferred to obtain a sinus culture before initiating antibiotics.

[The Facilitator Now Says: “Whatever treatment you suggested above was done, and she was scheduled for a sweat chloride test with a follow-up in 3–4 weeks. The patient returned for her visit with no improvement, and sinus surgery was scheduled. You reviewed the sweat chloride test results, which were 57 mmol/L and 55 mmol/L on repeated testing at a CF center with an appropriate amount of sweat tested.” Sweat chloride interpretation for people >6 months of age: If sweat chloride is low (< 39 mmol/L), CF is very unlikely; if sweat chloride is intermediate (40–59 mmol/L), CF is possible; if sweat chloride is high (>60 mmol/L), CF is likely.]

We are also told that sweat chloride (Cl) testing yielded a result of 57 mmol/L, which was confirmed on repeated testing (55 mmol/L). These results represent nondiagnostic intermediate sweat Cl levels

(reference value, <30 mmol/L; borderline, 30–60 mmol/L).⁴¹ So, what does our patient have? Given that her sweat Cl test was abnormal but not definitive (>60 mmol/L) for CF on two separate occasions, our patient warranted further evaluation for CF. This could be done by performing a genetic screening test for cystic fibrosis transmembrane receptor (*CFTR*) mutations.

[The Facilitator now says: “She subsequently has a polypectomy and sinus surgery with cultures that showed heavy growth of *P. Aeruginosa*. She received intravenous antibiotics and had genetic blood testing, which revealed that she was a heterozygote for $\Delta F508$ deletion mutation seen in “atypical” CF.”]

What Is the Significance of the Intermediate Sweat Cl Levels and Single Delta F508 Gene Mutation? We are told that the genetic blood testing revealed a single delta F508 gene mutation. Although this does not confirm the diagnosis of CF, it also does not completely rule out CF. Variant forms of CF have been described in which patients have an atypical clinical presentation, often with recurrent sinopulmonary infections or chronic diarrhea and NP but lacking other features of CF, such as clubbing or abnormal growth and height. Groman *et al.*^{42,43} studied a group of 74 “variant CF” patients with *CFTR* sequencing, and found that 29 had two mutations in *CFTR*, 15 had one mutation, and 30 had no mutations. They concluded that factors other than mutations in the *CFTR* gene could produce a “variant CF phenotype” clinically indistinguishable from nonclassic CF caused by *CFTR* mutations.

The terms “variant CF” or “atypical CF” have also been used to describe patients who have atypical clinical presentations of CF with normal or borderline sweat Cl levels (between 30 and 60 mmol/L), despite having two *CFTR* gene mutations.⁴¹ A more comprehensive definition of “atypical CF” was published in the Cystic Fibrosis Foundation Consensus Report,⁴⁴ which encompasses those with atypical clinical presentations and either (a) intermediate or abnormal sweat

Table 2 Key clinical and pathologic features that help distinguish the underlying cause of NPs in children

Clinical or Laboratory Feature	Significance	Possible Underlying Cause(s) of Nasal Polyps
Age of the child	<6 y, NP are rare except in CF	CF
Presence of asthma	Maladaptive Th2 inflammation associated with eosinophilic NP	Idiopathic NP, EMRS, AFRS, or Samter triad
Aspirin or NSAID intolerance	Overproduction of and increased sensitivity to cysteinyl leukotrienes	Samter triad
Radiologic feature of sinus opacification with hyperdensities	Signifies the presence of "allergic" or "eosinophilic" mucin	EMRS or AFRS
Radiologic feature of sinus opacification with hyperdensities and bony erosion	Signifies the presence of eosinophilic mucin associated with bony erosion	AFRS
Situs inversus	Suggests immotile cilia	Kartagener syndrome
Presence of <i>Pseudomonas aeruginosa</i> or <i>Burkholderia cepacia</i> sinus or lung infection	Emergence of drug-resistant pathogens	CF
Presence of chronic lung infection, pancreatic insufficiency, and/or chronic diarrhea	Suggests defective function of the <i>CFTR</i> gene	CF
Atypical NP pathology with paucity of eosinophils and increased neutrophils	Suggests that acute and chronic infection is driving polyp formation	CF, Kartagener syndrome, or primary ciliary dyskinesia

NP = nasal polyp; CF = cystic fibrosis; Th2 = T-helper cell type 2; EMRS = eosinophilic mucin rhinosinusitis; AFRS = allergic fungal rhinosinusitis; NSAID = nonsteroidal anti-inflammatory drug; CFTR = cystic fibrosis transmembrane receptor.

Cl levels, despite lacking two *CFTR* mutations, or (b) normal or intermediate sweat Cl levels and two *CFTR* mutations⁴⁴). In our case, I would first want to confirm the type of genetic mutation testing performed. A typical commercial CF genetic blood test involves testing for 97 mutations, although >1200 *CFTR* mutations have been described. If the blood test performed in this case was for 97 CF mutations, then additional testing is warranted by using *CFTR* gene sequencing.

Treatment Considerations after ESS. We are told that, in this case, ESS was performed. Many participants in the problem-based learning breakout sessions agreed with this as the next step in management, especially because the child was believed to have an NP. Indeed, ESS allowed for intraoperative sinus cultures, which confirmed the presence of *P. aeruginosa* infection, and this further impacted the choice of antibiotics. Other treatment considerations before subjecting a child to ESS include performing an adenoidectomy to remove the repository of bacteria associated with adenoidal biofilm^{16,45,46} or adenoidectomy combined with sinus aspiration and culture-directed intravenous antibiotics.³⁸ In our case, we were not given information specifically about Christy's adenoids, but adenoidectomy was certainly a consideration. Sinus aspiration may have been less attractive in this case because of the extensive bilateral nature of the disease and the presence of an NP. The choice of giving antibiotics orally or intravenous depends on the results of the sinus cultures, and, in this case, the presence of *P. aeruginosa* infection justified the use of intravenous antibiotics because use of fluoroquinolone antibiotics is usually discouraged in children.

As indicated above, the presence of *P. aeruginosa* sinus infection provides further suggestive evidence for the presence of underlying CF. In pediatric patients without CF, *P. aeruginosa* sinus infection is rare but not impossible. Its presence could also be due to repeated use of antibiotics and be associated with formation of bacterial biofilm (cf. Hamilos¹²). A defective innate immune signaling mechanism that involves the bitter taste receptor *Tas2R* is also possible. This innate

signaling pathway recognizes a quorum-sensing molecule from *P. aeruginosa* thereby resulting in production of bactericidal levels of nitric oxide.⁴⁷ An association has been found in patients with refractory CRS between having the nonfunctional *Tas2R38* genotype and sinus infection with *P. aeruginosa* at the time of sinus surgery.⁴⁷

Are There Any Important Prognostic Features that Impact the Outcome of ESS? The answer is yes. If Christy were confirmed to have CF, then this would be a poor prognostic factor because it would increase the likelihood of persistent problems with mucociliary clearance and infection after ESS, although ESS is clearly beneficial in children with CF (see below).⁴⁸ Two prospective studies examined, in children without CF, risk factors for protracted CRS after ESS and found that the presence of sinonasal polyps was a poor prognostic factor.^{49,50} This is consistent with the results of our observational study of intensive medical management of CRS³⁵ and adult studies of outcomes after ESS.⁵¹ The importance of NP to postsurgical outcome highlights the need for topical anti-inflammatory treatment to control mucosal inflammation and prevent polyp recurrence.

Topical sinus treatment is likely to be a difficult but very important aspect in managing our patient's CRS after surgery. Large-volume saline solution sinus irrigations have been shown to be more effective than small-volume irrigations.⁵² Use of hypertonic saline solution was more effective than isotonic saline solution in some studies but is less-well tolerated.⁵² Intranasal steroid sprays have been demonstrated to be effective in several studies (reviewed in Peters *et al.*¹⁰ and Fokkens *et al.*³⁰), but the extent to which they reach the sinus cavities is limited and often inadequate in my experience. For that reason, I find the use of topical steroid irrigations as a more-effective treatment. Budesonide is available as an aqueous solution and can easily be adapted for sinus irrigations.³ In a young child such as Christy, I would consider delivering budesonide to the sinuses *via* a nasal nebulizer. A recent study demonstrated that nebulized budesonide (1 mg *via* nebulizer twice a day) was highly effective at reducing symptoms and causing regression of NP in adult patients with NP when

given daily for 14 days.⁵³ Other topical steroids have been adapted for use in sinus irrigation in adults, *e.g.*, fluticasone “drops” (*cf.* Peters *et al.*¹⁰), but there is no published experience with other topical steroids in children. However, I would caution that budesonide is not approved by the U.S. Food and Drug Administration for this purpose and may not be covered by insurance plans. Also, its use carries a potential risk for systemic steroid toxicity, especially if it is used chronically, and response to this treatment should be monitored closely to help minimize the long-term steroid exposure.

Special Considerations Regarding ESS in Pediatric Patients with CF. Functional endoscopic sinus surgery (FESS) has been shown to improve the sinusitis-associated symptoms and quality of life in children with CF; however, there is at least a 50% disease recurrence rate in children with CF.⁴⁸ FESS has been found to be safe and beneficial, although it does not consistently result in improvement in lung function.⁵⁴ Some researchers advocate performing a modified endoscopic medial maxillectomy or maxillary mega-antrostomy to permit post-FESS debridement in the clinic, improve mucus clearance with nasal irrigations, and increase access for topical delivery of therapeutics,^{55,56} with excellent long-term outcomes in the patients that they treated. However, a systematic review found inconclusive evidence that any particular intraoperative technique, second-look procedures, intranasal corticosteroid injection, dornase alfa, or postoperative medical therapy resulted in superior FESS outcomes for children with CF.⁵⁷ Also, no relationship was found between *F508del* homozygosity and the presence of NPs, extent of sinus surgery, or rates of revision surgery in a group of 153 children with CF.⁵⁸

Summary and Potential Implications. This problem-based learning case nicely highlighted many key facets and controversies in CRS diagnosis and management in a young child and provided important insights based on a real-world case. I found this case highly instructive to me as a discussant because it compelled me to organize my presentation on the history, objective findings, laboratory data, and clinical course as they unfolded over time. In my discussion, I tried to address key questions that arose during the management of this patient, emphasizing recommendations based on recent evidence-based expert panel guidance documents supplemented with my own clinical experience.

Given the potential for uncomplicated “early” stage pediatric CRS to evolve into persistent CRS reversible only with ESS, a plea can be made for improved recognition of CRS and more aggressive early intervention, it is hoped, to prevent this progression and other potential long-term consequences, such as reactive bony sclerosis or hypoplastic maxillary sinus development. A similar argument could be made for effective management of persistent CRS to perhaps prevent evolution to late “maladaptive/eosinophilic” stage disease. These potential implications of the evolution of pediatric CRS are summarized in Figs. 3–5. For the primary care physician, improved recognition may necessitate enlisting the support of a sinus specialist before the symptoms of CRS have persisted for months or years. It may also necessitate, in some cases, repeated sinus CT imaging to demonstrate that sinus abnormalities have resolved. Low-dose sinus CT imaging devices or more conventional CT imaging with limited sinus protocols have evolved, which limit the radiation exposure associated with such imaging studies.⁵⁹ Other arguments can be made for prompt and comprehensive management of pediatric CRS, including the desire to reduce the burden of illness, reduce health care costs, avoid unnecessary antibiotic use and its attendant effects toward promoting antibiotic resistant infections, and, potentially, reduce the development of important comorbidities, *e.g.*, asthma.

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