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Whither Sinusitis?

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Introduction

It seems that no one gets just a cold anymore. When people get acute symptoms of nasal congestion and stuffiness, they say they have got a "sinus infection." Thirty-two million Americans were reported to have the diagnosis of sinusitis resulting in 11.6 million office visits per year. The diagnosis of sinusitis was reported at that time to cause 73 million restricted activity days, result in 13 million prescriptions, with direct medical costs of $2.1 billion.[1] The mean number of visits for rhinosinusitis per annum in children was reported to be 5.6 million.[2] But are symptoms attributed to sinusitis primarily symptoms of rhinitis, and are the frequent use of antibiotics for sinusitis justified? While guidelines have been generated by professional committees, they include complex algorithms[3,4] that provide insufficient clarity for primary care clinical decision making.

Let us start by considering definitions. First, what are the sinuses? They are essentially just hollow spaces in the skull. They are lined with mucosa similar to that in the nasal cavity, and they communicate with the nasal cavity through small openings. Sinusitis is swelling of the sinus mucous membrane and/or exudate into the sinuses. Rhinitis is inflammation, engorgement, or excessive secretions from the nasal mucous membranes that line the interior of the nasal cavity including the turbinates. Unlike sinusitis, which requires radiologic imaging to identify mucosal swelling and exudate, rhinitis causes readily identifiable symptoms. Increased nasal fluid of varying colors and consistency (*rhinorrhea*), congestion or blockage of the nasal passage from mucosal engorgement, and swelling of the turbinates combine to result in increased nasal airway resistance.

While there is often concomitant inflammation of the sinus mucous membrane and exudate into the sinuses in association with rhinitis, what are the consequences of that sinus pathology? Do symptoms attributed to sinusitis relate to identified sinus pathology? And do antibiotics alter the symptoms and pathology? These questions are addressed by a review of literature relevant to those questions.

Sinus Inflammation

Since sinus inflammation (*sinusitis*) requires radiologic confirmation, it is relevant to examine those studies that have described radiologic evidence of sinusitis. An extensive evaluation of the sinuses was reported by Maresh and Washburn in 1940.[5] Repeated sinus X-rays of 100 normal healthy children were taken at regular intervals from birth to 10 years of age. From the 3501 films that resulted, they made the following observations:

- "We have found in the films all the variations usually attributed to infection."
- "The mean percentage of 'pathologic' films are 30.7% of all films studied."
- "Thirteen children had "pathologic" antrums in over half of total films of sinuses."
- "Children with less than the mean number of colds had a higher percentage of clear sinuses."
- "The children with definitely allergic manifestations (26%) showed a higher percentage of 'pathologic' sinuses up to 6 years of age."

The relationship between colds and radiologic evidence of sinus inflammation observed by Maresh and Washburn was subsequently confirmed by Gwaltney and colleagues by examining computed tomography (CT) of 31 adults with symptoms of a common cold.[6] They found 27 (87%) with abnormal maxillary sinuses, 24 (77%) with occluded ethmoid infundibulum, 20 (65%) with abnormal ethmoid sinuses, 12 (39%) with abnormal sphenoid sinuses, and 10 (32%) with abnormal frontal sinuses. They concluded, "the common cold is associated with frequent and variable anatomical involvement of the upper airways, including occlusion and abnormalities in the sinus cavities."

A subsequent study in 60 children examined magnetic resonance imaging of sinuses during a viral respiratory infection.[7] Six days into the viral respiratory infection, 12% had only swollen turbinates, 20% had some mucosal thickening, and 36 (68%) had sufficient

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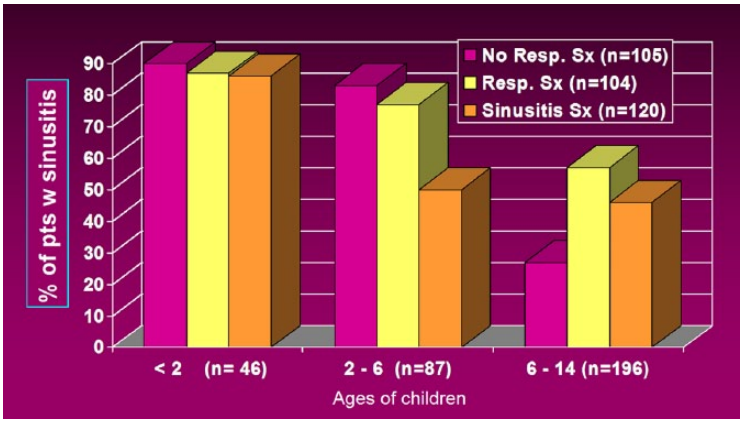

Figure 1. Review by 3 radiologists of sinuses in computed tomography scans of 329 children from infancy to 14 years referred for nonrespiratory symptoms (No Resp. Sx), respiratory symptoms (Resp. Sx), or suspected sinusitis (Sinusitis Sx). Two radiologists were blinded to the history or reason for referral, the third was providing the report but was unaware that a study was being done. Adapted from Shopfner and Rossi.[11]

mucosal changes to essentially fill the maxillary and frontal sinus cavities. Of those 36 with severe mucosal changes, 9 fully recovered clinically, 9 continued to have respiratory symptoms, and 8 had a new respiratory infection. While improvement gradually occurred, sinuses continued to have major mucosal changes. Of particular relevance, there was no association between symptoms and appearance of the sinuses.

Radiologic evidence of sinusitis had also been seen in 31% of 101 children with a recent respiratory infection referred for cranial CTs unrelated to sinusitis.[8] Even with no recent history of a respiratory infection, 18% of those children had abnormalities of their sinuses that would be read as sinusitis. In another study, when 137 children had sinuses examined when they were sent for cranial CTs for reasons other than sinusitis, half of those under age 13 years had opacified maxillary or ethmoid sinuses.[9] Among 1000 adults sent for cranial CTs, 666 had no history or clinical suspicion of symptomatic sinusitis, but nonetheless had radiologic abnormalities consistent with sinusitis in 51% of men and 34% of women. Specifically involved were 28% of ethmoids, 25% of maxillary, 11% of sphenoid, and 5% of frontal sinuses.[10] Review by radiologists of sinuses in CTs of 329 children from infancy to 14 years identified radiologic abnormalities of thickened mucosa or fluid in the sinuses as frequently in those children sent for cranial CT with no respiratory symptoms as those with current upper respiratory symptoms (Figure 1).[11] In that study, those sent for sinus CT because of clinically suspected sinusitis actually had somewhat less frequent radiologic sinus abnormalities observed. All readings by the radiologists in that report were made without knowledge of the clinical circumstances of those patients.

Thus, it appears that radiologic imaging of the sinuses identifies abnormalities consistent with inflammation of the sinuses in the absence of symptoms attributed to clinical sinusitis. Therefore, the presence of sinus inflammation does not by itself diagnose a medical disorder requiring treatment.

Symptoms Attributed to Sinusitis

What are the common symptoms attributed to sinusitis? They include localized pain over sinuses, headaches, and colored nasal drainage (green snot). The latter observation is, of course, a symptom of rhinitis. How specific or sensitive are the localized pain, headaches, and radiologic findings for sinusitis as a clinical problem?

In a study by Mudgil and colleagues,[12] 163 adults were referred by otolaryngology for a sinus CT because of facial pain or headache. They found no correlation between facial or head pain and the sinus CTs. Specifically, there were a mean of 5.5 sites of facial or head pain in which there was an abnormal CT, and a mean of 5.9 sites of facial or head pain in association with a normal sinus CT. Thus, headaches and facial pain are not reliably diagnostic of sinus inflammation.

Zimmerman and colleagues examined the relationship in children with asthma between headache, colored nasal discharge (green snot), and neutrophils in a nasal smear with sinusitis by X-ray.[13] Sinus X-rays were read as sinusitis in about 30% of those without any of those symptoms and about 15% more in those with green snot (Figure 2).

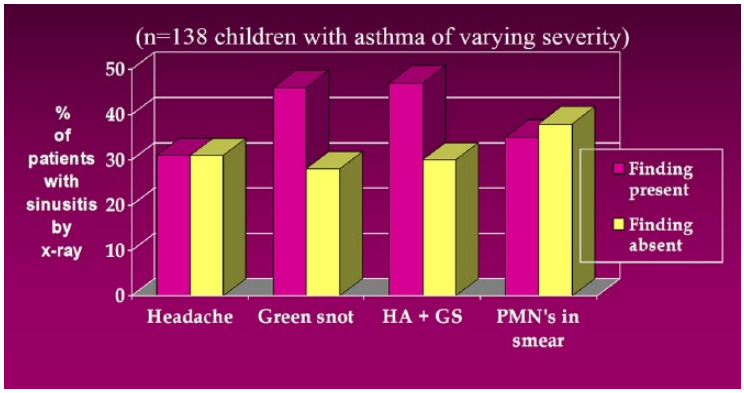

Figure 2. Radiologic findings of sinusitis in 138 children with symptoms commonly attributed to sinusitis including headache, colored nasal discharge (green snot), the combination of headache and colored nasal discharge (HA + GS), and polymorphonuclear leukocytes in nasal smear (PMNs in smear). Adapted from Zimmerman et al.[13]

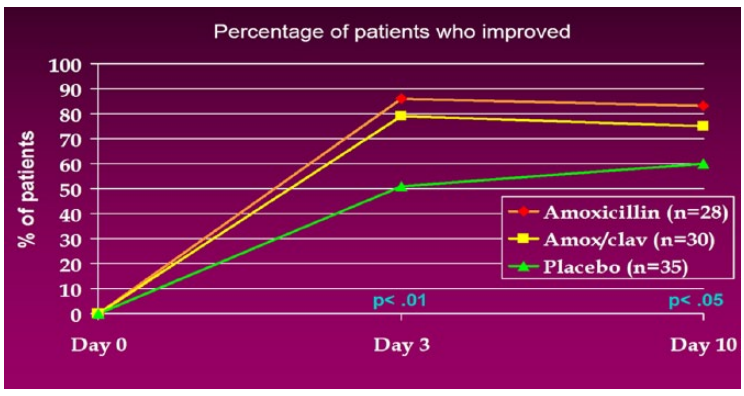

Figure 3. Response to randomized assignment for antibiotics or placebo among 93 selected children with symptoms and radiologic findings diagnosed with sinusitis. Adapted from Wald et al.[18]

Green snot was somewhat more likely to be associated with sinusitis by X-ray, but almost 30% of those without radiologic evidence of sinusitis also had green snot.

Cough is also attributed inappropriately to sinusitis in many reports.[14] A review of chronic cough concluded, "Acute cough may be more complex and have more diagnostic uncertainty than guidelines and performance measures presume. Efforts to reduce antibiotic prescribing for acute cough should address diagnostic complexity and uncertainty that clinicians face."[15] A systematic assessment of cough in children referred for tertiary care did not identify sinusitis among the etiologies,[16] which was consistent with our own experience.[17]

Despite the lack of relationship between symptoms attributed to sinusitis and corresponding radiologic imaging, antibiotic treatment of those symptoms remains common practice. We need to examine the data that relates to this practice.

Outcome of Treatment of Symptoms Attributed to Sinusitis

Since 1981, Dr Ellen Wald and colleagues have published more than 70 articles related to sinusitis in children. A randomized controlled clinical trial in 1986 examined the effects of antibiotics in 93 children with nasal discharge or cough present between 10 and 30 days after onset of symptoms.[18] All had radiologic evidence of sinusitis. Substantial improvement occurred with 50% improving by 3 days during the placebo. A significantly higher percentage of children improved with both amoxicillin and amoxicillin-clavulanate after 3 days (Figure 3). While the number of patients receiving placebo improved further during the next 7 days, there was no further increase in the number of children improved during the antibiotic regimens.

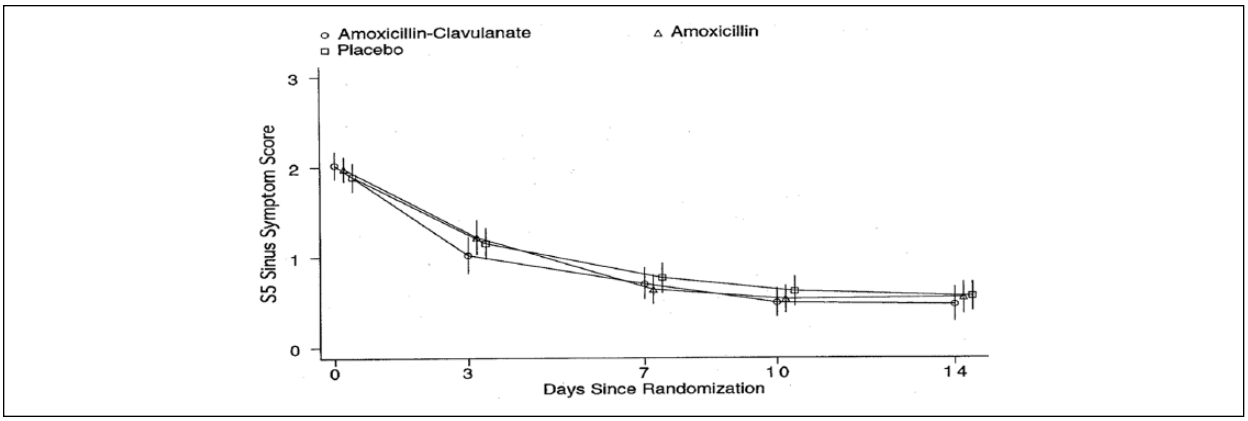

Figure 4. Children from 3 community pediatric practices who had a clinical diagnosis of acute sinusitis based on the same perceived criteria as the patients in the study shown in Figure 3. Patients were randomly assigned to receive amoxicillin (n = 58), amoxicillin-clavulanate (n = 4 8), or placebo (n = 55). Reproduced from Garbutt et al,[19] with permission.

Table 1. Outcome of 56 Children With Diagnosis of Sinusitis Randomly Assigned to Placebo of Amoxicillin-Clavulanate[a].

Clinical Outcome	Placebo (n = 28)	Amoxicillin/Clavulanate (n = 28)	*P*
Cure/improved	9	18	.032
Rx failure	19	4	<.001
Withdrawn	0	6	.023
Adverse events	4	12	.014
Time to improvement	2.63 ± 0.52	2.26 ± 0.69	.199

[a]Adapted from Wald et al.[22]

A later controlled clinical trial found no benefit from antibiotics in children from 3 community pediatric practices selected by the presence of symptoms described in the Wald study (Figure 4).[19] This led to dueling letters where Dr Wald describes the difference as likely related to insufficiently stringent patient selection.[20] Dr Garbutt countered with the argument that the 3 pediatric groups from which her patients were drawn represented a true community-based representation of decisions for treatment based on the criteria described by Dr Wald.[21] A subsequent study by Wald and colleagues identified only 139 of 3125 (4.4%) of children with a viral respiration infection who met Dr Wald's specified criteria of persistent, worsening, or severe symptoms that were then attributed to sinusitis and considered candidates for antibiotics.[22] Fifty-six of those were then included in a randomized trial of amoxicillin-clavulanate. Significant increase in both benefit and antibiotic-related adverse effects was associated with the treatment (Table 1).

Interestingly, the outcome of "sinusitis" was similar to the outcome of antibiotics for a controlled clinical trial of treating the rhinitis of a common-cold independent of any diagnosis of sinusitis.[23] The latter study included 300 patients, ages 16 to 64 years, with symptoms of a common cold in whom no significant difference was observed overall between those receiving antibiotics and those receiving placebo. However, a subset of 20% that had initial nasal cultures positive for *Hemophilus influenza, Streptococcus pneumoniae*, or *Moraxella catarrhalis* benefited from the antibiotics by a somewhat shorter duration of illness.[22] A 23% frequency of adverse effects were described in the antibiotic-treated patients. The authors judged that the common adverse effects of antibiotics outweighed the few patients who benefited that were not identifiable in advance (Table 2). Both the Wald study[22] and the study of antibiotics for the common cold[23] confirm clinical efficacy of antibiotics for symptoms of acute infectious nasal symptoms in a small minority of patients that are difficult to identify in advance, particularly in the primary care setting.

Additional adult studies of antibiotics have included one that recognized the study by Wald et al[18] found 3 days provided all the antibiotic effect with no further benefit from 10 days. Eighty adult patients were randomized to 3- or 10-day treatment with trimethoprim-sulfamethoxazole.[24]

Table 2. Outcome of a 58-Patient Culture Positive Subset of 288 Patients With Symptoms of a Common Cold Randomly Assigned to Receive Amoxicillin-Clavulanate or Placebo[a,b].

Clinical Outcome	Placebo (n = 28)	Amoxicillin/ Clavulanate (n = 30)
Cure	1	8
Persistent Sx	17	21
Worse Sx	10	1

[a]Those not culture positive derived no benefit from the antibiotics. A median symptom score of the 30 who received the antibiotic was significantly (.008) higher than the 28 who received placebo.[23]
[b]Adapted from Kaiser et al.[23]

Seventy percent improved at the same rate from both regimens. Sixty-five percent and 58% had improved sinus radiology in 3- and 10-day treatment groups, respectively. A randomized, placebo controlled study of 488 adults with diagnoses of acute maxillary sinusitis resulted in no clinical radiological differences between the placebo and amoxicillin.[25] In another study in adults with sinusitis complaints comparing amoxicillin with placebo, 32 of 67 on amoxicillin and 25 of 68 on placebo were reported as improved at 14 days.[26] A 4-regimen study of 240 adults with diagnoses of acute maxillary sinusitis were treated with oral antibiotics, inhaled corticosteroid, the combination of antibiotics and inhaled corticosteroid, and placebo.[27] Neither antibiotic nor corticosteroid was associated with significant benefit. One hundred and thirty adults with diagnoses of acute sinusitis confirmed by CT were randomized to antibiotics or placebo.[28] A small increase in clinical improvement was associated with antibiotic treatment, and 86% and 57% considered themselves recovered by day 10 on antibiotics and placebo, respectively. CT was improved in 37% compared with 23% on placebo.

A meta-analysis of 16 studies of adolescents and adults (3358 *patients*) concluded that only small differences occurred between placebo and antimicrobial treatment for acute maxillary sinusitis.[29] All of those studies were for acute sinusitis. Subacute sinusitis was examined in 123 children with mucoid drainage and/or cough for more than 3 weeks but less than 3 months with radiologic evidence of sinusitis.[30] Random assignment was to amoxicillin, amoxicillin-clavulanate, trimethoprim-sulfamethoxazole, or no antibiotics. All patients were treated for 3 weeks plus 3 more weeks with other antibiotics if only partial response at 3 weeks. At the end of 6 weeks, 75% to 80% improved, but there was no significant difference in the frequency of a favorable response associated with any of regimens.

The value of decongestants, antihistamines, and nasal lavage have also been used for symptoms attributed to acute sinusitis. A Cochrane review found no evidence to support those measures.[31]

What About Severe Acute Sinus Pain?

Acute sinus pain may result from an obstruction of the sinus ostia. The inability of the blocked sinus to equilibrate with a change in external pressure like in an airplane, or going down a mountain, can cause pain. The blockage causes a vacuum in the sinuses and head resulting in moderate to severe pain over the face and sinuses. Acute use of a decongestant nasal spray such as oxymetazoline may open the mucosa around the sinus ostia permitting equalization of pressure and relief of pain.

Much less common is what can be considered an acute abscess in a sinus. That is usually associated with severe localized pain, often with fever, and is a serious problem requiring prompt antibiotic treatment.

When Are Antibiotics Best Indicated?

Late development of fever following a cold is a worrisome sign of a bacterial infection. Tender facial swelling or exquisite localized facial pain over a sinus suggests an acute sinus abscess. If the nose itself is tender associated with fever, a nasal septal abscess should be suspected.[32] While antibiotics are indicated for these stringent criteria, these clinical complications of a cold are very uncommon compared with all of the clinical diagnoses of sinusitis made in practice.

Azithromycin has been studied as a means of preventing recurrent acute rhinosinusitis in children.[33] That intriguing study of 40 nonallergic children with a history of recurrent sinusitis warrants careful examination of the details. The rhinosinusitis in the study was defined as (1) persistent symptoms of an upper respiration infection lasting more than 10 but less than 30 days, (2) worsening symptoms after initial improvement, or (3) purulent nasal drainage for 3 days with high fever. However, there was no tabulation as to which of those 3 symptoms were present in the 40 patients. Moreover, more than 80% of the children were described as having immunoglobulin G subclass deficiency without further evaluation of immune function. During 1 year of azithromycin treatment, there were substantially fewer reports of rhinosinusitis than was seen in the placebo group. However, without examination of the specific symptoms prevented and further evaluation of immune dysfunction of those children, there is insufficient support for accepting that azithromycin prevents rhinosinusitis in a more general population.

What About Chronic Sinusitis?

Chronic sinusitis is a complicated issue. It may be manifested as asymptomatic presence of continuous opacification of sinuses. Almost universal among those with cystic fibrosis and primary ciliary dyskinesia, the degree of associated symptoms is highly variable. Some develop nasal polyps that can cause nasal obstruction, but the nasal polyps common with cystic fibrosis are different histologically from the nasal polyps associated with the Samter triad (*also known as aspirin exacerbated respiratory disease*). Anosmia is associated with chronic sinusitis in some but not in others. These different phenotypes are now understood to be associated with different endotypes characterized by distinct pathophysiologic mechanisms caused by different cellular and molecular mechanisms.[34] Treatment will therefore need to deviate from a traditional one size fits all approach, and attempts to target specific endotypes may eventually be based on corresponding biomarkers.

Summary and Conclusion

The sinusitis that is frequently diagnosed based on persisting nasal drainage (regardless of color), headaches, and areas of mild facial tenderness is used as a frequent rationale for antibiotics, despite the sparsity of supportive data. Since such symptoms are common, overprescribing of antibiotics has all too often resulted. The few studies that demonstrate benefit from antibiotics found only very modest benefit from a small subset of patients. The common gastrointestinal and occasional allergic adverse effects from antibiotics generally outweigh the benefit observed from the self-limited nature of symptoms attributed to sinusitis. Moreover, symptoms attributed to sinusitis correlate poorly with radiological evidence of sinus inflammation and radiological evidence of sinus inflammation correlates poorly with symptoms attributed to sinusitis. Rhinitis from a common cold or allergy is commonly associated with radiologic evidence of sinusitis, but symptoms tend to be self-limited and independent of the status of the radiologic evidence. For the minority where bacterial infection contributes to symptoms, the inability to identify those patients prior to deciding on treatment causes concern for the overuse of antibiotics. Antibiotics should therefore be limited to the infrequent cases of severe acute sinusitis manifested by late development of fever or exquisitely severe pain and tenderness over a sinus or the nose, generally associated with fever. The complexity of chronic sinusitis requires targeting endotypes, the specifics of which we need to learn more and was not further discussed in this review.

Author's Note

Some of the contents of this article were previously presented at Masters of Pediatrics, University of Miami, Miami, FL; January 15, 2003. An audiovisual recording of that presentation is available at http://collections.uiowa.edu/uihc/pediatrics/weinbergerm/whither_sinusitis/player_backup.html.

Acknowledgments

I was first made aware of the potential for lack of association of radiologic diagnosis of sinusitis with symptoms by my mentor, Dr Elliot Ellis, during my fellowship at National Jewish Hospital in 1969-1970. Dr Ellis provided me with some of the older references included in this article.[35]

Declaration of Conflicting Interests

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