

## DISCUSSION

**Dr. Slavin.** How important is CT scanning in actually demonstrating the anatomy of the ostiomeatal unit that you seem to be able to see pretty well by endoscopy?

**Dr. Lanza.** It is not the primary modality for us in the diagnosis of chronic or recurrent sinusitis. Most often we are able to base our diagnosis on the history and the findings from nasal endoscopy. The coronal CT scan is essentially a surgical road map and a guide to the bony landmarks of the nose and paranasal sinuses. The CT is also helpful as an adjunct for the diagnosis of sinus disease.

**Dr. Druce.** I am very impressed with the number of problems that can occur during surgery but also the reasons for persistent symptoms after surgery. I think part of the problem we see is that many people who do these procedures

are what are called "weekend endoscopists" in that they may do one or two procedures a month or do them infrequently after completion of a very short training course.

**Dr. Lusk.** I do want to emphasize what Dr. Lanza said, and this is not to get too impatient after the surgery is done. We certainly have scores of patients who do not improve immediately, and it may take weeks or months. However, I am convinced, as you pointed out, that it takes awhile for the mucociliary apparatus to return to normal. So one should not be discouraged if a few weeks later the patient does not seem to be any better.

**Dr. Zieger.** A recent article compares the outcomes of sinus surgery in childhood and divides them by age. In those children who were less than 5 years, the success rate was rather dismal, whereas in those patients more than 5 years or so, the success rate was somewhat adequate.

## The role of the immunologist in sinus disease

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*The clinical immunologist is playing an increasingly important role in the evaluation and management of sinus disease. Although most patients with sinus disease are not immunodeficient, a significant proportion of patients with chronic sinusitis unresponsive to medical and/or surgical therapy may have an immunodeficiency. Most immunodeficient patients for whom sinusitis is a major clinical problem tend to be those with humoral immunodeficiency diseases. The role of immunoglobulin replacement therapy is well established for patients with global immunoglobulin and antibody deficiencies (e.g., X-linked agammaglobulinemia and common variable immunodeficiency) and may be helpful in controlling refractory sinusitis in patients with more selective immunoglobulin deficiencies (e.g., IgG subclass deficiency and selective antibody deficiencies), but efficacy in these conditions remains to be established by controlled studies. Many immunodeficient patients have a history of repeated sinus surgery before the recognition of their immune defect. Even in immunodeficient patients treated with antibiotics and immunoglobulin replacement therapy, functional endoscopic sinus surgery is successful in only half of the patients. (J ALLERGY CLIN IMMUNOL 1992;90:511-5.)*

**Key words:** Immunodeficiency, immunoglobulin, agammaglobulinemia, IgG subclass deficiency, immunoglobulin replacement therapy, ethmoidectomy, endoscopic surgery, sinusitis

The role of the immunologist in sinus disease is a relatively new and evolving one. During the past de-

cade there has been an increased awareness of the magnitude of the problem of sinus disease and particularly a recognition that this is a major health problem of children.<sup>1-3</sup> Appropriately, most of our attention has been focused on respiratory allergy as a major predisposing factor for recurrent and chronic sinusitis.<sup>4,5</sup> However, it is now clear that some patients suffer recurrent and/or chronic sinusitis on the basis of previously unrecognized immunodeficiency dis-

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**TABLE I.** Frequency of sinusitis-prone patients in a population of patients with a variety of immunodeficiency diseases

| Immunodeficiency                 | Sinusitis/total |
|----------------------------------|-----------------|
| Common variable immunodeficiency | 9/9             |
| IgG subclass deficiency          | 8/8             |
| Selective antibody deficiency    | 6/6             |
| IgA deficiency                   | 5/5             |
| C4 deficiency (partial)          | 3/3             |
| X-linked agammaglobulinemia      | 1/4             |
| Ataxia telangiectasia            | 1/5             |
| Hyper-IgM immunodeficiency       | 1/2             |
| Severe combined immunodeficiency | 0/4             |

cases and that their response to conventional medical and surgical management of sinus disease may be different from that of their immunologically normal counterparts. Thus the clinical immunologist has at least four functions with respect to the sinusitis-prone patient: (1) recognition and delineation of underlying immunodeficiency, (2) specific treatment of the immunodeficiency disease when present, (3) medical management of sinusitis in the context of an immunodeficiency disease, and (4) collaboration with otolaryngologists in pre- and postoperative management of the immunodeficient patient to optimize surgical outcome.

The vast majority of individuals with sinus disease are obviously not immunodeficient; thus the clinical immunologist must select out those patients who are most likely to have immunodeficiency from a very large number of nonimmunodeficient patients. Most immunodeficient patients who have sinus disease have frequent recurrences of sinusitis after termination of antibiotic therapy or have chronic sinusitis. Moreover, immunodeficient patients who have had surgical procedures rarely have long-term benefit from these procedures. Therefore candidates for immunologic evaluation are patients who have had (1) frequent episodes of sinusitis (more than three per year), (2) failure of appropriate medical management, such as a return of symptoms less than 1 month after discontinuation of antibiotic therapy, or (3) recurrence of sinus disease after surgery. Many allergic patients will meet this criteria, and it is important to try to clinically discriminate between the allergic versus the immunodeficient, sinusitis-prone patient. Unfortunately, the symptoms of sinusitis in the immunodeficient patient are the same as those in the allergic or immunologically normal individual. Other characteristics may, however, assist in discriminating the allergic patient from the immunodeficient one. The allergic patient is

likely to have a family history of allergy, a seasonal pattern of respiratory symptoms, and a favorable response to antihistamines. Nasal pruritis, itching eyes, wheezing, eczema, and food allergy are more commonly associated with allergy than with immunodeficiency, although exceptions do exist. The occurrence of frequent bacterial infections, in addition to respiratory tract infections, should alert the physician to the possibility of immunodeficiency. The undiagnosed immunodeficient patient is virtually always taking an antibiotic and becomes ill shortly after antibiotics are discontinued. Recurrent pneumonias, meningitis, cellulitis, candidiasis, chronic diarrhea, and failure to thrive are hallmarks of some of the more severe childhood immunodeficiency disorders. However, in the most common immunodeficiency diseases, recurrent and chronic sinusitis with or without otitis media may be the only indication that a patient is immunodeficient. Since many immunodeficiency diseases are hereditary, a positive family history for immunodeficiency may be helpful in recognizing the immunodeficient patient. Because most sinusitis-prone patients are much more likely to be allergic rather than immunodeficient, merely on a statistical basis, I recommend an allergy evaluation for all these patients before embarking on an extensive immunologic evaluation. When an adequate evaluation fails to uncover underlying respiratory allergy or when efforts to control respiratory allergy do not alter the course of the patient's sinus disease, the possibility of unrecognized immunodeficiency must be seriously considered.

The immunodeficient patient who comes to clinical attention because of chronic or recurrent sinus disease most likely has a humoral immunodeficiency disease. These include immunoglobulin deficiencies (e.g., common variable immunodeficiency, X-linked agammaglobulinemia, or IgA deficiency), selective IgG subclass deficiencies, selective antibody deficiency (most frequently an inability to produce antibodies against the polysaccharides of *Streptococcus pneumoniae* or *Haemophilus influenzae*), and complement component deficiency. Patients with defects in T-lymphocyte function, such as those with severe combined immunodeficiency disease or neutrophil dysfunction (e.g., chronic granulomatous disease), will usually have more severe infections, and if sinusitis is present, it is not a prominent problem. Although sinusitis occurs in human immunodeficiency virus-infected patients, it is rarely the reason they come to clinical attention. Fungal sinusitis is rare, particularly in children. Table I lists the frequency of sinusitis in children with immunodeficiency diseases seen in the Pediatric Immunology Clinic at St. Louis Children's Hospital. The clinical and immunologic characteristics of the

immunodeficiency diseases most often associated with chronic/recurrent sinusitis have been recently reviewed by the author.<sup>6</sup>

Based on the knowledge of the types of immunodeficiency diseases associated with chronic and recurrent sinusitis, the immunologic evaluation of the sinusitis-prone patient can be focused on these entities. Measurement of serum IgG, IgM, IgA, IgE, and IgG subclasses should be carried out on all patients. For patients over 2 years of age, studies of the antibody response to pneumococcal polysaccharide and unconjugated *H. influenzae* type B polysaccharide may identify patients with selective antibody deficiencies that may exist alone or in association with IgG subclass deficiency (usually IgG2 or IgG2 to IgG4 deficiency). Measurement of serum complement components C3 and C4 as well as total hemolytic complement (CH50) is also helpful. If patients have low levels of two or more immunoglobulin classes (e.g., IgG and IgA), B- and T-lymphocyte population analysis should be undertaken to discriminate between X-linked agammaglobulinemia, which lacks B cells, and common variable immunodeficiency in which B cells are often present. Patients with transient hypogammaglobulinemia of infancy may also have low levels of two or more immunoglobulin classes but will have normal T- and B-cell populations and will make antibody to tetanus toxoid, which patients with X-linked agammaglobulinemia and common variable immunodeficiency cannot do. The yield of immunodeficient patients with the type of evaluation protocol described above will vary based on the clinical setting in which it is used. In an unselected population such as that seen in a primary care physician's or local allergist's practice, the yield is likely to be very low. In contrast, when patients with refractory sinus disease were recently studied in a large regional referral practice, 55% of the patients had either low immunoglobulin levels or poor responses to bacterial polysaccharide vaccines.<sup>7</sup>

Most sinusitis-prone immunodeficient patients have either an immunoglobulin or antibody deficiency disorder for which immunoglobulin replacement therapy is required. Intravenous immunoglobulin infusions are considered the treatment of choice for these patients.<sup>8</sup> Although immunoglobulin replacement therapy is clearly indicated for sinusitis-prone patients with common variable immunodeficiency and X-linked agammaglobulinemia, the data and clinical experience are more limited in the selective humoral immunoglobulin and antibody deficiency disorders. Some reports have suggested that immunoglobulin replacement is helpful in controlling sinusitis and otitis media in patients with IgG2 subclass deficiency and an inability to synthesize

antibodies to bacterial polysaccharide vaccines.<sup>9, 10</sup> These were open-label studies, and no double-blind placebo controlled study has been published to date. In the past immunoglobulin replacement therapy has not been recommended for patients with selective IgA deficiency; however, some IgA-deficient patients do benefit from immunoglobulin replacement. Immunization studies of "selective" IgA deficient patients may uncover selective antibody deficiencies, thus explaining their favorable response to replacement therapy. When treating IgA-deficient patients with intravenous immunoglobulin, an IgA-poor preparation should be used.

Medical management of episodes of sinusitis in the immunodeficient patient are the same as that for the nonimmunodeficient patient. Topical therapy with saline solution irrigation and nasal beclomethasone or triamcinolone sprays are thought to be helpful. Systemic decongestants may also be helpful; neither have been investigated in a controlled manner. The choice of antibiotics should be based on an understanding of the microbiology of sinusitis in these patients. However, very little data are available. Cultures of the ethmoid bullae in immunodeficient patients with chronic sinusitis taken during endoscopic surgery yielded bacteria commonly seen in nonimmunodeficient patients with chronic sinusitis.<sup>11-13</sup> These included *Streptococcus pneumoniae*, *Moraxella catarrhalis*,  $\alpha$ -hemolytic streptococci, *H. influenzae* nontypeable, coagulase-negative staphylococcus, *Neisseria* species, *Staphylococcus aureus*, *Corynebacterium*, group D streptococcus, and anaerobes. For exacerbations of sinusitis in these patients, we find amoxicillin with clavulanic acid, erythromycin-sulfisoxazole, and cefuroxime axetil most useful. Patients are usually treated for 4 weeks. Some patients will require both immunoglobulin replacement therapy and daily antibiotics to control symptoms of sinusitis.

The role of sinus surgery in the immunodeficient patient has not been defined. Many immunodeficient patients have a history of having undergone some form of sinus surgery without benefit before the diagnosis of their immunodeficiency. We<sup>11</sup> recently studied 11 patients with a variety of immunodeficiency diseases and chronic sinusitis who underwent endoscopic ethmoidectomy and maxillary antrostomy. Four patients had transient immunoglobulin deficiencies, whereas the remaining patients had permanent immune defects. The most favorable results were observed in patients with transient defects. Although patients with permanent defects had improvement in their symptoms after surgery, most continued to require daily antibiotics as well as monthly intravenous immunoglobulin therapy. After surgery most of these patients

could be maintained symptom free with a single daily dose of prophylactic antibiotic and by rotating antibiotics at 3- to 4-month intervals. Thus on the basis of preliminary studies, endoscopic ethmoidectomy appears to be helpful in reestablishing patency of the sinuses once a transient immune defect has resolved. A larger series of patients with permanent immunodeficiencies must be studied before any conclusions can be drawn in this patient population. However, it is clear that surgery is of little value in immunodeficient patients if they do not simultaneously receive specific therapy for their immunodeficiency (i.e., immunoglobulin replacement). If sinus surgery is considered in an immunodeficient patient, the clinical immunologist and otolaryngologist must coordinate their efforts so that surgery is performed only after the patient has had the benefit of all appropriate medical measures. Postoperative management may also have to be modified for these patients.

The main focus of this article has been on the practical aspects of the management of sinus disease from the perspective of the clinical immunologist. It is apparent that we do not know all the immunologic defects that may predispose patients to recurrent or chronic sinus disease and that our ability to treat sinus disease in patients with known immunodeficiency disorders leaves much to be desired. In addition to the need for clinical studies of sinus disease in this patient population, it must be recognized that the sinusitis-prone patient with no known allergic disease or identifiable immunodeficiency is an important patient population for basic investigation. Some of the mildest forms of immunodeficiency disease (e.g., IgG subclass deficiencies and selective antibody deficiencies) have susceptibility to recurrent or chronic sinusitis as their major if not sole health problem. As with the study of immunodeficiency diseases in the past, immunologic investigation of the sinusitis-prone patient with our armamentarium of new molecular immunologic methods is likely to yield important insights into the function of the human immune system.

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## DISCUSSION

**Dr. Wald.** It seems as though many of these children whom we label as selective antibody deficient improve over a few years. If so, can you nurse them along with medical therapy and maybe not need surgery at all?

**Dr. Polmar.** I have had the experience that yes, some of the patient's symptoms resolve and thus surgery is unnecessary.

**Dr. Druce.** I would like to explore the question a little bit more about the necessity of an allergy evaluation because I would like to perhaps explore what the rationale for this is.

**Dr. Polmar.** I think my response to that is, as a clinician, the evaluation starts with a history and physical examination. If that is not suggestive, I do not look for confirmatory skin tests.

**Dr. Rachelefsky.** Would you clarify the antibiotic therapy that you use in some of these immunodeficient patients in terms of length of time of administration and what antibiotics you prefer.

**Dr. Polmar.** Most immunodeficient patients have either recurrent or chronic sinus disease; therefore when they have an exacerbation of sinus disease, drugs such as potassium clavulanate (Augmentin) and cefuroxime axetil, as Dr. Wald had described, are among my favorites. I have occasionally had to use clindamycin in patients. I have used guided therapy with aspiration of the maxillary sinus. On occasion when a patient has not responded to outpatient management, we have admitted them to the hospital for intravenous therapy.

**Dr. Rachelefsky.** I wanted to clarify the issue about  $\gamma$ -globulin and subclasses. Would you put somebody on  $\gamma$ -globulin with just a subclass deficiency, by your measure-

ment, or would they have to have something more in terms of poor antibody response?

**Dr. Polmar.** That is a very good question. The issues are as follows. If you have a patient with a credible subclass deficiency (G2, G3) with or without selective antibody deficiency (such as pneumococcal polysaccharide, unresponsiveness), the patient would be maintained on prophylactic antibiotics. If the patient does not respond to prophylactic antibiotics, we would attempt a trial of intravenous  $\gamma$ -globulin.

**Dr. Fireman.** This type of discussion that we are having regarding subclass deficiency refers mainly to younger children. When you get past the age of 4 or 5 years, I think your approach would not be quite the same.

**Dr. Polmar.** The number of older patients who have normal immunoglobulins and have defect in functional antibody is very, very small.

**Dr. Rachelefsky.** I think Dr. Fireman is trying to make a very important point, and that is that the interpretation of the laboratory data and the functional defect in the patient must be interpreted differently in the younger child versus the child over 6 years of age. Immune abnormalities may resolve in the younger child but may be permanent in the older child.

**Dr. Fireman.** If you have the young child and you see a response to a single antigen type, I feel comfortable with that. If you have an 8-year-old who has a response to just one, then I don't feel comfortable.

**Dr. Rachelefsky.** If you can't control their infection and they have an immunologic defect (i.e., an antibody deficiency) and you have nothing else to offer that patient, I believe that a trial of  $\gamma$ -globulin therapy is valid.

## The role of allergy in sinusitis in children

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*Allergic rhinitis and sinusitis are independently common disorders. Studies document the presence of both disorders in the same patient 25% to 70% of the time. Because this is above the prevalence of allergic rhinitis in the general population, the literature supports that allergy is an important associated factor in sinusitis. Younger children appear to be even more at risk of sinusitis, perhaps because of small anatomic structures, more frequent viral infections, and more exposure to indoor allergens and irritants. Immunodeficiency appears to play an independent role in resistant, severe sinusitis. (J ALLERGY CLIN IMMUNOL 1992;90:515-7.)*

**Key words:** Allergy, sinusitis

Even at birth children may develop sinusitis, in this case by bacteria pushed into the ethmoid sinuses during vaginal delivery. By 6 months of age most children are sitting, and most are walking by age 1 year. This places the maxillary ostia in a superior position so that gravity now works against the mucous flow around and out of the sinuses. The channels of the osteomeatal complex are long and thin and may be easily obstructed with the smaller anatomic structures of very young children.

### PREDISPOSING FACTORS

Five factors have been implicated as predisposing to sinusitis: (1) *Anatomic*, including adenoidal hypertrophy, deviated septum, foreign bodies, immotile cilia, polyps, and tumors; (2) *trauma*, including barotrauma (e.g., diving) and dental procedures; (3) *diseases*, including allergic rhinitis, bronchiectasis, cystic fibrosis, immunodeficiency, and respiratory infections; (4) *drug abuse*, including overuse of topical decongestants; and (5) *irritants*, including tobacco smoke, chlorine, and air pollution.

The most commonly associated factors are by far upper respiratory tract infections and allergy. Both of these conditions cause mucosal swelling and affect mucous secretions and perhaps ciliary function. Therefore it is not surprising that an association exists. Yet it is equally clear that respiratory tract infections and allergy do not cause bacterial sinusitis per se.

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