

SUPPLEMENT TO
THE JOURNAL OF
ALLERGY
AND
CLINICAL IMMUNOLOGY

VOLUME 99

NUMBER 6, PART 3

Sinusitis: Bench to Bedside

Current Findings, Future Directions

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Sinusitis, an inflammatory disease of the sinus, is one of the most commonly reported diseases in the United States, affecting an estimated 14% of the population. The prevalence of sinusitis is rising. Between 1990 and 1992, persons with sinusitis reported approximately 73 million restricted activity days—an increase from the 50 million restricted activity days reported between 1986 and 1988. Because critical questions remain unanswered about its cause, pathophysiology, and optimal treatment, sinusitis continues to generate significant health care costs and affects the quality of life of a large segment of the U.S. population. To identify critical directions for research on sinus disease, the American Academy of Allergy, Asthma and Immunology and the American Academy of Otolaryngology–Head and Neck Surgery Foundation, Inc., convened a meeting in January 1996 in collaboration with the National Institutes of Allergy and Infectious Disease. This document summarizes the proceedings of that meeting and presents what is intended to be the background for future investigation of the many unanswered questions related to sinusitis. (*J Allergy Clin Immunol* 1997;99: S829-48.)

Key words: Sinusitis, allergy, otolaryngology, sinus surgery, public health–sinusitis

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0091-6749/97/\$5.00 + 0 1/0/82059

Abbreviations used

AFS:	Allergic fungal sinusitis
CF:	Cystic fibrosis
CFTR:	Cystic fibrosis transmembrane conductance regulator
CT:	Computed tomography
GM-CSF:	Granulocyte-macrophage colony- stimulating factor
HRQL:	Health-related quality of life
NO:	Nitric oxide
NPY:	Neuropeptide Y
SP:	Substance P
TNF:	Tumor necrosis factor
URI:	Upper respiratory infection

The paranasal sinuses are air-filled spaces within the bones of the head. In healthy adults the air and bone are separated by a ciliated epithelium containing goblet cells, nerves, blood and lymphatic vessels, and glandular rich connective tissue. The biologic functions of the sinuses remain unknown. It has been hypothesized that sinuses exist to provide vocal resonance and sound protection and to decrease the weight of the skull; other roles include olfaction, humidification, and regulation of intranasal pressure and mucus.

DEFINITION AND CLASSIFICATION OF ACUTE AND CHRONIC SINUSITIS

Sinusitis requires a more precise definition and classification. Because the inflammatory process that

causes sinusitis is frequently associated with inflammation of the nasal passages, the term *rhinosinusitis* might more precisely define this disease state. Several considerations support this contention. Rhinitis typically precedes sinusitis, and sinusitis without rhinitis is rare. The mucosa of the nasal and sinus tissues are contiguous, and the symptoms of nasal obstruction and nasal discharge are prominent in sinusitis. In certain clinical situations, either rhinitis (i.e., allergic rhinitis) or sinusitis (e.g., acute frontal sinusitis) may occur alone, but many cases feature some involvement of the contiguous secondary site. A study by Gwaltney et al.¹ used CT to document radiographic changes in the sinuses of otherwise healthy patients with an uncomplicated presumed viral upper respiratory infection ("common cold") of brief duration. The study found radiographic evidence of sinusitis in 95% of subjects, supporting the use of the term *rhinosinusitis*.¹ Thus rhinosinusitis may be a more appropriate term than either rhinitis or sinusitis alone.

Sinusitis is often classified chronologically as an acute, recurrent acute, subacute, or chronic (persistent) disease process. At this time acute sinusitis is defined as the symptom complex accompanying inflammation of the sinuses present for less than 8 weeks in adults and less than 12 weeks in children. The clinical presentation of acute bacterial sinusitis often follows a viral upper respiratory infection (URI), and persistence of the URI for more than 7 to 10 days usually indicates the development of sinusitis. A subset of patients—often those with a history of previous sinus infections—have a more abrupt onset of sinus-related symptoms with or without an associated URI. With appropriate therapy, the signs and symptoms of acute sinusitis usually resolve completely.

Subacute sinusitis is the manifestation of persistent minimal to moderate signs and symptoms of sinus inflammation, sometimes lasting for long periods of time.

Chronic sinusitis is frequently defined as signs and symptoms of inflammation of the sinuses persisting more than 8 to 12 weeks. A recent conference² defined chronic sinusitis as persistent inflammation documented with imaging techniques at least 4 weeks after initiating appropriate medical therapy in the absence of an intervening acute episode. In contrast to acute sinusitis, the role of bacterial infection in subacute and chronic sinusitis is less certain.

PUBLIC HEALTH IMPACT

A number of national data sets shed light on the great expense and increasing health care burden that sinusitis places on the U.S. population. For example,

sinusitis was the most frequently reported chronic disease in the 1993 National Health Interview Survey, a yearly interview survey of the noninstitutionalized U.S. civilian population. Nearly 15% of all respondents of the 1993 survey reported having sinusitis that lasted at least 3 months.³ Sinusitis rates are relatively high in the Midwest and South compared with the Northeast and Western regions of the United States. No apparent association exists between sinusitis and family income or urban residence.

Between 1982 and 1993 the prevalence of sinusitis increased dramatically (Table I). Between 1990 and 1992 approximately 73 million restricted activity days per year were reported by persons who had sinusitis. This figure represents a 50% increase from the approximately 50 million restricted activity days per year reported between 1986 and 1988.⁴

The 1993 National Hospital Discharge Survey, a yearly survey of hospital discharges for non-Federal U.S. hospitals, documented 16,000 discharges for acute sinusitis (ICD-9 code 461) and 29,000 discharges for chronic sinusitis (ICD-9 code 473).⁵ These data indicate that women are hospitalized more often than men for both acute and chronic sinusitis.

The 1991 National Ambulatory Care Survey, a periodic national physician survey of patient visits to private physicians' offices, reported approximately 11.6 million visits for chronic sinusitis. The data confirm that more women than men visited physicians' offices for sinusitis. Persons between 25 and 64 years of age and children less than 15 years of age utilized the most services. Sinusitis was the fifth leading cause for antibiotic prescriptions during ambulatory care visits between 1985 and 1992.⁶ In 1992, 13 million antibiotic prescriptions were prescribed for acute and chronic sinusitis—more than a twofold increase from 5.8 million prescriptions in 1985.⁶

In 1992, direct medical costs of sinusitis reached almost \$2.4 billion, a conservative estimate. Direct costs include hospitalizations for acute and chronic sinusitis, visits to both private physicians' offices and hospital outpatient units for chronic sinusitis, and prescriptions for antimicrobial treatment for acute and chronic sinusitis. These costs do not include the expense of managing a coexistent illness such as allergic rhinitis or nasal polyps or the expense of surgery and its related costs. In addition, no data have been aggregated to indicate the billions of dollars of indirect costs resulting from sinusitis or the costs for several expensive and important treatments, such as ambulatory endoscopic surgery and diagnostic CT imaging. Thus the total cost of sinusitis is certain to be much larger than \$2.4 billion, establishing sinusi-

TABLE I. Costs of sinusitis

People with sinusitis	14.7% of population ¹
Sinus surgeries, 1994	170,000 to 200,000 ⁸²
Restricted activity days per year, 1986-88	50 million ²
Restricted activity days per year, 1990-92	73 million ²
1993 U.S. hospital discharges, acute sinusitis*	16,000 ³
1993 U.S. hospital discharges, chronic sinusitis*	29,000 ³
1991 physician office visits for sinusitis	11.6 million ⁴
1985 antibiotic prescriptions for sinusitis	5.8 million ⁵
1992 antibiotic prescriptions for sinusitis	13 million ⁵
1992 direct medical costs of sinusitis	\$2.4 billion ^{6†}

*Does not include admissions for inpatient or outpatient sinus surgery.

†Does not include cost of surgery.

tis as one of the most expensive disorders experienced by the U.S. population.

Sinusitis and quality of life

A precise definition of health-related quality of life (HRQL) remains elusive, but HRQL generally refers to how patients feel and are able to function in their day-to-day lives as a result of their illness. Improvements in survey methodology increasingly provide valid and reliable tools to obtain this information.⁷

Two types of instruments, a generic health assessment and a disease-specific assessment, are generally combined to effectively measure HRQL. The generic or general health assessment provides a global view of the patient's well-being, but generic HRQL measures may not be sensitive enough to detect small but clinically important changes that occur as the result of intervention.^{8,9} Disease-specific instruments focus on impairments important to patients with a given condition. In general, they provide more sensitivity than generic instruments, as has been demonstrated in chronic sinusitis.¹⁰ By combining the generic and disease-specific health assessments, one can avoid the disadvantage of each and portray a more complete picture of illness.

One of the most widely tested and currently used instruments for general health assessment is the SF-36 (Medical Outcomes Study, Short-form, 36-item Health Survey).¹⁰ This instrument, which is used to measure HRQL in select populations, has shown that patients with chronic sinusitis (compared with age-adjusted normative data) experienced significant decrements in domains such as physical role functioning, bodily pain, general health, vitality, and social functioning. Chronic sinusitis elicited HRQL measures similar to other severe chronic illnesses studied with the SF-36, including chronic obstructive pulmonary disease, congestive heart failure, and angina pectoris.

A disease-specific HRQL measure for sinusitis increases our ability to monitor patient outcomes before and after intervention. The Chronic Sinusitis Survey, an instrument designed to monitor patient outcomes after surgical and medical interventions, has been demonstrated to be valid, reliable, and sensitive to clinically important changes.¹¹⁻¹³ To address other aspects of sinusitis-related quality of life, it may be necessary to develop additional disease-specific measures.¹⁴ However, HRQL instruments can and should endure rigorous assessment for reliability and validity, the benchmarks of comparison when choosing an instrument for a clinical study.

Unlike patients with hearing or vision loss, patients with sinusitis suffer in ways that are more difficult to measure but are nonetheless critical to their functioning and well-being. To improve our understanding of the ways sinusitis and its treatments affect quality of life, quality of life measures should be a vital part of clinical studies with patients who have sinusitis.

PHYSIOLOGY OF THE SINUS

Developmental anatomy

From the late 1800s through the mid 1900s, researchers detailed the anatomic terminology of the sinuses. Although revived interest in this area has elevated our awareness of the importance of the anatomy of the paranasal sinuses, inconsistent anatomic terminology is used. Establishing standard terminology would help clarify communication about this disease.

The only "normal" anatomic picture of the paranasal sinuses exists on an artist's canvas. "Abnormal structures," such as a concha bullosa or an ethmoidmaxillary cell (infraorbital ethmoid cell or Haller cell), may or may not lead to a pathologic condition. The structure of a person's paranasal sinuses is as unique as a set of fingerprints. Even from side to side in the same person, anatomic features may vary markedly. CT studies have been performed to exam-

ine the prevalence of these normal structures in both healthy and diseased patient populations. Concha bulbosae may be found in 20% of normal subjects but are more frequent in patients with chronic or recurrent sinusitis.

The anatomic development of the paranasal sinuses may be divided into prenatal development and the postnatal aeration of the sinuses that results in the "mature" anatomy. We know little about the role of potential cellular growth factors in the development of the ethmoid air cells within the fetal frontal recess, suprabullar recess, and ethmoid infundibulum. Data on these growth factors would help us better understand situations such as the various permutations of drainage of the frontal sinus into the frontal recess and subsequently into the ethmoid infundibulum.

Epithelial function and host response

Alterations in epithelial function may play an important role in the pathogenesis of sinusitis. Not only is epithelial hyperplasia a common feature of chronic sinusitis, but altered production of epithelial cell products could play a role in cellular inflammation. Epithelial cells are capable of producing a range of cytokines, such as IL-8, IL-6, IL-11, RANTES, MCP-1, and granulocyte-macrophage colony-stimulating factor (GM-CSF). Altered production of such cytokines could affect the recruitment, survival, and activation state of inflammatory leukocytes. Moreover, altered production of nitric oxide by the epithelium could be important in changing the antibacterial protection of the sinuses.

Infection of epithelial cells with common respiratory viruses such as rhinoviruses, respiratory syncytial virus, and influenza can induce the production of several cytokines.¹⁵⁻¹⁷ Studies with rhinovirus show that this response does not depend on any overt cytotoxic actions of the virus. Production of IL-8 could recruit neutrophils and some types of T-lymphocytes into the sinus mucosa, whereas RANTES is chemotactic for eosinophils. Eosinophil survival in the sinus mucosa would be supported by increased production of GM-CSF, which also primes these cells for enhanced responses to activating stimuli. Once activated, eosinophil products can alter epithelial ion transport processes and induce ciliostasis.

On the basis of these observations, it is attractive to hypothesize that inflammation influenced by changes in epithelial function could in some manner facilitate bacterial colonization. This process could be influenced by production of nitric oxide, which is generated in large quantities by the nasal epithelium. Several bacterial products can also affect both epithelial function and cytokine production and could further extend the cycle of inflammation. Eventually this inflamma-

tory cycle could become self-perpetuating and lead to long-term epithelial thickening and goblet cell hyperplasia. To test these hypotheses, however, it is important to perform detailed studies of the sinus mucosa by analyzing washings and biopsies and by studying cultural epithelium.

Chronic sinusitis: Associations with eosinophilic inflammation

Chronic sinusitis represents an ongoing inflammatory process for which inciting agents have been difficult to identify or prove. Chronic sinusitis with or without nasal polyposis is characterized by inflammatory thickening and polypoid changes in the sinus mucosa.¹⁸⁻²⁰ The histologic hallmark is marked tissue eosinophilia.¹⁸⁻²¹ The majority of the eosinophils express the activation marker EG2, a phenotype associated with degranulation and other signs of activation, such as cytokine and mediator production. Nasal polyp biopsies probed for various cytokine mRNA by in situ hybridization revealed a marked increase in inflammatory cells expressing mRNA for GM-CSF, IL-3, and tumor necrosis factor- α (TNF- α).²¹⁻²³ These cytokines are known to promote eosinophil accumulation through the up-regulation of endothelial cell adhesion molecules, including vascular cell adhesion molecule-1, and to cause eosinophil activation and prolonged survival (GM-CSF, IL-3). Activated eosinophils in nasal polyps produce GM-CSF and TNF- α mRNA, and eosinophils per se account to some extent for the presence of these cytokines in nasal polyp tissues. However, the driving force for eosinophil accumulation in chronic sinusitis remains unknown.

Various cellular elements such as constitutive cells (epithelial cells, fibroblasts, and mast cells) and monocytes produce cytokines within nasal polyps.²⁴⁻²⁶ Epithelial and fibroblast explants produce abundant quantities of GM-CSF, IL-6, and IL-8.^{23, 24} These studies suggest that the epithelium and constitutive cells contribute significantly to chronic eosinophilic inflammation, possibly producing a vicious cycle in which eosinophil infiltration is triggered by abnormalities within the epithelium and perpetuated further by the damaging effects of eosinophil-derived proteins and mediators on the epithelium.

A role for T lymphocytes and TH2 cytokines in the development of chronic sinusitis/nasal polyposis has not been clearly defined. Most studies have indicated that approximately 40% of patients with chronic hyperplastic sinusitis with nasal polyposis have associated allergies.²⁷⁻²⁹ Nasal polyps from these patients show increased numbers of CD4⁺ T lymphocytes and increased numbers of inflammatory cells positive for IL-4 and IL-5 mRNA.^{27,29} The features of these

polyps, combined with eosinophilia, mimic the late phase of allergic inflammation in the nasal mucosa.³⁰ Recent work shows the presence of CD4⁺ lymphocytes, mainly in polyps, in the mucosa of patients with recurrent sinusitis.^{31,32} However, studies of polyps from nonallergic subjects have shown that the number of CD3⁺ T lymphocytes and the number of IL-4 or IL-5 mRNA⁺ cells are not increased.^{28,29} Because eosinophilia is a prominent feature of both allergic and nonallergic nasal polyposis, these data suggest that a nonallergic mechanism exists for eosinophilia in chronic sinusitis.

It is important to investigate the inflammatory mechanisms that drive chronic sinusitis. Better methods are needed to dissect the pathologic process of chronic inflammation to understand the critical cellular elements, cytokines, and mediators involved. This task can be approached by direct examinations of pathologic specimens. In addition, specific cellular mechanisms, cytokines, or mediators can be examined in response to pharmacologic intervention aimed at abrogating selected elements in the inflammatory cascade. Immunopathologic studies should carefully control for confounding effects of medication use. Consideration should be given to performing microbiologic studies in conjunction with these investigations, because superimposed infection is potentially critical to the appearance of the inflammatory process.

There are limitations to the information that can be derived from studies of chronically inflamed tissues. However, potential inciting agents such as viral or other microbial pathogens can be examined. In addition, the need exists to develop models of disease pathogenesis (or recurrence) that incorporate an initial attempt to revert the sinus mucosa toward normality. Various strategies could be used, including surgery, treatment with antibiotics, elimination of allergic factors, treatment with topical or systemic corticosteroids, other pharmacologic approaches, or a combination of these strategies. The sinus mucosa is then more suitable to study in response to various types of exogenous stimuli.

Research is needed to identify factors that initiate or perpetuate chronic sinusitis, including the characteristic eosinophilic inflammatory infiltrate. These factors include bacterial, viral, or fungal organisms or microbial products.

Genetic factors

Although chronic sinus disease has been observed in multiple family members, the roles of genetic factors in sinusitis remain unclear. Two well-defined genetic disorders, cystic fibrosis (CF) and primary cilia dyskinesia (Kartagener's syndrome), are associ-

ated with persistent sinus disease. Cloning of the gene responsible for CF has provided new insights into electrolyte transport in respiratory epithelia. The CF transmembrane conductance regulator (CFTR) functions as a cyclic adenosine monophosphate-activated chloride channel and as a regulator of two separate channels: one that conducts chloride and one that conducts sodium. Mutations in the CFTR gene can affect one or both functions.

In patients with a classic form of CF, both functions are disrupted. Interestingly, some genetic defects cause subtle alterations in CFTR function. The resulting phenotype in patients carrying these "mild" mutations is attenuated; only one or two features of the disease are observed. Indeed, persons who have chronic sinus disease and elevated sweat chloride concentrations but no other symptoms of CF have been reported to carry mutations in each CFTR gene. Together these observations suggest that defects in CFTR and/or one of the proteins that interact with CFTR may account for a fraction of patients with persistent sinus disease. Genetic tools are available to analyze the entire CFTR gene in select groups of patients. Screening of patients with sinus disease recalcitrant to medical and surgical therapy may provide insights into the frequency of this association. Future studies could involve other genes that encode components of apical membrane electrolyte transport in sinus epithelia.

Collecting DNA from families with multiple members affected by the disease would be most helpful in this type of study, because genetic linkage studies might be used to assess the likelihood that a candidate gene is responsible for disease. If a sufficient number of family samples are obtained, a more extensive search of the human genome could be undertaken for genes involved in sinusitis. This approach, called *positional cloning*, might identify a gene that encodes a novel protein or a protein previously not known to cause sinus pathology. However, all of these genetic studies will require universally accepted diagnostic criteria for chronic sinusitis.

The role of nitrous oxide

Recently it was shown that nitric oxide (NO) is produced in large quantities in healthy human paranasal sinus epithelium. Concentrations of this gas in the sinuses can rise close to the highest permissible environmental pollution levels.³³ A role of NO in sinus host defense has been suggested because of its well-known bacteriostatic and antiviral properties. Furthermore, NO may up-regulate ciliary activity.^{34,35}

Sinus NO enters the nasal cavity via the ostia and contributes largely to the levels of NO found in nasal-

ly exhaled air. It appears that only small amounts of NO are released from the nasal mucosa. Therefore, a rough estimation of sinus NO production and the passage of this gas into the nasal cavity may be performed noninvasively by analyzing NO levels in nasally derived air. In children with chronic sinus disease resulting from primary ciliary dyskinesia or CF, nasal NO levels are markedly reduced compared with those of age-matched healthy controls. It has been suggested that this simple test could prove useful in the early diagnosis of these chronic airway disorders.³⁶ We do not know whether the low nasal NO levels in patients with CF or primary ciliary dyskinesia reflect a genuine reduction in mucosal NO production or a reduced passage of NO from the sinuses to the nasal cavity.

Inhaled high-dose exogenous NO has been used to treat pulmonary hypertension.³⁷ This vasodilator gas selectively dilates vessels that supply well-ventilated areas of the lung, resulting in increased arterial oxygenation and reduced pulmonary artery pressure. Interestingly, NO derived from the sinus bathes the lower airways and the lungs during normal respiration. Results of a recent study indicate that inhalation of endogenous NO may also have biologic effects in the lungs.³⁸ In patients who are intubated and who are deprived of endogenous NO inhalation, arterial oxygenation increases acutely if nasal air containing NO is aspirated from the patient's nose and added to the inspiratory flow of the ventilator. These findings indicate that sinus NO may act as an airborne or "aero-crine" messenger, produced in the upper airways and transported by the airstream to a distal site of action in the lungs.

Neural physiology

Trigeminal sensory, parasympathetic, and sympathetic neurons innervate the sinus mucosae. Little information is available about the functions of each type of neuron in normal sinus physiology and sinusitis pathophysiology. However, functions can be postulated on the basis of our understanding of the contiguous nasal mucosa, tracheobronchial mucosa, skin, and other structures.³⁹⁻⁴¹

Nociceptive (pain-carrying) sensory neurons are relevant to sinusitis because they convey the sensations of acute pain, headache, congestion, and fullness that are cardinal symptoms of both acute and chronic sinusitis. Nociceptive neurons are thin, non-myelinated C fibers that innervate respiratory epithelium, blood vessels, and possibly those glands that may be present. Nociceptive neurons are thought to be polymodal and sensitive to thermomechanical and chemical stimuli.⁴² Endogenous mediators that stim-

ulate nociceptive neurons during tissue ischemia, inflammation, and atopy include H^+ , K^+ , free radicals, bradykinin (B2 receptor), and histamine (H1 receptor). Other inhaled irritant factors such as SO_2 , O_3 , and cigarette smoke can stimulate nasal and tracheobronchial neurons, but it is unclear if these can activate sinus nociceptive neurons given the low rate of air exchange in normal sinuses. Capsaicin, the hot, spicy essence of chili peppers, has been an excellent tool for studying the functions of nociceptive neurons. Topical capsaicin causes the release of substance P (SP) and other neuropeptides that in turn activate a variety of nasal responses, individual glandular secretion, and increased vascular permeability.

Activation of epithelial nociceptive endings is thought to generate an action potential that is conducted throughout the entire neuron to the trigeminal association areas of the brain stem and cervical spine. Depolarization extends to all the "dendritic" branches of the neuron in the epithelium and other innervated structures and leads to release of neuropeptide transmitters from neurosecretory swellings ("varicosities") in these locations. The neuropeptides may include SP, neurokinin A, calcitonin gene-related peptide, gastrin-releasing peptide, and possibly other peptides.³⁹⁻⁴¹ This efferent mechanism of afferent nerves is termed the axon response and leads to "neurogenic inflammation." Evidence suggests that axon responses cause increased ciliary activity in rabbit maxillary sinus, rat tracheal goblet cell exocytosis, a small increase in superficial blood flow in porcine nasal mucosa, and granulocyte exudation in human nasal mucosa.⁴³⁻⁴⁶

The effects of individual peptides in the sinuses have not been fully evaluated but can be postulated on the basis of analogies from nasal mucosa and other sites.³⁹⁻⁴¹ SP may induce epithelial cell ciliary activity, goblet cell exocytosis, postcapillary endothelial cell contraction that permits plasma extravasation, cytokine generation,⁴⁷ and, as shown in human skin,⁴⁸ induction of endothelial cell adhesion markers such as E-selectin and vascular cell adhesion molecule that promote eosinophil and neutrophil diapedesis. Allodynia, the increase in pain responses to innocuous stimuli,⁴² may be the result of inflammation-induced dysregulatory effects on nociceptive and other nerve populations and their central interneurons that could lead to the exquisite tenderness of acute sinusitis or the unrelenting pain or sense of congestion or fullness of chronic noninfectious sinusitis.

Sensory nerve activation recruits parasympathetic reflexes in the nasal and tracheobronchial mucosae.³⁹ Cholinergic reflexes are thought to contribute to ciliary motion and goblet cell exocytosis, but evidence for epithelial cholinergic neurons is lacking. Other

neurotransmitters in cholinergic neurons may include vasoactive intestinal peptide and possibly NO. The presence of parasympathetic reflexes in human paranasal sinuses has not been well investigated.⁴⁶

Axon response–parasympathetic reflex responses may be anticipated to promote the production of sinus mucus secretions.⁴⁶ The sources of secretions are dictated by the histologic findings. Goblet cells are the major source of exocytosed mucins in maxillary sinuses. It is believed that epithelial cells generate NO, endothelin, IL-6, and IL-8; levels increase under inflammatory conditions. When compared with the nasal turbinates, sinuses have a relative paucity of submucosal glands with their serous and mucous cells. Levels of the serous cell products lysozyme and lactoferrin are increased in the nasal secretions of recurrent sinusitis subjects,⁴⁹ although changes in sinus aspirates have not been studied.

Sympathetic neurons that innervate blood vessels contain norepinephrine plus neuropeptide Y (NPY),³⁹ both of which are potent vasoconstrictors. Norepinephrine has a rapid onset and short duration of activity, whereas NPY has a slow onset but long-lasting effect. Despite the extensive use of α -adrenergic agonists in sinusitis, their efficacy and sites of action are still unclear. Sympathetic neurotransmitters may also function to limit neurogenic inflammation by binding to α 2-adrenergic and/or NPY inhibitory autoreceptors that inactivate nociceptive and parasympathetic neurons.⁴²

Although these postulated roles of nociceptive, parasympathetic, and sympathetic neurons in sinus pathophysiology and mucus production are tantalizing, the lack of basic information about sinus physiology permits only educated guesses about the roles of neurogenic inflammation and these potent neurotransmitters in sinusitis.

ENVIRONMENTAL FACTORS

No convincing evidence exists to support the role of environmental pollutants and toxicants in causing or prolonging sinusitis. However, whereas most studies on this subject have focused on the potential carcinogenic effects of toxicants on the upper aerodigestive tract, a scant few have addressed their potential for causing subacute and chronic inflammatory disorders of the nasal passages. For example, ozone is known to cause increased respiratory symptoms by compromising the host defense mechanism and by disrupting cellular membranes through its powerful oxidizing properties. In some cases an inhaled toxicant (such as CO₂, NO₂, and SO₂) is selectively absorbed by the nasal mucosa, giving rise to a concentrated effect of irritation and/or inflammation.

This cellular damage can initiate a series of cascading events in the inflammatory process, such as the release of inflammatory mediators, causing vascular extravasation of inflammatory cells and tissue edema. Such events lead to nasal mucosal swelling, decreased air flow, and the possibility of ostiomeatal complex obstruction.

Certain occupations may expose workers to more occupational hazards than others. These occupations include woodworking and carpentry; dye, paint, and solvent manufacturing; leather tanning; oil and gas distilleries; chemical plants; and hazardous waste disposal units. Host susceptibility may influence the inflammatory reaction to toxicant exposure, perhaps on a genetic basis. Interaction with or sensitization by a preexisting nasal condition such as allergic or vasomotor rhinitis may also potentiate the inflammatory reaction by an environmental toxicant. A “susceptibility/exposure index” would relate the factor of host susceptibility to the level and duration of exposure, an important epidemiologic evaluation. This type of potentiation is illustrated in studies of IgE responses induced by inhalation of diesel fuel particulates.⁵⁰

To determine the areas of risk, who is at risk, and how risk might be reduced, it is important that sinusitis surveillance programs based on sound epidemiologic principles be implemented by health professionals who deal with disorders of the respiratory tract. If research determines that sinusitis is a common complication of occupational and household exposures to nasal mucosal toxicants, health professionals must develop preventive measures to decrease risk and provide medical oversight.

ASSOCIATED CONDITIONS

Nasal polyps and sinusitis

Nasal polyps represent the ultimate manifestation of chronic inflammation. Nasal polyps most commonly arise from the lateral wall of the nose, although the anterior ethmoids and other sinuses may also be the primary site of origin. This inflammatory entity differs distinctly from the normal nasal mucosa and is characterized histologically by (1) cystically dilated, inspissated mucous glands that are completely different than the seromucinous glands of the inferior or middle turbinates; (2) a large influx of inflammatory cells, with the eosinophil predominant; and (3) dedifferentiation of the epithelium, including basal cell hyperplasia, goblet cell hyperplasia, and squamous metaplasia.

The microenvironmental theory of lateral nasal airway inflammation suggests that an extensive network of cytokines released by the resident structural cells (epithelial cells and fibroblasts) is up-regulated.⁵¹

These cells produce a number of molecules, including TNF- α , IL-4, IL-5, IL-6, IL-8, and colony-stimulating factors such as GM-CSF. These polypeptides attract inflammatory cells, particularly eosinophils and basophils from the microcirculation, and prolong their survival. In turn these inflammatory cells can produce cytokines such as IL-3, TNF- α , and GM-CSF in an autocrine up-regulated fashion; these cytokines then recruit more inflammatory cells. The factors that lead to the initial insult in the lateral wall of the nose are not known but could be bacteria, viruses, allergens, or pollutants. The regulation of these events in the nasal polyp is minimally understood and requires more study.

CF is commonly associated with nasal polyps, but nasal polyps occur most frequently in chronic sinusitis and occur universally in association with aspirin sensitivity. Inflammation in the polyp can cause de-differentiation of the polyp epithelium, possibly leading to defective migration of the CFTR protein into the cell membrane.⁵² This phenomenon could alter sodium absorption and chloride secretion, which might lead to water retention—the pathophysiologic hallmarks of nasal polyposis. In non-CF nasal polyps a defect in the apical sodium channel also exists, which is characterized by an increase in sodium absorption. This increased sodium absorption can be abrogated by amiloride, which might represent a new direction in the treatment of recurrent nasal polyposis. Thus it is possible that polyps form because of inflammatory changes that result in abnormal electrolyte fluxes in the nasal epithelium.

Asthma and sinusitis

Sinusitis frequently complicates asthma, and medical and/or surgical therapy for underlying sinusitis can improve asthma. In addition, in some patients with chronic cough who are thought to have asthma, the cough is probably the result of sinusitis (secondary to the associated postnasal drip). When the sinusitis is treated, the cough is eliminated or significantly diminished. Although an association exists between sinusitis and asthma in children, little objective data exist to prove that sinusitis causes or worsens asthma.

Research is needed to evaluate the relationship between sinusitis and asthma. Sinusitis appears to be common in children with respiratory allergy, as first demonstrated by Rachelefsky et al,⁵³ who observed that of 70 children with allergic rhinitis, 37 (53%) had abnormal sinus x-rays and 15 (21%) had one or more opacified maxillary sinuses. In a summary of experience with sinusitis and its relationship to asthma, Adinoff and Cummings⁵⁴ noted that active sinus

intervention improved asthma, and they noted a trend (though not significant) toward better results of pulmonary function testing and reduced methacholine reactivity in the actively treated patients compared with the patients treated with placebo.

Businco et al.⁵⁵ evaluated 80 children between the ages of 4 and 14 years who had asthma. Sinus x-ray films revealed abnormal findings in 55 of the 80 children; however, "abnormal" was defined as a 2 mm thickening of one or more maxillary sinus(es). The children were treated with either inhaled nasal corticosteroid with an antihistamine/decongestant or ampicillin plus an antihistamine/decongestant. Patients were evaluated 30 days following treatment. After both interventions the decreased severity of asthma and the findings of the sinus x-ray films improved significantly. However, the study did not include placebo or control groups.

In 1984 Rachelefsky et al.⁵⁶ studied a nonrandomized group of 48 children with a mean age of 8.2 years who had moderate to severe asthma and almost daily wheezing for at least 7 months. With pharmacologic or surgical intervention for associated sinusitis, 80% were able to discontinue their asthma medicine, 80% had normal findings on x-ray films, and the majority of patients had normalized pulmonary function and could stop taking their asthma medications. Continued follow-up in these patients revealed that their asthma recurred when sinusitis subsequently developed.

Another study examined gradations of asthma and abnormal sinus x-ray findings of 138 children with conditions ranging from cough-variant asthma to severe asthma.⁵⁷ The percentage with abnormal sinus x-ray findings ranged narrowly between 27% and 36%. No predictive difference in radiologic abnormality existed with regard to the severity of the asthma. The authors concluded that the sinus abnormality was not related to the asthma; however, they did not treat the sinusitis to see if they could eliminate the symptoms of asthma and improve the disease process.

Past studies that attempted to evaluate the association of asthma and sinusitis in pediatric patients have not been well designed in terms of randomization and placebo/control and did not account for the variability of childhood asthma. Therefore a carefully designed, prospective, randomized, placebo-controlled study would help answer these clinical questions.

Appropriate surgical intervention for medically resistant sinusitis has also been shown to benefit patients with coexistent asthma. This is also true both for bilateral intranasal sphenoethmoidectomy and functional endoscopic sinus surgery in children and adults. The mechanism for sinusitis-induced asthma is

not known but several possibilities have been suggested, including damage from the eosinophil, a cell found in both sites, inflammation from mediators produced by the sinus mucosa, and vagal neural reflexes. It is also possible that disease involving one contiguous tissue (the nasal/sinus mucosa) might involve the other airway mucosa. A recent hypothesis suggests that a pharyngobronchial reflex triggered by seeding of the inflammatory process into the pharynx results in extrathoracic airway hyperresponsiveness.

Rhinitis and sinusitis

Clinicians commonly associate nasal inflammation and sinus inflammation, often assuming that rhinitis antedates much of sinus disease and that treatment of rhinitis can prevent or improve sinus disease. Actually, the evidence for causality and even an association between rhinitis and sinusitis is not always straightforward.

Reinforcing the possibility of association, Rachelefsky et al.⁵³ and Shapiro⁵⁸ have described an increased incidence of sinusitis defined by history, physical examination, and imaging criteria in children referred to the allergist-immunologist for evaluation of rhinitis. In addition, skin testing proved that a large proportion of children in both groups were atopic, supporting a connection between allergic rhinitis and sinus disease. Among a group of children with recalcitrant sinusitis who were evaluated for allergy and immunodeficiency, approximately 50% were atopic, again supporting the connection between allergic rhinitis and sinusitis.⁵⁹ In a sample of patients undergoing surgery for chronic sinus disease, only the group with extensive disease exhibited an association between chronic sinusitis and allergy.⁶⁰

A large-scale evaluation of a primary care patient population would help determine whether a relationship truly exists between chronic rhinitis—specifically allergic rhinitis—and sinus disease. However, in designing such a trial, agreeing upon a definition of sinusitis for use in screening a large number of patients will pose a major challenge. In a recent study of 200 consecutive patients evaluated for chronic sinusitis in an allergist's office, allergic rhinitis was found in 56%, vasomotor rhinitis in 23%, and nasal septal deviation in 23%.⁶¹

The question of whether continuity exists between the nasal and sinus mucosa with regard to inflammatory processes, including cellular infiltration and cytokine profiles, has not yet been resolved. Lavage and biopsy studies that sample the nasal and sinus mucosae will help improve our understanding of the role of the nose in the scheme of sinus disease.

ROLE OF INFECTIOUS AGENTS IN ACUTE SINUSITIS

Recent work has shown that radiologic evidence of sinusitis is frequently found in patients who have a viral-associated common cold.¹ Thus colds are in reality a viral rhinosinusitis, which makes viral-associated sinusitis among the most frequent acute infection in humans. It is not known if virus invasion of the sinus cavity is necessary to produce these changes, but viruses (rhinovirus, influenza virus, and parainfluenza virus) have been recovered from up to 15% of sinus aspirates in patients with suspected acute community-acquired sinusitis.⁶² Viral sinusitis and infundibulitis may be important predisposing factors for the development of sinusitis in an estimated 0.5% to 2.5% of adult patients with upper respiratory infections in whom secondary acute bacterial sinusitis develops.^{63,64} It is estimated that 10% of colds in children lead to sinusitis.

The cause of acute community-acquired bacterial sinusitis has been well defined by sinus puncture studies that date back to the 1950s. Several important principles in the study of infectious disease, including bacterial titers, correlation with gram stain, and association with tissue or fluid leukocytosis, suggest a causal relationship between a positive bacterial culture and sinusitis. *Streptococcus pneumoniae* and *Hemophilus influenzae*, the most important pathogens, cause more than half of the cases in adults. Other streptococcal species, *Moraxella catarrhalis*, *Staphylococcus aureus*, and mixtures of anaerobic bacteria also each cause a small proportion of cases. While the incidence of the various bacterial species has not changed, their antimicrobial sensitivities have changed, creating important problems for antimicrobial therapy.

Although the roles of viruses and bacteria in the cause of acute infectious sinus disease are well established, the role of microbial infection in chronic sinus disease is less well defined. Few studies have performed sinus aspirations and quantitative bacterial culture in patients with chronic sinus disease. Currently it is difficult to quantify the role of bacterial infection in sinusitis. On the basis of available results, it is possible to recognize three categories of bacterial infection that may have different degrees of importance in chronic sinus disease.

The first category includes sinus aspirate cultures from which *S. pneumoniae*, *H. influenzae*, and other well-established bacterial causes of acute sinusitis are recovered in titers of $\geq 10^4$ CFU/ml.⁶⁵ These results were obtained from patients with chronic sinus disease, some of whom experienced acute sinus symptoms and others from whom a culture was obtained at

baseline status when they were scheduled for immediate sinus surgery. It seems likely that these bacterial infections have a role in the disease, but it is not clear whether they participate in the basic process initiating the chronic sinus disease.

The second category of bacterial infection includes persistent *S. aureus* or *Pseudomonas aeruginosa* cultures. These bacteria are usually seen in patients who have undergone sinus surgery and continue to experience symptoms of chronic sinus disease despite CT and rhinoscopic evidence of satisfactory surgical removal of anatomic obstruction. These infections are associated with persistent crusting and/or impaction of thick and sometimes "concretized" secretions in widely patent sinus cavities. In these patients, prolonged treatment with appropriate antibiotics may suppress the infection and lead to improvement, although permanent cure is not common. These two observations suggest that *S. aureus* and *P. aeruginosa* do, in fact, cause disease in this setting.

The third category of bacterial infections include cultures yielding *Staphylococcus epidermidis*, other coagulase negative staphylococci, corynebacterium species, and anaerobic bacteria. These bacteria have been recovered from surgical specimens and, when quantified, are usually present in low titers.⁶⁶⁻⁷¹ In this setting the role of these bacteria in causing disease is less clear and their role as pathogens is suspect.

To better understand and manage patients with viral and bacterial sinusitis, a number of important questions need to be addressed. These questions include knowing more about how viruses cause sinus disease, what risk factors lead to secondary bacterial infection, and what new approaches to treatment will prove useful in these conditions. We have many important questions about the role of bacteria in chronic sinus disease. Do bacteria have an underlying role in the cause of chronic sinus disease? Are they involved in the bony changes sometimes seen in chronic sinusitis? If so, what species are involved, and what are the pathogenic mechanisms? Some patients are recurrently infected with specific types of bacteria and apparently cannot or do not mount an effective immunologic response. Also, if bacteria are not the primary cause of chronic sinus disease, do they have a role in its perpetuation or severity?

Allergic fungal sinusitis

Allergic fungal sinusitis (AFS) is the fungal sinus affliction about which we know the least. It is caused by a variety of fungi, and we do not know the mechanisms that initiate or perpetuate the disease. It has been suggested that its pathogenesis is similar to

allergic bronchopulmonary aspergillosis. Various serum markers, including total and fungal-specific IgE, and serum and mucin eosinophilic cationic protein have been investigated to predict disease recurrence with no conclusive correlation. Monthly endoscopic mucosal staging has also been suggested to monitor disease progress. Left untreated, AFS is associated with bone reabsorption and remodeling and may markedly distort the face. Possible progressive epithelial damage resulting from eosinophil influx associated with the presence of fungi and apparent allergic responses may initiate a self-perpetuating, cyclical inflammatory/immunologic response only temporarily suppressed by oral steroids. Current treatment requires both corticosteroids and surgery, usually functional endoscopic sinus surgery, although we still do not know the optimal treatment program.

The treatment for AFS involves a combination of surgical approaches and aeration of the sinus with use of antiinflammatory therapies including oral and topical corticosteroids. Prednisone at 0.2 mg/kg per day may suppress the inflammation and sometimes restores the mucosa to normal. If the steroid dose is too low or is stopped too soon, the disease may recur even up to 22 to 34 months after surgery and up to 6 months after discontinuation of corticosteroids. The disease often progresses into the development of a polypoid sinus mucosa (with thick eosinophil-laden mucin with a peanut butter consistency.) The role of immunotherapy in the treatment of this disorder has yet to be determined. We need more studies to define the clinical settings that lead to AFS, how we can recognize the disease more readily, and how to treat the disease most effectively. Recent work suggests that antifungal agents such as itraconazole may be helpful in allergic bronchopulmonary aspergillosis. Controlled studies need to be performed to evaluate the role of antifungal therapy in patients with AFS.

PHARMACOTHERAPY

Antimicrobial therapy for sinusitis in adults

Antimicrobial therapy has been shown to reduce or eliminate bacteria in the maxillary sinus and to improve symptoms in acute community-acquired bacterial sinusitis.⁶⁹ However, because most cases of acute community-acquired sinusitis have a viral component that also affects the clinical course¹ and because acute sinusitis is usually a self-limited disease, defining the relative efficacy of various agents and regimens may be difficult.

For patients with acute bacterial sinusitis for whom organisms have been rather consistently identified, the antimicrobial selected should be effective against strains of *S. pneumoniae* with intermediate penicillin

resistance, as well as beta lactamase-producing strains of *H. influenzae* and *M. catarrhalis*. Table II lists the minimal inhibitory capacity (MIC₉₀s) against intermediate-resistant pneumococci of antimicrobial agents that have commonly been used to treat acute community-acquired bacterial sinusitis.⁷⁰ Only agents with MIC₉₀s of ≤4 against intermediate-resistant pneumococci are likely to be effective against these organisms because of the blood levels that can be achieved. A number of antimicrobial agents previously useful in treating acute sinusitis now have MIC₉₀s of ≥8 against intermediate-resistance pneumococci, which limits their usefulness for treating acute sinusitis.

In chronic sinusitis, bacteria are less consistently obtained from the sinuses and the complexity of the flora increases, with a shift toward multiple organisms, gram-negative organisms, *S. aureus*, and more antimicrobial resistance. In these patients antibiotic therapy should usually be based on culture and sensitivity results. In patients who have continued disease after sinus surgery, chronic *S. aureus* and *P. aeruginosa* infections are a special problem. Often sinus CT examination of these patients shows osteitis as evidence of bone involvement as part of the disease process.

The continuing rise in antimicrobial resistance complicates the antibiotic selection process and increases the failure rate of empiric treatments. Strains of intermediate and high-level drug-resistant pneumococci are now widespread in many but not all areas of the United States and are increasing in prevalence. Physicians treating acute community-acquired bacterial sinusitis need timely information on the resistant patterns of pathogens in their area, especially *S. pneumoniae*. Unless the rate of resistance is known to be low, caution should be used in selecting antimicrobials to which *S. pneumoniae* strains have developed increased resistance. In addition, clinical follow-up becomes more important, and timely culture and sensitivity testing is increasingly desirable, especially if persistent infection may be causing significant symptoms or if the patient is being considered for surgical treatment options. The use of antimicrobials with suboptimal activity also has the potential for hastening the emergence of resistant bacteria.

Several factors affect the optimal duration of therapy for sinusitis. Ten to 14 days of antimicrobial therapy has repeatedly been shown to eradicate or markedly reduce bacteria in the sinus cavity in patients with acute sinusitis and is the generally accepted duration of treatment.⁷¹ In patients with persistent or chronic sinus disease, there is little pub-

TABLE II. MIC₉₀s of 216 penicillin-intermediate strains of *S. pneumoniae* to antimicrobial agents commonly used to treat acute community-acquired sinusitis

Antimicrobial agent	MIC ₉₀
Amoxicillin*	1
Amoxicillin-clavulanate	1
Cefpodoxime†	2
Cefuroxime	4
Cefprozil†	8
TMP/SMX	8
Clarithromycin‡	8
Azithromycin†	8
Cefixime	16
Cefaclor	64
Loracarbef	64

*Not effective against β-lactamase-producing *H. influenzae* and *M. catarrhalis*.

†Not evaluated in pre- and post-treatment sinus aspirate culture studies.

‡Effectiveness against *H. influenzae* not evaluated in pre- and post-treatment sinus aspirate culture studies.

Data from Wald ER. J Pediatr 1995;127:339-47.

lished information on which to base duration of treatment. Longer and repeated courses of antimicrobial therapy are usually given to these patients, but clinical response is often unsatisfactory. Work is urgently needed on the pathogenesis of chronic sinus disease and on the role of infectious agents in initiating or complicating the process to allow more rational use of antimicrobial treatment.

Antibiotic therapy for sinusitis in children

For children with sinusitis, antibiotic selection requires knowledge of likely infectious pathogens. Table III profiles the bacteriology of acute and subacute sinusitis in children.

Previous studies have established the efficacy of antibiotic therapy for children with acute and subacute sinusitis. Children treated with antibiotics recover more quickly and more often than do children treated with placebo.⁷² With these pathogens in mind, the choices for antibiotic therapy are shown in Table IV.

Amoxicillin is often recommended as first-line therapy because it is usually effective and it is inexpensive and safe. Safety continues to be important, especially when treating children with uncomplicated infections who have not recently been treated with antibiotics. Table IV includes alternative antibiotic selections for children who do not respond or who worsen while receiving amoxicillin. Most of these antibiotics have been studied both in children and adults for either otitis media or sinusitis. For patients living in a geographic area with a high prevalence of

TABLE III. Bacteriology of acute and subacute sinusitis in children

<i>Streptococcus pneumoniae</i>	30%
<i>Moraxella catarrhalis</i>	20%
<i>Haemophilus influenzae</i>	20%
<i>Streptococcus pyogenes</i>	4%

penicillin-resistant pneumococci, the preferred antimicrobials include amoxicillin/clavulanic acid, cefuroxime axetil, and cefpodoxime proxetil.

Available data regarding the microbiology of chronic sinusitis in children are limited and confusing because of the variable definitions of chronic sinusitis, the failure to obtain specimens aseptically, the lack of quantitative results, and concurrent use of other antibiotics.⁷³ In patients with acute exacerbations of chronic sinusitis (intermittent episodes characterized by purulent nasal discharge), the usual microorganisms associated with acute sinusitis (i.e., *S. pneumoniae*, *M. catarrhalis*, and *H. influenzae*) are causative⁷⁴⁻⁷⁵ and treatment should include the same antimicrobials shown in Table IV. In patients with chronic persistent sinusitis (nasal congestion, purulent rhinorrhea or cough, alone or in combination for more than 8 weeks), the role of specific bacterial agents is less clear and, accordingly, the need for antibiotic treatment is controversial.⁷⁶⁻⁷⁷

Corticosteroids

Like many of the treatments of sinusitis currently being used, the use of corticosteroids remains controversial. The properties of corticosteroids that make them potentially useful include their ability to reduce mucosal swelling and thereby facilitate drainage of the sinuses, the reduction in tissue eosinophilia accompanying corticosteroid administration, and the proven efficacy of corticosteroids in shrinking nasal polyps. Moreover, topical corticosteroids have been proved effective and are widely accepted in treating allergic and nonallergic rhinitis. Thus many clinicians believe that corticosteroids are essential in the treatment of all forms of sinusitis; however, only scant controlled studies support this conjecture.

The few relevant studies of the use of corticosteroids in the treatment of sinusitis can be summarized briefly. One study compared groups treated with either topical dexamethasone alone or dexamethasone combined with topical neomycin and patients treated with placebo. The patients in the dexamethasone groups improved significantly compared with the patients who received a placebo.⁷⁸ A second study showed equivalent results when resolution of abnor-

TABLE IV. Antibiotics for treatment of sinusitis in children

- Amoxicillin
- Amoxicillin/clavulanic acid*
- Erythromycin/sulfisoxazole
- Sulfamethoxazole/trimethoprim
- Cefaclor
- Cefuroxime axetil*
- Cefprozil
- Cefpodoxime proxetil*
- Loracarbef
- Clarithromycin
- Azithromycin
- Clindamycin†

*These antibiotics are preferred when (1) the patient lives in a geographic area in which there is a high prevalence of β -lactamase-producing bacteria or a high prevalence of penicillin-resistant pneumococci, (2) the infection is severe, or (3) the infection fails to improve while the patient is receiving amoxicillin.

†Clindamycin is preferred when the patient is known to be infected with penicillin-resistant *Streptococcus pneumoniae*.

mal radiographs in groups treated with antibiotics were compared with subjects treated with topical beclomethasone.⁵⁵ In a third study, adding topical flunisolide to antibiotic treatments improved global evaluations and possibly reduced exacerbations.⁷⁹ However, none of these studies unequivocally proves efficacy or justifies general advocacy of topical corticosteroids in sinusitis. To determine the outcomes of the medical management of sinusitis, large studies should compare antibiotic and topical corticosteroid treatment for patients with either chronic or recurrent symptoms.

Prospective studies of the use of corticosteroids are needed to answer the following questions: In acute sinusitis, do topical corticosteroids play a role in effective management? In recurrent sinusitis, do topical corticosteroids reduce recurrence rates? In chronic sinusitis, do corticosteroids induce symptomatic relief? What is the precise role of topical corticosteroids in the management of nasal polyps? In patients with either recurrent or chronic sinusitis, should topical nasal corticosteroids be used prophylactically, and if so, for how long? What is the role of systemic corticosteroids in the management of acute, chronic, or recurrent sinusitis? What are the side effects or topical steroids? What are the roles of topical or systemic steroids in the treatment of nasal polyps?

Decongestants and mucoevacuants

Topical and systemic decongestant therapies have been recommended to adjunctively treat acute and

chronic sinusitis. Decongestants are vasoconstrictor agents that reduce the thickness of the nasal mucosa. They act on α -adrenoreceptors or are involved in the release, re-uptake, or degradation of noradrenaline.

Most of the blood in nasal mucosa is contained in sinusoids, which functionally serve as capacitance vessels. Thus vasoconstrictors represent the optimal drug class to decongest the nose by constricting capacitance vessels. α -1 Receptors respond to catecholamines with vasoconstriction. Current sympathomimetics are primarily oral medications; α -2 receptors respond to imidazoline derivatives, and current preparations are primarily topical. No controlled studies document the beneficial effects of topical or systemic vasoconstrictors in sinusitis.

Adjunctive therapy

Clinicians generally (but not universally) agree that in principle the adjunctive use of systemic mucolytic agents or physical mucoevacuant measures should benefit patients with chronic sinusitis.⁸⁰ However, very little or no data are available to support such treatment.

Most pharmacologic mucolytic agents are used primarily for treatment of the lower respiratory tract. Because sinusitis and lower respiratory tract infections both produce thick secretions, the utility of mucolytic agents has been extended to sinusitis. Most systemically administered mucolytics are derived from herbs or have a bitter or pungent taste.⁸¹ Large quantities produce nausea, but in subemetic doses they may produce vagal stimulation, which in turn stimulates the bronchial mucus glands.

Guaifenesin is now the mucolytic most commonly used in treating sinusitis. A single study of its effectiveness has been published.⁸² In a double-blind study, Wawrose⁸² administered 2400 mg daily of guaifenesin or placebo to 23 HIV-positive patients with chronic rhinosinusitis and found that the treatment group reported statistically significant improvement in nasal congestion and thick secretions compared with control subjects.

Physical mucoevacuant measures range from the simple use of patient-made saline solution snuffed from the cupped hand or administered via a bulb syringe, to pulsed irrigation of the nasal cavity and postoperative sinus cavities administered with use of a Water-Pik device and a nasal adapter. The modalities of steam, heated mist (including delivery intranasally under pressure) and dry, hot air have been studied in patients with allergic rhinitis and the common cold. However, none of this work has been extended to sinusitis.

RADIOGRAPHIC IMAGING

Even though imaging is increasingly used to evaluate patients with rhinosinusitis, the major role and benefit of this practice remains unclear. Two imaging modalities are used—plain films and CT scanning. Both modalities were compared by Lusk et al.⁸³ in a pediatric population; plain films were shown to be inaccurate in 75% of cases. Several investigators used plain films and measured the thickness of the inflammatory mucosa within the major sinuses to define sinusitis.⁸⁴ It remains unclear how the presence and extent of inflammatory disease shown on x-ray studies correlates with the patients' clinical presentation and course. Only after this correlation is clearly understood can we use imaging to examine patients with sinusitis and determine how they should be managed and what therapy should be used. Clinical, endoscopic, transillumination, and other noninvasive, non-radiographic diagnostic imaging could and should be used to provide the information sought from x-ray imaging. Such noninvasive practices could significantly reduce costs and help patients avoid x-ray exposure.

CT is the radiographic modality of choice to examine the nasal cavity and paranasal sinuses. The coronal plane best simulates the endoscopic view, and ≤ 3 mm scans provide the most accurate representation of the regional anatomy. Because CT is primarily performed to provide anatomic information, it should be performed when the patient's mucosal inflammation is under optimal control.⁸⁵ Inflammatory mucosa obscures the fine bony detail, resulting in a more limited evaluation. Thus optimal information is achieved when the CT study is performed 4 to 6 weeks after the initiation of medical therapy.

In postoperative patients and patients with chronic recurrent sinusitis, bony thickening is increasingly detected by CT. Many patients can correlate their symptoms (pain) with the location of this process. Unfortunately, the reason for bony thickening is not understood, and the following questions remain unanswered. What is this process? Is this an osteitis? How does this process influence the patient's symptoms, and can it be treated? Surgeries continue to be aimed at adjacent mucosal inflammatory disease without addressing the bony process.

ENDOSCOPY

Nasal endoscopy has greatly improved our ability to diagnose nasal and sinus disease and assess the response to medical and surgical therapy. Patients with recalcitrant complaints referable to the nose or paranasal sinus are particularly good candidates for this procedure. Flexible or rigid endoscopy is typical-

TABLE V. Absolute indications for surgery for rhinosinusitis

Sinusitis is causing a brain abscess or meningitis, a subperiosteal/orbital abscess, cavernous sinus thrombosis, another contiguous infection, or an impending complication (e.g., Pott's tumor)
Sinus mucocele or pyocele
Fungal sinusitis (all varieties)
Nasal polyps (massive, i.e., causing obstruction of most or all of the nasal lumens)
Neoplasm or suspected neoplasm (causing sinus obstruction)

ly performed after a careful history and physical examination. Advantages to each of the endoscopic modalities exist. The technique of nasal endoscopy is well described.⁸⁶

Properly performed nasal endoscopy need not be painful for the patient. Endoscopic sampling of nasal/sinus pathology should be studied to determine the underlying cause and optimal treatment regimens. Although endoscopically obtained cultures are thought to be valuable in the management of recalcitrant chronic bacterial sinusitis, their precise role in the treatment of sinusitis requires further analysis.^{87,88} Mucin can be sent for histopathologic analysis to assist in the diagnosis of allergic fungal sinus disease.

Mucosal biopsy specimens may be used to rule out ciliary dyskinesia, to assess causes of granulomatous disease, and to determine the nature of polyps suspected of being inverted papilloma or other neoplasms.

The future of nasal endoscopy lies in the introduction of thinner (1.7 mm) nasal endoscopes and contact nasal endoscopy. Contact nasal endoscopy with a rigid endoscope offers an in situ examination of the pathology in the nasal cavity. This may offer an opportunity to evaluate the response of the pathology to the medical treatment.

SURGERY

Because widely accepted definitions for the types of sinusitis and a clear definition of appropriate medical therapy are lacking, it is challenging to identify those types of inflammatory sinus diseases and the proper time in their temporal development for surgical intervention. The "absolute indications" for surgery for rhinosinusitis are easily defined (Table V), but the "relative indications" for which most surgery is (appropriately) performed are much more difficult.

Chronic rhinosinusitis (arbitrarily defined as 12 or more weeks of disease) is the most common "relative

TABLE VI. Important considerations for surgery for rhinosinusitis

Anatomic factor(s) that impede sinus drainage (e.g., substantial septal deviation, concha bullosa, paradoxically curved middle turbinate)
Abnormalities in the mucociliary clearance (Kartagener's syndrome)
Deficiency (e.g., HIV) or suppression (e.g., status post transplantation) of immune system
Insulin-dependent diabetes mellitus
Cystic fibrosis
Sinobronchial syndrome asthma
Aspirin sensitivity triad
Sarcoidosis/autoimmune/connective tissue disorder
Nasal polyps
Allergic rhinitis: poorly controlled by avoidance, pharmacotherapy, or immunotherapy
Failure of prior surgical therapy
Failure of adenoidectomy (children)
Failure of sinus irrigations (children and adults)
Presence of, or suspicion of, resistant organisms
Grade 4 or 5 anesthesia risk classification, or other relative contraindication to elective local/general anesthesia
Major coagulopathy

indication" for surgery for rhinosinusitis. In general, a thorough trial of medical therapy should be performed before surgical intervention in patients with chronic rhinosinusitis. Such medical therapy may include antibiotics, mucolytics, decongestants, steroids, and/or immunotherapy. However, a wide variety of factors (Table VI) will modify the timing of surgical therapy as well as the type and extent of surgical intervention.

In the majority of patients who have chronic rhinosinusitis refractory to an adequate trial of medical therapy, surgery decreases symptoms and improves the quality of life. However, outcomes studies are needed to ascertain the type and appropriate length of medical therapy before surgical intervention. An outcomes study on the management of sinusitis must control for the factors that modify the responses to therapy, including (1) anatomic abnormalities, (2) patient age, and (3) the sinus(es) involved. To better define the appropriate time for surgical intervention, we must develop standardized reporting of the results of surgical intervention specific to the disease addressed, the modifying factors, and the time of follow-up.

As stated earlier, all sinuses are not the same. Classic rhinosinusitis involves the maxillary sinus and the anterior ethmoid sinuses with the common symptoms of facial pain, rhinorrhea, postnasal drip, anosmia, and dental pain. In this circumstance,

surgery is directed to the middle meatus and the infundibulum. The posterior sinuses, composed of the posterior ethmoids and sphenoid, may present with a more complex set of complaints and change the progression to surgery. For example, sphenoid sinusitis may present with a higher prevalence of orbital problems, such as optic neuritis and visual loss. The frontal sinus may also provide its own set of medical and surgical challenges. A patient with forehead pain or edema may need an immediate trial of oral and/or intravenous antibiotics, with surgical intervention if symptoms do not resolve. The reason for this aggressiveness in frontal sinusitis is to avoid intracranial infection or bony infection such as osteomyelitis.

General considerations

The goals of surgery are to provide adequate sinus drainage and thereby reduce inflammation, to change the nasal anatomy to fit Proetz's principles, and to provide access to the sinuses for appropriate biopsies, irrigation, and cultures. Surgery may also be used to aerate the sinuses, to remove foreign bodies and polyps, and to prevent or reduce the morbidity of orbital, bony, and intracranial complications.

The classic indication for surgery for rhinosinusitis is failed medical treatment. The essential questions in medical treatment are: Which type of sinusitis is being treated, and what is the optimal medical therapy? Chronic rhinosinusitis is frequently a multifactorial problem and may include different predisposing factors such as anatomic, infectious, immunologic, allergic, ciliary, or mucus-related factors. Medical treatment of rhinosinusitis must be modified to fit a combination of causes in each individual patient, providing a wide range of medical therapies.

The indications for surgery for rhinosinusitis may vary on the basis of the type of surgery considered. The classic approach in the 1990s is to perform transnasal sinusectomies. However, this approach poses several questions related to the extent of manipulation, the nature of mucosal removal, the size of the ostia produced, and the selection of the sinuses and sides operated on. For the frontal sinus, many surgeons may face dilemmas as they select intranasal and extranasal procedures. Ancillary procedures such as adenoidectomy, septoplasty, and turbinectomies may also be selected. Septoplasties may be performed to improve the airflow through the nose, to provide access to the posterior sinuses, and to allow for ready manipulation of the nose and sinuses with the endoscopes, both intraoperatively and for postoperative care. The turbinates may be partially removed or moved to allow improved access to the sinuses or to reduce mucosal hypertrophy.

Age is an important variable in considering surgery. Although most authors readily classify prospective sinus surgery patients as children and adults, some attention should be made to more anatomic or physiologic issues that vary on the basis of growth and development of the nose, dentition, midface, orbits, forehead, and sinuses. In adults, changes occur with senescence that may alter the symptomatic innervation and modify the mucosal removal and postoperative care.

Revision surgery for residual or recurrent disease demands special attention. Noses and sinuses that have been previously manipulated may present unique diagnostic and surgical challenges. First, significant areas of scarring and bony regrowth that are not normally seen may be present. Second, a higher predominance of gram-negative and anaerobic organisms may be present. Indications for surgery in these patients may depend on a different natural history of the disease or a series of missed diagnoses and surgical problems.

Pediatric considerations

Because of the lack of firm scientific evidence identifying the appropriate role of prolonged medical therapy in sinusitis, indications for surgery of the paranasal sinuses in children are broadly described. Particular considerations in children are a lack of knowledge regarding the natural history of rhinosinusitis, anatomic features that require special techniques for surgery, and concerns regarding the potential effects of both surgery and chronic infection on paranasal growth. In general, surgery in children should be performed very conservatively and selectively.

Sinus surgery in children entails special considerations that do not apply to adults. Sinus surgery is more difficult in children; the smaller, more delicate anatomic features of children require special skill and instrumentation to avoid damaging the mucosa and to promote normal healing. Unlike in adults, the turbinates in children need to be preserved. Growth change has been discussed previously. The role of adenoidectomy and sinus irrigation needs review and may be recommended before sinus surgery. Scarring and synechia require further study, and no studies of pediatric rhinosinusitis have provided objective data. Current information indicates that scarring can occur rapidly, and second-look or third-look procedures can be necessary postoperatively to allow proper healing. In addition, recurrent infections still occur in young children, and although most children improve, few are cured. Several studies show a higher incidence of surgeries performed in patients who have an underly-

ing cause such as CF, immunodeficiency, marked allergy, or mucociliary dysfunction.

Outcomes

Good short to intermediate follow-up data are now available on the subjective results of surgery for rhinosinusitis. With use of functional endoscopic sinus surgery, overall symptomatic improvement usually has been reported in the range of 80% to 97.5% of patients. However, intermediate results of objective changes in the postoperative patient are less satisfactory, and several studies have demonstrated a poor correlation between subjective and objective evaluations.

Kennedy⁸⁹ studied a limited number of patients with both subjective and careful objective evaluation. Patients were recruited both prospectively and retrospectively. To evaluate for bias in the patients recruited into the study retrospectively, questionnaires were also mailed to a similar postoperative patient group who did not return for follow-up during the study period. The extent of preoperative disease was staged radiographically and patients were questioned to evaluate for the major diseases associated with rhinosinusitis and with regard to smoking and allergies. All patients were also treated medically. Mean follow up was 18 months. Subjective improvement occurred in 97.5% of patients, with a greater than 50% improvement in symptom score in between 80% and 90% of patients (depending on disease stage). No significant difference was found in subjective results between different radiographic stages of disease. Of 42 patients with asthma, 86% reported improvement. However, objective endoscopic resolution of disease was highly dependent on radiographic disease extent. Whereas totally normal mucosa was seen in 85% of patients with stage 1 disease, totally normal mucosa was seen in only 25% of patients with stage 4 disease. This data is particularly interesting when combined with the HRQL sinusitis data mentioned earlier.

At this time longer term prospective studies are required to evaluate the natural history of chronic rhinosinusitis and its response to surgical intervention and prolonged medical therapy. The respective roles of subjective and objective evaluation need to be further evaluated. However, it is clear that symptomatic improvement does not correlate well with resolution of disease. Therefore, if a study is being performed for evaluation of a staging system or if the aim of the study is to evaluate for resolution of disease, it is paramount to perform evaluation.

As a first step toward internationally accepted staging criteria for sinus disease, a group met in Princeton in 1991 and decided to begin to grade sinus disease on the basis of CT. They agreed to follow the Lund-

Mackay system in which each sinus (anterior ethmoid maxillary posterior ethmoid sphenoid and frontal sinus) is given a numeric score on the basis of the extent of CT opacification (0 = no opacification; 1 = partial opacification; 2 = total opacification). The osteomeatal complex is given a score of either 0 or 2 depending on whether it is involved.

To appropriately evaluate disease resolution, parameters for objective evaluation need to be developed, raising the question of whether endoscopic evaluation is sufficient or whether all patients should undergo postoperative CT. Kennedy⁸⁹ chose to use endoscopy but considered the sinus to be normal only if endoscopy demonstrated that each sinus was completely normal (i.e., no mucosal thickening, discharge, adhesions, inflammation, or polypoidosis).

With the advent of endoscopic evaluation it is clear that patients can be followed up after surgical intervention and that in many cases persistent disease can be treated either medically or by local debridement before it becomes symptomatic. However, the long-term cost-effectiveness of managing sinus disease in this fashion and the long-term effects of this type of management on patients' overall health clearly need to be studied. Similarly, with the advent of endoscopes and the ability to perform endoscopic follow-up, it is clearly possible to avoid a situation in which the patient returns after prior surgery with massive nasal polyposis and nasal obstruction requiring extensive revision surgery.

Image-guided surgery is in its infancy. It is now commonly used in neurosurgery and, if used in endoscopic surgery, could assist in guiding the surgery and help decrease these complications. As this equipment becomes more available, image-guided surgery will need to be evaluated and the advantages determined.

CONCLUSIONS AND RECOMMENDATIONS FOR RESEARCH

Sinusitis is an exceptionally important disease viewed from any perspective. Medical interest and analysis of various treatments for this disease has only recently begun to develop; until recently, surgery involved techniques developed 100 years ago. Surgical procedures have undergone a radical change in the past decade. Because of the limited time frame for the determination of the long-term results of functional endoscopic surgery, the efficacy of this procedure beyond the first year after surgery is poorly defined as yet. Even the discussion of sinusitis in the classic texts of medicine or allergy are scant and inadequate. Thus the importance of this disease far outweighs the current scientific basis for its diagnosis and treatment, and it is only with conferences that

define the extent of our knowledge that the envelope can be extended.

It is evident that we need to study all aspects of sinusitis, from who gets this disease and why to how to properly diagnose and treat it. This workshop provided an unprecedented opportunity for epidemiologists, pediatricians, internists, surgeons, and allergists/immunologists to discuss sinusitis and highlighted for us the dearth of answers currently available and the deficiencies in our knowledge that we face when we treat these patients.

Broadly stated, the following areas constitute important directions for research:

- 1) Define the clinical, radiographic, and pathologic state and describe the epidemiologic characteristics of sinusitis, facilitating studies of natural history and assessment of therapeutic outcomes.
- 2) Investigate alterations in sinus epithelial function and biology as potential causes or contributing factors in sinusitis.
- 3) Determine the role of infectious agents, including viruses, bacteria, and fungi, in the cause of chronic sinusitis.
- 4) Investigate host response to pathogens, environmental toxicants, irritants, and allergens in terms of sinus mucosal pathophysiologic, neuronal, and immune responses and identify genetic factors in the development of sinusitis.
- 5) Investigate the cellular and mediator-induced mechanisms of chronic inflammation in sinusitis and nasal polyp formation.
- 6) Understand the epidemiologic, pathophysiologic, and therapeutic implications of the relationships between sinusitis and asthma, sinusitis and rhinitis, and sinusitis and aspirin sensitivity.
- 7) Define the role of antibiotics and other medical therapies (including topical and systemic corticosteroids, decongestants, and mucosucavacants) in acute, chronic, and recurrent sinusitis.
- 8) Define the indications, preoperative and postoperative staging criteria and clinical, pathologic, microbiologic, and radiographic responses to sinus surgery in selected patients with chronic sinusitis by various age groups.

This list by no means exhausts available research needs; this workshop, sponsored collaboratively by the American Academy of Allergy, Asthma and Immunology and the American Academy of Otolaryngology-Head and Neck Surgery highlighted many other questions for future study. The authors hope that this workshop is an important first step toward heightening awareness of sinusitis and setting priorities for the direction of future research.

With a disease that costs society billions of dollars each year and affects a significant portion of the population, it is appropriate to begin the push for more funding, more research, and more answers.

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