

of the sinus. However, if the association of increased nasal secretion production and sinus MRI abnormality observed in this study is confirmed, it indicates that these sinus abnormalities are of some clinical importance.

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Prospects for ancillary treatment of sinusitis in the 1990s

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The basis for ancillary therapy of sinusitis derives from anecdotal accounts and personal beliefs rather than definitive data. The recent appreciation that noninfectious inflammatory causes predispose to infectious sinusitis has stimulated renewed interest in developing and documenting efficacious ancillary therapies that could supplement or abrogate antibiotic use. Ancillary therapies of sinusitis could be directed toward (1) preventing viral upper respiratory tract infections (immunizations, virucidal-impregnated tissues, and proper hand-washing techniques); (2) blocking rhinoviral replication and suppressing mediator release with supraphysiologic nasal hyperthermia, although contradictory studies exist with regard to efficacy; (3) promoting sinus and nasal ventilation with both topical and oral α -agonists and exercise; (4) improving mucociliary clearance by reducing mucus viscosity and elasticity with saline solution irrigation, mucoregulators (N-acetylcysteine, S-carboxymethylcysteine, and iodinated glycerol), and ciliary stimulants (adenosine triphosphate); and (5) suppressing/modulating cellular inflammation (eosinophilic, basophilic, and neutrophilic) with topical nasal corticosteroid sprays and mediator antagonists. Recommendations are forwarded for future investigations of promising nonantibiotic ancillary therapies of chronic sinusitis. (J ALLERGY CLIN IMMUNOL 1992;90:478-95.)

Key words: Sinusitis, hyperthermia, α -agonists, mucoregulators, mucociliary clearance, N-acetylcysteine, iodinated glycerol, adenosine triphosphate, topical corticosteroids, mediator antagonists

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Chronic sinusitis may originate from either infectious or inflammatory causes. Infectious sinusitis, which may be suppurative or nonsuppurative and classified as acute, subacute, or chronic, represents infective inflammation of the mucosa of the sinuses with frequent concomitant involvement of the nasal phar-

Abbreviations used

URI:	Upper respiratory tract infection
ATP:	Adenosine triphosphate
MCC:	Mucociliary clearance
PPA:	Phenylpropanolamine
NAR:	Nasal airway resistance
VMR:	Vasomotor rhinitis
IG:	Iodinated glycerol
SCMC:	S-carboxymethylcysteine
NAC:	N-acetylcysteine
GG:	Glyceryl guaiacolate
SER:	Serratiopeptidase
NFLX:	Norfloxacin
CEE:	L-cysteine ethylester hydrochloride
MBP:	Major basic protein
ECP:	Eosinophil cationic protein
NSAIDs:	Nonsteroidal antiinflammatory drugs
ASA-RSA:	Aspirin-sensitive rhinosinusitis asthma

ynx. Episodes of infections may arise as primary events after a viral URI or recurrently and secondary as a complication of another nasal inflammatory process (allergic or nonallergic eosinophilic rhinitis with or without aspirin sensitivity), antibody deficiency states (Bruton's agammaglobulinemia, common variable immune deficiency, selective IgG subclass deficiencies, selective IgA deficiency, ataxia telangiectasia, Wiskott Aldrich syndrome, acquired immune deficiency syndrome, etc.), complement abnormalities (C3b inactivator and C3 deficiencies), leukocyte abnormalities (chronic granulomatous disease, hyper IgE syndrome, Chediak-Higashi syndrome, etc.), structural defects (cleft palate, ciliary defects, osteopetrosis, and foreign bodies), or cystic fibrosis. Noninfectious inflammatory causes of chronic sinusitis include extension from or complications of allergic rhinitis, asthma, eosinophilic nonallergic rhinitis, aspirin sensitivity, primary nasal polyposis, and allergic fungal sinusitis.¹ These noninfectious inflammatory disorders have the eosinophil with/or without nasal basophilic (mast cells/basophils) cells as the major pathologic cellular elements and frequently deteriorate to secondary bacterial sinusitis. Attention to eradication of the noninfectious cellular infiltrate must be aggressively addressed to prevent secondary bacterial sinusitis. Chronic production of viscid exudate, edema, and inflammatory responses to pathogens characteristically block sinus ostia, which interfere with mucociliary function and expulsion of inflammatory contents. These events may cause recurrent or chronic infectious sinusitis, thickened sinus mucosa, sinus cysts, or polyps. In addition, the sinus mucosa

in both purulent and serous sinusitis evidences markedly increased amounts of mucus because of a dramatic sixfold increase in newly formed seromucous glands.² Proper diagnosis and aggressive chronic treatment directed toward the primary conditions listed here are necessary to prevent the complications of untreated or inadequately treated disease. The present discussion will concentrate on the ancillary treatments or procedures that may assist in the therapy of sinusitis; the discussion of oral, parenteral, and topical antibiotic therapy, surgery, immunotherapy, and environmental control will appear elsewhere in these proceedings.

Despite the mounting evidence of the importance of antibiotics and surgical treatment of sinusitis in both children and adults, only a paucity of controlled replicative data exists on the possible benefit derived from ancillary therapy to these traditional therapies. These potentially useful ancillary treatments and procedures are listed in Table I. They include the following: (1) prevention of viral and bacterial infections, barotrauma, and allergen exposure (covered by other discussants); (2) reduction of nasal obstruction and increase in sinus ostia size (stimulation of vasoconstricting nasal reflexes and use of topical and systemic α -agonist decongestants); (3) promotion of improved nasal mucociliary function (saline solution irrigation, humidity, steam, ATP, and mucoactive agents); and (4) suppression of mucosal inflammation (topical or systemic corticosteroids and mediator antagonists).

STIMULATION OF VASOCONSTRICTING NASAL REFLEXES

Rationale for use

Posture. Maxillary ostia functional diameter compromised by about 50% during chronic sinus disease becomes reduced an additional 20% during recumbency.³ In those patients who have existing unilateral obstruction (polyps, deviated septa, etc.) or who experience unilateral sinusitis, lateral recumbency to the unaffected side should be encouraged, which should improve nasal patency of the contralateral (affected) side and prevent increases in nasal obstruction if the affected side were lateral-side recumbent.⁴ Patients with bilateral nasal obstruction during rhinosinusitis may obviate the detrimental effects of recumbency by sleeping in the supine position, body midline, and bolstered by several pillows or by elevating the head of the bed 45 degrees.

Exercise. Vigorous physical exercise improves nasal function in up to 75% of healthy subjects or patients with perennial allergic rhinitis⁵ by reducing nasal airflow resistance and nasal blood flow for as long as 30 to 60 minutes by activating the sympathicoad-

TABLE I. Ancillary therapy of chronic rhinosinusitis: Clinical practice, documented efficacy, and recommendations for the future

Therapy	Ancillary therapy of chronic rhinosinusitis		
	Commonly recommended	Definitive efficacy by DBPC studies	DBPC studies recommended
Exercise	Yes	ND	Yes
Hyperthermia	Yes	ND	Yes
ATP	No	ND	Yes
α -Agonists: Topical	Yes	ND	Yes
α -Agonists: Oral	Yes	ND	Yes
Saline Irrigation	Yes	ND	Yes
β -Adrenergics	No	ND	No
Anticholinergics	No	ND	? for NHR
Antihistamines	Yes	ND	? for safety
Theophylline	No	ND	?
IG	No	ND	Yes
Cysteine derivatives	No	ND	Yes
Guaifenesin	Yes	ND	No
Cromolyn	No	None after URI	No
Corticosteroids: Topical	Yes	ND	Yes
Corticosteroids: Systemic	Yes	ND	Yes
ASA/NSAIDs	No	Yes?	?
Leukotriene antagonists	No	ND	Yes
PAF antagonists	No	ND	Yes
Capsaicin	No	ND	? for NHR
Protease inhibitors	No	ND	Yes
Mucin gene regulation	No	ND	Yes

ND, Not determined; DBPC, double-blind, placebo-controlled; NHR, nasal hyperreactivity; PAF, platelet-activation factor.

renal system. The mechanism for this exercise-induced vasoconstriction appears related to an increase in sympathetic nerve discharge at the postganglionic nerve endings within the walls of the nasal capacitance vessels rather than directly by an increase in circulating catecholamines.⁶ About 20% of patients with allergic rhinitis, in contrast to nonhealthy subjects, have a rapid reversal to baseline obstruction as quickly as 5 to 10 minutes after exercise despite a maximal nasal decongestive response.⁷ In healthy individuals intense physical exercise in healthy and healed sinuses significantly increases the functional maxillary ostium diameter about 10%. Unfortunately, exercise failed to increase ostia diameter in subjects who have persisting sinus disease; this implies that structural factors rather than mucosal edema causes blockage of the ostia.³ In addition, approximately 10% of patients with sinusitis experienced an abnormal increase in nasal airway resistance on the ipsilateral nares to the sinusitis after physical exercise.³ These findings challenge researchers to determine whether exercise exerts a beneficial or detrimental effect during acute or chronic sinusitis.

PREVENTION OF VIRAL URI

Because viral URIs predispose to sinusitis in both healthy subjects and patients with chronic rhinosinusitis, measures to prevent URIs are warranted. Possibly beneficial simple hygienic measures include (1) avoiding touching of nasal or ocular membranes with unwashed hands and using facial tissue impregnated with virucidal agents; (2) promoting antiviral measures, environments, and surfaces at home, school, and work; (3) supporting influenza vaccination of patients with chronic rhinosinusitis; and (4) delaying day care and contact with large numbers of young children, particularly infants and toddlers suffering from chronic sinusitis, if financially feasible.

Hyperthermia

Rationale for use. The effects of nasal hyperthermia on the common cold have received recent review⁸ prompted by the observation that supraphysiologic temperatures (up to 43°C) block rhinoviral replication in vitro.⁹

Controlled clinical trials of hyperthermia in sinusitis. Four controlled studies¹⁰⁻¹³ have evaluated the ef-

fect of hyperthermia on viral URIs. Three of the studies used a special device, the "Rhinotherm" (delivery through two exhaust hoses), and the other used a device called a "Virotherm" (delivery through face mask), which delivered by nasal inhalation fully saturated 43° C air at a flow rate of 40 L/min,^{10, 13} which resulted in mean intranasal temperatures of $39.7 \pm 0.5^\circ\text{C}$ and $38.6 \pm 0.6^\circ\text{C}$ at depths of 1 and 4.5 cm, respectively, from the nostrils, and temperatures about 8° and 4° C, respectively, above intranasal temperatures after insufflation of air at room temperature.¹⁴ Two initial studies claimed between a 73% and 81% improvement in nasal symptoms by 24 hours after three 30-minute¹⁰ or 22-minute¹¹ treatments at 90-minute intervals compared with an 18% to 23% favorable response in placebo-treated control subjects suffering from naturally acquired acute URIs.^{10, 11} Methodologic details from these reports were insufficient to critically evaluate the adequacy of the randomization process, the comparability of the active and placebo groups, and the ease of determining the mock treatment of low flow air at 30° C. Subsequently, nasal hyperthermia delivered by the "Virotherm" was compared with inhaling humidified air at 30° C at the same flow rate in separate, randomized, and controlled experiments in subjects who had either naturally or experimentally acquired rhinoviral infections.¹³ Under these conditions patients are generally unable to distinguish between the two temperatures. During naturally occurring rhinoviral infections, the hyperthermia group (only one 20-minute session) had greater improvement for all days of treatment; however, despite randomization the control group had significantly greater symptoms at baseline, which precluded unequivocal acceptance of the findings. Interestingly, 40% to 50% of both hyperthermia and mock-treatment subjects reported a reduction in the degree of nasal congestion immediately after treatment. Subsequent subgroup analyses to overcome the noncomparability of groups at baseline, although claiming to still show important differences, were not convincing. In studies of experimentally infected subjects, intensive hyperthermic therapy (three 30-minute sessions) compared with mock treatment led to a 20% decrease in both symptoms and total nasal secretions, although both increased from baseline even in the hyperthermic group. No reductions in subjects who secreted rhinovirus or viral antibody response were noted on follow-up. Less intensive treatment had no effect.¹³ Most recently, use of the "Rhinotherm" in a group of patients with naturally occurring colds in the winter of 1989 failed to demonstrate an improvement of symptoms with two 20-minute treatments compared with mock treatment at room temperature.¹² From this dis-

cussion, it appears that hyperthermia will not be the panacea for rhinoviral colds and cannot be expected to prevent sinusitis. Because these studies reveal divergent findings, it is obvious that the practice of nasal inhalation of hot humid or dry air will continue until definitive results emerge. The potential hazards of such therapy should be raised, because ciliary beat frequency of epithelial tissue reveals an irreversible arrest between 40° and 55° C in vitro. In this light, it is at least somewhat reassuring that nasal inhalation of humidified vapor at $50.5 \pm 5.8^\circ\text{C}$ for 10 minutes failed to adversely affect nasal cellular distribution or viability and even significantly increased ciliary beat frequency by 11%.¹⁵ These findings suggest that the nose functions well to regulate nasal temperature ranges to safe levels despite exposure to high external temperatures.¹⁶

Studies have reported a significant increase in nasal MCC after ingestion of 500 ml of hot tea with lemon by healthy volunteers.¹⁷ MCC increased from an average of 20% to 35% by 5 minutes and returned to baseline by 30 minutes after sipping hot water or sipping or straw drinking hot chicken soup (200 ml of each at 65° C) compared with sham straw drinking, cold water sipping, or hot water sipping by straw. A linear increase in respiratory epithelial ciliary beat frequency with increasing temperature from 22° C to 40° C may be responsible in part for the aforementioned effect.¹⁸ No effect was seen on nasal airway resistance.¹⁹

IMPROVING NASAL AND SINUS OSTIAL PATENCY

The importance of normal maxillary ostial function in the prevention and resolution of sinus disease can be appreciated by the direct correlation of impaired ostia function and sinus disease.²⁰ An ostium diameter of less than the normal adult size of 2.5 mm results in lower oxygen concentrations within the maxillary sinus, which correlates inversely with recurrent sinusitis.²¹ In addition, nasal obstruction arising from inflammatory or mechanical causes has been recognized for years to increase paranasal inflammation and sinusitis.

α -Adrenergic decongestants (Table II)

Both topical and oral decongestants commonly are used as adjuncts to antibiotic therapy in the treatment of both acute and chronic sinusitis for the purpose of maintaining or widening ostia patency and reducing turbinate swelling/congestion.

Oral adrenergic agents. The capacity of oral α -agonist decongestants alone (pseudoephedrine, 60 to 120 mg) or PPA (30 to 100 mg)²² to reduce nasal

TABLE II. Selected nasal decongestants used in sinusitis

Generic (brand) name	Onset (hr)	Duration (hr)	Dosage (sprays/mg)
Topical agents			
Sympathomimetic amines			
Phenylephrine (Neo-synephrine/NS, Dristan)	<0.1	1-4	1-2 qid
Imidazoline derivatives			
Naphazoline (Privine, 4-Way)	<0.1	2-6	1-2 tid
Tetrahydrozoline (tyzine)	<0.1	3-6	1-2 tid
Oxymetazoline (Afrin, Nostrilla, Duration, NTZ)	<0.1	5-12	1-2 bid
Xylometazoline (Otrivin, Sinex, NS II)	<0.1	6-12	1-2 bid
Systemic agents			
Phenylpropanolamine (Propadrine)	0.25-0.5	3-4	25/50 mg tid
		8-12	75 mg bid
Pseudoephedrine (Sudafed)	0.25-0.5	4-8	30/60 mg tid
		8-12	120 mg bid

qid, Four times daily; tid, three times daily; bid, twice daily.

resistance and stuffiness within 30 minutes, which persists for up to 240 minutes after intake in healthy subjects and for variable periods in patients with various rhinitic conditions, has been reconfirmed over the past 30 years. Whether increases in nasal patency favorably affect the outcome of acute or chronic sinusitis remains to be proved because studies are lacking. PPA in an oral dosage of 100 mg compared with placebo led to an insignificant widening of the functional size of the maxillary ostia of 20 adults suffering from acute rhinosinusitis, which is in contrast to exerting a widening effect in healthy subjects.²³ In an open study of six adults with healed or diseased sinuses, although baseline ostia diameters were significantly higher in the healed (2.1 ± 0.2 mm) than the diseased (1.5 ± 0.2 mm) patients, maxillary ostia diameters significantly increased 50% in healed sinuses and 30% in diseased sinuses after use of PPA. Total nasal resistance concomitantly decreased significantly about 33% by 90 minutes after use of PPA in both groups.²⁴ In acute viral URIs, pseudophedrine (120 mg) and PPA (100 mg) caused similar reductions in nasal airway resistance that persisted for at least 6 hours.²⁵ The decongestant effects of PPA were noted in patients in the semirecumbent but not complete recumbent position, which should encourage the use of a propping-up position, in which the upper part of the body is elevated at least 30 degrees during sleep. These preliminary and yet potentially important findings require (1) confirmation by placebo-controlled investigation, (2) determination whether PPA or other possibly safer oral α -agonists²⁶ exert such improvements in ostia patency and nasal function to an extent that will serve a significant role in the treatment

and/or prevention of acute or chronic sinusitis, and (3) comparison of efficacy and safety with topical decongestants such as oxymetazoline and similar agents, which exert a greater decongestant effect on nasal resistance in the short term than do oral α -agonists (pseudoephedrine).²⁷ The low therapeutic index of PPA in healthy adults as demonstrated by its hypertensive effect at both a 150 mg dosage and at 75 mg when supplemented with 400 mg caffeine²⁸ combined with its frequent use in sinusitis deserves further safety and efficacy studies.

Topical adrenergic agents. α_1 -Adrenergic receptor sympathomimetic catecholamines (phenylephrine) and α_2 -adrenergic receptor imidazoline derivatives (naphazoline, tetrahydrozoline, oxymetazoline, and xylometazoline) constitute the two classes of effective topical nasal decongestants by acting on the capacitance nasal mucosal vessels that control mucosal congestion. The class of adrenergic receptor stimulated by these topical adrenergic agents may have some clinical importance, because capacitance vessels have both α_1 - and α_2 -receptors, whereas nasal resistance vessels, which control mucosal blood flow, have only α_2 -receptors. These differences result in α_2 -adrenergic receptor agonists reducing nasal airway resistance but at the expense of compromising mucosal blood flow by their effect on resistance vessels. α_1 -Adrenergic agents do not suffer this disadvantage. In addition to the topical α_1 -adrenregic agent phenylephrine, PPA (both an α_1 - and β -adrenergic agent) has been found in a concentration of 2.5% to be an excellent topical nasal decongestant. On the other hand, the detrimental effect exerted on resistance nasal vessels by α_2 -adrenergic agents can be significantly

reduced by diluting the preparations 1/10 of their commercial concentrations (xylometazoline from 1 mg/ml to 0.1 mg/ml), a concentration that provides less but still significant nasal decongestion.²⁹ Other differences between the two classes include generally longer duration of action and less risk of systemic sympathomimetic effect of the imidazoline derivatives, although the latter is uncommon for both classes.

Sustained or long-term use of these topical adrenergic agents has been condemned for fear of developing rhinitis medicamentosa, tachyphylaxis, tolerance, or atrophic rhinitis (compromising mucosal blood flow by α_2 -stimulation). Two short-term prospective studies have approached this subject. The use of xylometazoline (0.15 ml of a 1 mg/ml solution) three times daily long term for 6 weeks did not affect MCC or cellular or tissue morphology that was determined by scanning electron microscopy in 20 normal subjects either when healthy or during a viral URI.³⁰ A more recent study determined the objective NAR response to serial concentrations of xylometazoline and exercise before and 3 weeks after long-term use of xylometazoline (similar dose as in prior study) in 12 patients with nonallergic, noninfectious chronic VMR and 10 healthy control subjects.³¹ After 3 weeks use of xylometazoline, NAR in subjects with VMR compared with healthy controls (1) had a significant increase that at baseline was already threefold higher; (2) exhibited a similar dose response to xylometazoline and exercise without evidence of tolerance development; and (3) developed suboptimal decongestion. These observations revealed that rebound congestion, which is characteristic of rhinitis medicamentosa and which may derive from interstitial edema, occurs in patients with chronic nasal disease (in this case VMR). As such, subjects with chronic sinusitis may also be at increased risk for developing rebound nasal congestion from topical adrenergic agents and as such should be advised to avoid the use of such agents for more than 3 to 7 days during acute exacerbations. In addition to the real potential for rebound congestion, long-term use of topical adrenergic agents should be discouraged and avoided, particularly the α_2 -agents, because they increase the risk for the development of atrophic rhinitis caused by compromised nasal blood supply as previously noted.

These topical adrenergic agents may be useful for short-term treatment of patients with chronic sinusitis during (1) acute viral or bacterial infections, (2) before air travel to prevent symptom exacerbation or ear problems, (3) acute nasal congestion not responding to exercise, (4) reduced MCC,³² and (5) initiation of

treatment with intranasal antiinflammatory agents to enhance drug delivery.³³

Controlled clinical trials of α -agonists in sinusitis

Acute sinusitis. In the only published report of oral decongestants for this condition, a 1-week course of PPA (100 mg twice daily) was compared with placebo as adjuncts to antibiotic treatment (penicillin V, 800 mg twice daily), in 20 adults who had clinically acute rhinosinusitis with patent maxillary ostia but without radiologic confirmation of sinusitis.²³ No difference in symptoms or side effect scores over the 7 treatment days or acute change in NAR after 60 minutes on day 1 occurred between PPA or placebo groups, which indicates the lack of added benefit of oral decongestants in antibiotic-treated acute rhinosinusitis. In adults with acute sinusitis, PPA (100 mg twice daily for 10 days), when compared with three different antibiotics, showed significantly slower radiologic improvement (about 50% less) and poorer cure on evaluation at 5, 10, and 15 days' follow-up. A nontreatment placebo group did not exist to prevent the determination of whether PPA has the capacity to alter the natural history of acute sinusitis.³⁴

Chronic sinusitis. No published controlled studies exist on the use of long-term oral decongestants in the treatment of chronic sinusitis.

Suggested therapy. With the lack of any controlled study attesting to the efficacy of α -adrenergic agents in the treatment of chronic sinusitis, recommendations of treatment must be extremely cautious. Because these adrenergic agents reduce nasal mucosa edema and improve MCC, they may help in the expulsion of retained mucoid and infectious material from the sinuses. Prospective studies, however, are lacking and are needed to assess the value of adrenergic agents to determine their benefit/risk profile in the treatment of chronic sinusitis.

IMPROVING MCC

Nasal mucociliary function becomes impaired in most patients who have chronic URIs, including sinusitis and otitis. Intrinsic ciliary beat frequency and ultrastructure are not inherently impaired in chronic sinusitis, because impaired ciliary function caused by chronic sinusitis reverses to normal after removal and cleansing of the mucosa from infected mucus and other material.³⁵ Supportive of these findings, it appears that respiratory ciliated cells have a functional reserve that permits them to autoregulate their mechanical output in response to changing respiratory mucus viscosity.³⁶

Impaired MCC may occur chronically and persist-

tently in as many as 60% of children with chronic upper and/or lower respiratory tract infections.³⁷ The dynamic viscoelastic properties of nasal mucus from 37 children, aged 5 to 15 years, with chronic sinusitis of greater than 3 months' duration, determined by oscillatory rheometry, revealed a lower dynamic viscosity and elasticity before and a significant fivefold geometric increase after successful sinusitis resolution. Repeated antral lavage also significantly increased the dynamic elastic properties of mucous secretions in these children with sinusitis.³⁸ Ancillary treatments, which have attempted to improve impaired MCC of chronic sinusitis and which will be discussed below, have included local irrigation with saline solution, mucoactive agents, energy supplements, α -agonists, β -adrenergic agents, and antihistamines.

Nasal saline irrigation

Rationale for use. Reports claim that repeated daily warm saline solution irrigation favorably affects MCC.³⁹ Pulsed saline solution by nebulization improved MCC significantly in chronic sinusitis⁴⁰ and chronic bronchitis.⁴¹ Using the saccharine test to determine MCC, daily saline irrigation delivered with a special right-angled adapter attached to a water pic device containing a reservoir filled with isotonic saline solution (1 teaspoon of salt to 800 ml of warm water) at 20 pulses/sec (a rate similar to normal nasal flow rate) increased MCC at least twofold in 13 patients with chronic sinusitis, 11 of whom had complete disappearance of visible pus.⁴² Benefits from saline solution irrigation probably derive more from direct immediate removal of secretions, pus, or crusts rather than from liquefaction of nasal mucus, because expectorated sputum shows only a minor 30% increase in water content and a decrease in viscosity after 3 hours of exposure to a water aerosol.⁴³ Methods available for the administration of nasal saline include the following: (1) Commercial buffered saline sprays; application of 2 to 10 sprays of these agents 4 or more times daily may help remove tenacious mucus and crusts so common in patients with rhinosinusitis, and (2) bulb syringe; a 1-ounce plastic ear syringe is used to instill a saline solution ($\frac{1}{4}$ teaspoon of table salt to 7 ounces of warm tap water) intranasally with the head maintained parallel to the horizontal and held over a sink. The saline solution in the bulb syringe is alternatively expressed into the two nasal cavities, which forces the fluid in one and out the other nostril. This procedure may be performed once to several times daily depending on the magnitude of discharge and degree of benefit. (3) Water pic saline lavage; this technique has already been previously described.

Wetting agents

Rationale for use. Propylene and polyethylene glycol improve symptoms of nasal stuffiness, postnasal drip, and NAR to an extent similar to saline solution without side effects in a 4-week study of patients with chronic rhinitis.⁴⁴ Longer term studies should examine the effect of such wetting agents in the treatment of chronic sinusitis.

Energy supplementation

Rationale for use. Ciliary dyskinesia or the immotile cilia syndrome, which includes the Kartagener's syndrome subgroup (situs inversus, bronchiectasis, and chronic sinusitis), manifests as chronic sinusitis as well as otitis media and pneumonia.⁴⁵ ATP in concentrations of 10 mg/ml improves ciliary beat frequency and synchrony in patients with dynein arm deficiencies.⁴⁶ Prompted by the stimulatory effect of ATP on dyskinetic cilia, the effect of ATP on cilia from healthy and diseased sinus epithelial explants has been examined and revealed that (1) adenine nucleotides including ATP concentrations were similar in healthy and diseased epithelium and sinus secretions⁴⁷ and (2) ciliary beat frequency significantly increased about 5% and up to 20% at 1 and 20 mg/ml concentrations of ATP, respectively, in both healthy and diseased explants.⁴⁸ Subsequent in vivo studies revealed that topically administered single-dose ATP (10 mg/ml) significantly accelerated nasal MCC (about 50%) in healthy subjects⁴⁹ and in most patients with impaired nasal MCC caused by chronic or recurrent URIs and lower respiratory tract infections.⁵⁰

Controlled clinical trials of ATP in sinusitis. Two preliminary, placebo-controlled crossover studies on the efficacy of ATP insufflation for 2 weeks in children and adults who had chronic nonallergic rhinitis with recurrent URIs and/or lower respiratory tract infections revealed positive effects but inherent methodologic deficiencies existed.^{51, 52} Further larger scale, placebo-controlled, long-term studies are necessary to determine whether topical ATP at optimal concentration will function to improve the impaired MCC present in chronic sinusitis and thereby accelerate resolution and prevention of infections.

β -Adrenergic agents

Rationale for use. β -Adrenergic agents, such as terbutaline, increase lung clearance and tracheal mucous transport in healthy subjects,⁵³ in patients with chronic bronchitis, cystic fibrosis, and asthma,⁵⁴ and in animals during allergen challenge.⁵⁵ Ciliary beat frequency appears accelerated in the presence of β -

agonists.⁵⁶ On the other hand, because β_2 -adrenergic agents, such as fenoterol at 200 to 400 μg , increase NAR significantly (about 20%, and yet imperceptibly) because of stimulation of β_2 -receptors on nasal capacitance vessels,⁵⁷ this adverse effect will probably preclude the use of these agents for the treatment of sinusitis despite exerting beneficial actions on MCC.

Anticholinergics

Rationale for use. Because nasal glandular activity results from parasympathetic activity and because hyperreactivity to methacholine characterizes chronic rhinitis, efforts to modulate cholinergic activity has led to the recent development of ipratropium bromide, a topically potent⁵⁸ and safe anticholinergic agent that is the quaternary derivative of isopropyl noratropine. Randomized, double-blind, placebo-controlled studies have demonstrated that the intranasal administration of ipratropium (80 μg four times daily to 400 μg before cold-air challenge) demonstrates both efficacy and safety in the treatment of (1) vasomotor rhinitis, (2) perennial nonallergic rhinitis, (3) the common cold, (4) cold air-induced or hot soup-induced rhinorrhea, (5) gustatory rhinitis, and (6) methacholine sensitivity.⁵⁹ As reviewed recently,⁵⁹ at least nine placebo-controlled studies document the capacity of ipratropium to reduce watery rhinorrhea (from 11% to 42%) in patients who have perennial rhinitis that is unresponsive to other modalities. The usefulness of ipratropium nasal spray appears limited to reducing watery rhinorrhea but not viscid purulent secretions, because it appears to only modulate nasal glandular fluid without affecting tears, sinus secretions, goblet cell secretions, or exudate. Ipratropium has no effect on itching, sneezing, or nasal obstruction.

The ability of ipratropium to reduce methacholine hyperreactivity in chronic rhinitis and also to reduce nasal physiologic secretory activity may be useful for subjects with chronic rhinosinusitis. In contrast to the significant (>30%) and prolonged (>90 minutes) inhibition of MCC exerted by a single inhalation of atropine (0.025 mg/kg),⁶⁰ aerosolized ipratropium failed to affect MCC in healthy⁶¹ and bronchitic subjects⁶² at therapeutic dosages and even augmented MCC at higher doses.⁶³ Consistent with these findings in the lung, ipratropium exerts an inconsistent effect on MCC in adult asthmatic patients.⁶⁴ Intranasal instillation of ipratropium at either therapeutic (320 μg daily) or high (1600 μg daily) doses failed to reduce MCC significantly as assessed by the saccharine test.⁶⁵ These observations suggest that ipratropium is probably safe for patients with chronic sinusitis, although efficacy studies are needed. On the other hand, the

intranasal administration of atropine should probably be avoided because of its unknown but possibly inhibitory effect on nasal MCC. The widely held clinical conviction that antihistamines may adversely affect acute and/or chronic sinusitis gains support from the potential for nasal MCC inhibition by the anticholinergic properties of nonspecific antihistamines.

Antihistamines

Rationale for use. No reasonable rationale exists for the use of antihistamines in the treatment of infectious sinusitis, because histamine does not appear to be implicated in this disorder. Moreover, the anticholinergic properties of the nonspecific antihistamines that reduce nasal secretion may theoretically, although not documented, cause inspissation of chronic sinus contents. In patients who have concomitant allergic rhinitis that requires treatment with an antihistaminic agent, a selective H_1 -antihistamine that does not have "drying" anticholinergic properties, such as the newer nonsedative class, may be a safer option for use. In contrast, because the common viral cold does not appear mediated by histamine⁶⁶ but possibly by bradykinin,⁶⁷ selective nonsedative, nonanticholinergic antihistamines are not indicated.⁶⁸

Controlled clinical trials of antihistamines in sinusitis. No controlled clinical trials of antihistamines in sinusitis exist. A study examining the safety of these agents in acute and chronic sinusitis appears warranted. The potential of the nonsedative antihistamines to affect inflammatory cell accumulation and function based on properties other than histamine antagonism needs exploration as noted below.

Expectorants, mucolytics, mucokinetics, and mucoregulatory agents (Table III)

Rationale for use. In addition to the reduced MCC and ostia patency that characterize chronic and recurrent sinusitis, recent evidence points to the presence of abnormal nasal glandular secretions in patients with recurrent sinusitis (discussed elsewhere in this symposium). The regulation, modulation, and expectoration of mucus by mucoactive agents (Table III) has been studied predominately in sputum and lower respiratory tract disorders, such as chronic bronchitis, chronic obstructive lung disease, asthma, and cystic fibrosis, but only infrequently in nasal and sinus mucus or sinusitis. A brief discussion of the more frequently used agents for lower respiratory tract disease will be undertaken to highlight areas that may have potential for the treatment of chronic sinusitis.

IG. As a potent mucolytic with ciliary excitant actions,⁶⁹ IG had received wide clinical use in the treatment of chronic bronchitis and other respiratory dis-

TABLE III. Mucoactive agents: Classification, definition, and representation

Classification	Mechanism of action/examples of agents
Expectorants	Increase reflexively submucosal gland mucus output (guaiaicol, IG, acetylcysteine)
Mucokinetics	Improve mobilization/clearance of mucous secretions (acetylcysteine, SSKI, 5%-10% NaCl, capsaicin)
Mucolytics	Fragment mucus glycoproteins, DNA, macromolecules (acetylcysteine, DNAase, trypsin, hyaluronidase)
Mucoregulators	Promote synthesis of normal components of mucus (acetylcysteine, carbocysteine, ambroxol)
Mucorrheics	Increase transepithelial respiratory H ₂ O secretion (acetylcysteine, hypertonic saline)
Detergents	Reduce adhesiveness of mucus to mucosal surfaces (tyloxapol, ethasulfate)
Ciliary stimulants	Increase rate and/or efficacy of ciliary beating (ATP, saline, acacia)

Modified from Ziment I, et al. *J Respir Dis* 1991;12:21.

TABLE IV. IG compared with placebo in chronic obstructive bronchitics on corticosteroids: A randomized 8-week study

Symptom	% change in symptom score from baseline		
	IG (n = 54)	Placebo (n = 43)	p value
Cough frequency	- 18%	- 5%	0.004
Cough severity	- 16%	- 2%	0.021
Chest discomfort	- 11%	+ 4%	0.020
Dyspnea	- 10%	+ 4%	0.107
Global assessment	- 14%	0%	0.006

Modified from Petty TL. *Chest* 1990;97:75.

orders for the past half century despite little objective and controlled data of its efficacy until the present time. Motivated by a double-blind, placebo-controlled crossover study of 15 patients with stable, chronic bronchitis in whom IG treatment for 1 week improved cough frequency and led to a significant correlation ($r = 0.82$) between quantity of expectorated sputum and improvement in tracheobronchial clearance,⁷⁰ a National Mucolytic Study was created to determine the efficacy and safety of IG in chronic obstructive bronchitis in adults.⁷¹ This randomized, double-blind, placebo-controlled, parallel design study demonstrated that 60 mg of IG four times daily ($n = 180$) compared with placebo ($n = 181$) for eight weeks led to significant (1) improvements in cough frequency and severity, chest discomfort, ease of expectoration, and overall global assessment of well-being and (2) reductions in mean duration in days of acute exacerbations. These significant improvements with IG

were observed particularly in patients who had moderate to severe disease or those requiring long-term administration of corticosteroids (Table IV). Although the cause of chronic obstructive bronchitis and chronic sinusitis may be quite different, the two disorders share similar clinical (cough, difficulty at mucous removal, recurrent bacterial infections), and pathophysiology (hypersecreted and tenacious mucus, increased submucosal glands, epithelial alterations, etc.) manifestations. These disease similarities might indicate a similar therapeutic role of IG in chronic sinusitis and should prompt study of IG in this condition.

CYSTEINE DERIVATIVES: ACEYLCYSTEINE AND SCMC. NAC, a derivative of L-cysteine extracted from animal integument, represents the most actively investigated mucokinetic agent in the world for the past 30 years. Through interaction of its free sulfhydryl group with disulfide bonds, NAC functions to disrupt the mucoprotein of mucus into smaller units, which renders it less able to interact with DNA and thereby reduces its viscosity and increases its potential for evacuation.⁷² In addition, potential clinical applications for NAC as a mucokinetic agent include its role as an (1) expectorant (stimulates gastropulmonary vagal reflex); (2) bronchorrheic (stimulates mucosal secretions); (3) mucoregulator (normalizes mucoprotein secretion over time); (4) chelator (disrupts ionic binding of calcium in mucoprotein); and (5) antioxidant (as a precursor to glutathione, acts as a major free oxygen radical scavenger to prevent airway damage) (Table III).⁷³ Nebulization of NAC either as a 10% or 20% solution significantly reduced sputum consistency between 70% and 80% compared with only 30% with saline solution in patients with chronic obstructive lung disease. A few patients developed

mild obstruction on spirometry.⁷⁴ Anecdotal studies have suggested some benefit of aerosolized NAC in asthma; however, occurrences of acute bronchospasm from its irritant effect have limited its usefulness.

The oral formulation of NAC, which is unavailable in the United States, appears effective in chronic bronchitis and circumvents the disadvantages associated with its aerosolization, as noted in recent studies in Europe.⁷⁵⁻⁷⁸ NAC, at doses of 400 to 600 mg daily, appears to reduce from 0.5 to 1.0 acute exacerbation per winter in patients with chronic bronchitis (Table V). Another cysteine derivative, SCMC, a purported mucoregulator, may function as an antikinase, secretagogue, synthesizer of sialomucins, and a free radical scavenger.⁷⁹ In a double-blind, randomized, 3-month study of three groups of 73 patients with chronic bronchitis, SCMC (3 or 2.25 gm daily), compared with placebo, achieved significant improvements in (1) ease of expectoration, (2) cough frequency, (3) dyspnea, (4) sputum volume and viscosity, (5) forced expiratory volume in 1 second (FEV₁), and (6) overall moderate to marked improvement in symptoms (71% on SCMC vs 40% on placebo) without incurring an increase in adverse side effects.⁸⁰

GG (GUAIFENESIN). GG, a derivative from wood creosote, has received wide clinical use since its introduction in 1912 despite the lack of definitive efficacy data. Although an early reputed double-blind, placebo-controlled, crossover study noted that GG, 2.4 gm daily for 1 week, reduced sputum adhesiveness but not viscosity or volume in chronic bronchitis,⁸¹ other better controlled studies failed to observe any benefit from GG on sputum viscosity, sputum volume, or spirometry in a 20-day treatment period of 10 patients with chronic bronchitis⁸² or for cough frequency during the common cold in 65 healthy subjects.⁸³ As such, it cannot be expected that GG holds much potential in the treatment of chronic sinusitis.

MISCELLANEOUS MUCOREGULATORS. Other so-called mucoregulators that have experienced mixed clinical successes in chronic bronchitis include bromhexine (an extract from the malabar nut tree), ambroxol (a derivative of bromhexine),⁸⁴ 2-mercaptoethane sulfonic acid,⁸⁵ and others, as reviewed recently.⁷⁹

Studies of mucokinetics and mucoregulators in chronic sinusitis. Few studies have examined the effect of these agents on nasal and sinus mucus from subjects with sinusitis. One investigation examined in an open study the in vivo effects of a course of an oral antibiotic for 2 weeks (NFLX, 600 mg daily) and three oral mucokinetic agents for 4 weeks (SER), 30

mg daily; SCMC, 1500 mg daily; and CEE, 300 mg daily) on the viscoelasticity of nasal mucus in 51 adults, ages 17 to 81 years, with clinical, rhinoscopic, and radiologic evidence of chronic sinusitis of unspecified duration.⁸⁶ As noted in Table VI, nasal mucus viscoelasticity (determined by oscillatory rheometry), which was suboptimal at baseline, revealed significant improvements in viscosity measurements after NFLX and CEE and elasticity measurements after treatment with SER and CEE. The effect of NFLX on improving elasticity but not viscosity suggests that its antibacterial properties may effectively function to lower the DNA content of the mucus by reducing bacterial colonization and infection and secondary reactive inflammatory cell infiltration. The proteolytic enzyme SER-induced improvement in viscosity but not elasticity supports cleavage of the mucus glycoprotein molecules, which is similar to that observed in vitro.⁸⁷ CEE, a sulfhydryl mucolytic similar to and with similar biotransformation as NAC, may have improved both viscosity and elasticity through alteration of glycoprotein conformation or cleavage of covalent bonds of the nasal mucus. Whether such viscoelasticity improvements by oral therapy with CEE and SER materialize into therapeutic benefit in chronic sinusitis urgently warrants investigation.

NAC has yet to be investigated adequately in chronic sinusitis; only one poorly conceived and inadequately sampled study of its clinical use could be found (abstract only).⁸⁸ With respect to SCMC use in chronic sinusitis, changes in MCC were determined after SCMC (1.5 gm daily for 4 weeks; $n = 14$) or repeat antral lavage (average 15.5 lavages over 5.4 months; $n = 22$) in patients, ages 13 to 68 years, with chronic sinusitis of more than 3 months' duration. Both SCMC and antral lavage significantly improved MCC in those patients with abnormal baseline MCCs. Clinical assessments were omitted.⁸⁹ In an uncontrolled study of the treatment of chronic maxillary sinusitis in 44 patients unresponsive to 7-day treatments of antibiotics and other conventional therapy, the nasal inhalation of bromhexine, a substituted benzylamine, for 5 minutes for 5 to 7 days, led to significant radiologic improvement.⁹⁰

Controlled clinical trials of mucoregulators/mucokinetics in sinusitis. No controlled clinical trials of mucoregulators or mucokinetics in sinusitis exist. Given the apparent efficacy and relative safety of oral NAC and iodinated glycerol in chronic bronchitis, investigations of their use in the treatment of chronic sinusitis should be encouraged. These studies should be designed with long-term follow-up including objective measures of efficacy with sinuscopy.

TABLE V. Oral NAC compared with placebo in chronic bronchitis: Randomized, long-term, double-blind, placebo-controlled studies

Multicenter (reference)	NAC (n)	Placebo (n)	NAC dose	Duration (mo)	Reductions or improvement: NAC vs placebo			
					Sputum quantity	Sputum thickness	Sputum purulence	Cough severity
Italian (140)	254	241	200 mg bid	6	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$
Swedish (141)	98	105	200 mg bid	6	ND	ND	ND	ND
British (142)	85	96	200 mg tid	5	ND	ND	ND	ND

NS, Not significant; ND, not determined; *bid*, twice daily; *tid*, Three times daily.

TABLE VI. Comparison of oral NFLX, SER, SCMC, and CEE on nasal mucus viscoelasticity in chronic sinusitis: An open, nonrandomized, 2- to 4-week study

Viscoelasticity	NFLX (n = 15)	SER (n = 16)	SCMC (n = 24)	CEE (n = 20)
Elasticity (G')				
(Pa)				
Pretreatment	359.0 ± 149.8	94.2 ± 27.2	256.0 ± 101.4	299.3 ± 136.5
Posttreatment	100.1 ± 29.2*	85.5 ± 27.2	191.1 ± 68.1	102.7 ± 24.9†
Viscosity (n')				
(Pa/s)				
Pretreatment	5.3 ± 1.8	1.7 ± 0.4	6.3 ± 3.8	2.3 ± 0.7
Posttreatment	0.9 ± 0.2	0.9 ± 0.3*	1.6 ± 0.5	1.1 ± 0.3*

Modified from Majima Y et al. *Am Rev Respir Dis* 1990;141:79.

* $p < 0.05$.

† $p < 0.01$.

ERADICATE/SUPPRESS SINUS INFLAMMATION

Involvement of the sinuses in allergic rhinitis gains support from the demonstration by single-photon emission computerized tomography of increased sinus mucosa activity seasonally during active hay fever that becomes inactive postseasonally.⁹¹ A detailed discussion of the interaction of allergic disease and sinusitis will be approached elsewhere in these proceedings. The presence of eosinophil influx in disorders other than those IgE mediated is well documented now, and their clinical, immunologic, and radiologic characteristics have been reviewed elsewhere.¹ Patients who have these eosinophilic nonallergic disorders characteristically (1) deny a clinical history suggestive of allergy; (2) have normal IgE levels and negative or noncorrelating immediate skin tests; (3) have nasal congestion and rhinorrhea, minimal pruritis, and frequent anosmia; and (4) have frequent sinus radiographic abnormalities.

The pathophysiologic mechanisms of allergic rhinitis have been studied extensively and will be discussed elsewhere. A histopathologic evaluation of paranasal tissue from subjects with asthma or allergic rhinitis and concomitant sinus involvement revealed (1) extensive infiltration with eosinophils, (2) striking association between the presence of extracellular deposition of MBP and sinus mucosa damage, (3) diseased respiratory epithelium similar to that occurring in asthma, and (4) evidence that the eosinophil functions as a proinflammatory cell in the chronic sinus inflammation.⁹² In addition, eosinophil products, ECP and MBP, appear to modulate in a counterregulatory manner respiratory mucus release from human and feline airway explants. ECP caused a dose-dependent increase in respiratory glycoconjugate and lactoferrin release, whereas MCP significantly inhibited respiratory glycoconjugate release from respiratory explants.⁹³ Efforts to reduce the underlying inflammation of sinus disease would be expected to benefit this

Reductions or improvements: NAC vs placebo		
Exacerbations rate (No./winter)	Spirometry	Side effects
$p < 0.001$ 0.8 vs 2.0	NS	NS
$p < 0.01$ 1.2 vs 1.7	NS	NS
$p = 0.08$ 2.1 vs 2.6	NS	NS

condition and reduce secondary infectious sinusitis; however, controlled studies are lacking.

Cromolyn

Rationale for use. Cromolyn, a chromone derivative of the plant material khellin, blocks both the immediate and late nasal response to allergen challenge. Although the mechanism(s) responsible for these effects remains imperfect, several antiinflammatory properties of cromolyn that have been demonstrated for allergic rhinitis may provide some benefit for the noninfectious inflammation that occurs in noninfectious sinusitis, including (1) stabilization of nasal/sinus mast cells, (2) suppression of human inflammatory cell (eosinophils, neutrophils, and monocytes) activation by varying triggers, and (3) inhibition of mediator activity. Despite its effectiveness in both seasonal and perennial allergic rhinitis, intranasal cromolyn treatment failed to benefit in any manner the symptoms in the syndrome termed *nonallergic rhinitis with eosinophilia* (NARES).⁹⁴

Controlled clinical trials of cromolyn in sinusitis

POSTCATARRHAL RHINOSINUSITIS. A randomized, double-blind, controlled, 3-week study comparing the efficacy of cromolyn (2.6 mg, four times daily) versus saline placebo in the treatment of 91 subjects (ages 13 to 82 years) more than 10 days after acute URI with documented maxillary thickening on ultrasound examination (mean thickening 9 mm) noted no significant differences in clinical symptoms or sonographic findings between the treatment groups. These findings discredit the use of cromolyn after URIs in an attempt to prevent the development of postviral nasal hyperreactivity.⁹⁵

Corticosteroids

Rationale for use. For the treatment of noninfectious rhinosinusitis, glucocorticoids are the most potent antiinflammatory agents. Antiinflammatory ac-

tions of glucocorticoids in nasal disorders have received recent review.⁹⁶ By inhibition, suppression, and modulation of inflammatory cells (basophils, mast cells, eosinophils, etc.) and mediators of inflammation, corticosteroids could potentially prevent damage to and/or preserve the integrity of the chronically activated mucociliary transport system in chronic sinusitis.

TOPICAL CORTICOSTEROIDS. Potent, topically active, nasal corticosteroids (Table VII) with a low potential for systemic side effects⁹⁷ have been shown by double-blind, placebo-controlled studies to be effective in the treatment of seasonal and perennial allergic rhinitis, perennial nonallergic eosinophilic rhinitis, and nasal polyps before and as prophylaxis for recurrence after evulsion.⁹⁷

Rationale for use. High antiinflammatory potency combined with safety position these topical corticosteroids as potentially effective agents in reducing the inflammatory component of chronic sinusitis. In addition to having a wide degree of safety as reviewed recently, these topical nasal corticosteroids do not appear to adversely affect human ciliary function⁹⁸ or MCC.⁹⁹ Whether the local nasal action of these potent topical corticosteroids is sufficient to affect sinus inflammation remains speculative.

Controlled clinical trials of corticosteroids in sinusitis. The potent topical antiinflammatory and antieosinophilic and basophilic effects of the topical corticosteroids have been used widely in chronic sinusitis despite the paucity of studies to justify such action.

A nonplacebo controlled study examined the efficacy of a topical corticosteroid (tixocortol pivalate) as an adjunct to neomycin sinus irrigation in the treatment of allergic and bacterial sinusitis.¹⁰⁰ In this double-blind study 60 patients (ages 15 to 51 years) were randomly assigned to 11 daily irrigations through a sinus drain into one maxillary sinus of either neomycin (17,000 IU) alone or in combination with tixocortol pivalate (50 mg). Significant improvements in both treatment groups were noted for reduced rhinorrhea, pain, and pus. The tixocortol-neomycin group had a significantly higher incidence of subjects with ostia patency at 5, 7, 9, and 11 days after treatment. Statistical analyses suggested that a higher incidence of ostia patency improvement occurred in subjects whose sinusitis had a bacterial cause compared with those who had an allergic cause of the sinusitis. Data were omitted comparing the clinical response of the two groups. The omission of a placebo control group prevented real determination of the benefit derived from the sinus irrigation versus the treatments themselves.

TABLE VII. The potential of selected potent, topical intranasal corticosteroids for efficacy in chronic rhinosinusitis

Generic (brand) name	Topical potency relative to hydrocortisone = 1*	Systemic potency†	Delivery	µg/ spray	Adult dosage‡ (initial)
Beclomethasone dipropionate (Beconase/Aq, Vancenase/Aq)	5,000	3.5	Freon powder	42	2 sprays bid
Flunisolide (Nasalide)	3,000	12.8	Aqueous soln	25	2 sprays bid
Triamcinolone acetoneide (Nasacort)	1,000	5.3	Freon powder	55	1-4 sprays qd
Budesonide§ (Rhinocort)	10,000	1.0	Freon powder	50	2 sprays bid
Fluticasone propionate## (Flunase)	20,000	N/A	Aqueous soln	50	1 spray bid

Soln, Solution; N/A, not available; bid, twice daily; qd, every day.

*Vasoconstrictor effect in man. Harris DM. Postgrad Med J 1975;51 (suppl 4):20.

†Thymus involution in rat/mice after ear application. Tse CT, Bernstein IL. Pharmacol 1984;4:334.

‡Larger doses than generally recommended for allergic rhinitis may be necessary to control and prevent symptoms in chronic nonallergic rhinosinusitis.

§Not yet FDA approved in the United States.

TABLE VIII. Topical DT compared with DT/N and placebo in mucopurulent rhinosinusitis: A 2-week randomized study

Variable	DT (n = 20)	DT/N (n = 20)	Placebo (n = 10)
Drainage (%)			
Pretreatment	100	100	100
Posttreatment	40‡	30‡	80
Blockage (%)			
Pretreatment	55	50	70
Posttreatment	25	10*	60
Abnormal sinus x-ray films (%)			
Pretreatment	55	40	60
Posttreatment	35	20	60
MCC > 30 min (%)			
Pretreatment	60	55	50
Posttreatment	25	20	50
Abnormal NAR (%)			
Pretreatment	40	40	40
Posttreatment	5*	10	30

Data compiled from Sykes DA, et al. Lancet 1986;2:159.

* $p < 0.05$.

† $p < 0.01$.

‡ $p < 0.001$.

A randomized, double-blind, placebo-controlled study compared the relative efficacy of the intranasal administration of the low-potency topical corticosteroid (Dexamethasone [D], 20 µg/spray) and the topical α-agonist (Tramazoline [T], 120 µg/spray) nasal spray with (DT/neomycin [N], $n = 20$) or without (DT, $n = 20$) an added topical antibiotic (N, 100

µg/spray) to each other and to an identical-appearing placebo control ($n = 10$) in 50 adult patients (ages 20 to 74 years) with chronic mucopurulent rhinosinusitis of unspecified duration (Table VIII).¹⁰¹ The treatments were administered in metered dose inhalers at 1 spray four times daily for 2 weeks. Baseline characteristics, MCC, NAR, and radiographs were similar among the groups. Significant improvements in drainage, blockage, MCC, and NAR occurred within the DT and DT/N groups but not the placebo group. In addition, a higher prevalence of patients in the placebo group compared with DT/N group had persistent drainage and blockage at 2-week follow-up. No significant difference in response occurred between the DT and DT/N groups at follow-up. Weaknesses in this study included the failure to (1) control for the duration of rhinosinusitis; (2) exclude subjects with normal sinus radiographs (~50%); (3) analyze quantitative comparisons of symptom scores, NAR, and MCC among groups; (4) demonstrate improvement in sinus radiographic abnormalities; and (5) enroll an adequate sample size.

More recently, flunisolide nasal spray (100 µg, three times daily for 7 weeks) was compared with placebo in a 7-week trial as an adjunct to amoxicillin/clavulanic acid (Augmentin) (500 mg, three times daily for 3 weeks) in the treatment of sinusitis in 116 patients over 14 years of age (Table IX).¹⁰² By 3 weeks, sinus radiographs and symptoms improved significantly in both groups, but global assessment of improvement and reduction in turbinate swelling significantly favored the flunisolide group. At the end of phase II, clinical global assessments were marginally better in the flunisolide group, but sinusitis flares oc-

TABLE IX. Topical flunisolide nasal spray versus placebo as adjuncts to Augmentin therapy for maxillary sinusitis

Factor	FN/Augmentin (n = 56)	PI/Augmentin (n = 60)	FN vs PI
Phase I (3 wk) (Augmentin/sprays)			
X-ray improvement	Yes	Yes	NS
Global assessment	Improved	Improved	p = 0.007
Phase II (4 wk) (sprays only)			
Global assessment	Improved	Improved	p = 0.08
Sinusitis flare	26%	35%	NS

Data compiled from Meltzer EO, et al. J ALLERGY CLIN IMMUNOL 1992;89:301.

FN, Flunisolide; PI, placebo.

curred similarly in both groups. These data suggest that topical potent corticosteroids may be a useful ancillary treatment to antibiotics in sinusitis.

Additional prospective-controlled studies are needed to examine the efficacy and safety of these topical potent corticosteroids in acute and chronic infectious sinusitis and also in the long-term management of the eosinophilic rhinosinusitis syndromes with associated sinusitis.

Systemic corticosteroids

Rationale for use. Inflammatory disorders of the sinuses that are or become unresponsive to topical corticosteroids because of their inability to penetrate sinus tissue, to reduce large obstructing polyps, to open occluded ostia, to clear inspissated material, or to affect underlying infection are treated empirically with systemic corticosteroids (typically oral) for generally short intervals, although controlled studies are lacking to justify such practices. In allergic rhinitis a single depo-injection of methylprednisolone was effective for at least 4 weeks compared with placebo in reducing nasal obstruction but not sneezing or nose blowing.¹⁰³ A recent, randomized, 1-year study of baseline comparable adults with nasal polyps compared the efficacy of a single 2 ml dose of Diprosan (n = 26) (betamethasone dipropionate and betamethasone disodium phosphate) to surgical polypectomy (n = 27). Both groups received 100 µg of beclomethasone dipropionate twice daily during the 1-year study (Table X). By 2 weeks into the study a greater improvement in smell and NAR occurred in the corticosteroid-injected than polypectomized group; at 1 year both treatment groups were similarly better than at baseline with respect to smell and NAR.¹⁰⁴ These results imply that corticosteroids, if not contraindicated, should be the first treatment for nasal polyps rather than surgery. Whether topical corticosteroids alone would be adequate alone without an initial burst of systemic steroids requires study.

TABLE X. Depobetamethasone plus topical beclomethasone compared with polypectomy plus topical beclomethasone for nasal polyps: A 1-year follow-up of a prospective, randomized study

Variable	DB/BPD (n = 26)	PP/BPD (n = 27)	p
Age (<60 yr) (%)	62	70	NS
Sex (% male)	85	67	NS
History of atopy (%)	50	41	NS
Recurrent polyps (%)	73	56	NS
Bilateral polyps (%)	69	59	NS
Intact smell (%)			
Pretreatment	58	58	NS
2 wk posttreatment	92	67	<0.05
12 mo posttreatment	77	73	NS
Nasal peak flow (L/min)			
Pretreatment	132 ± 91	145 ± 95	NS
2 wk posttreatment	273 ± 86	209 ± 118	<0.02
12 mo posttreatment	282 ± 91	255 ± 95	NS

Data compiled from Lildholdt T, et al. Acta Otolaryngol 1988; 105:140.

DB/BPD, Depobetamethasone plus topical beclomethasone; PP/BPD, polypectomy plus topical beclomethasone.

Intraturbinate steroid injections are frequently recommended by otolaryngologists for the treatment of chronic rhinosinusitis. Until studies demonstrate that such intraturbinate injections are clinically superior and safer than topical or short-term oral or intramuscular corticosteroids, they should be avoided or used with extreme caution and patient consent because of the rare yet tragic results of blindness induced by such injections as reviewed recently.¹⁰⁵

Controlled clinical trials of systemic corticosteroids in sinusitis. No controlled clinical trial of systemic corticosteroids in sinusitis exists, but such studies are in dire need. Efforts should be made to conduct studies in chronic sinusitis modeled after those examining the

resolution of chronic serous otitis with effusion with a stepped treatment regimen of antibiotic and oral corticosteroid.¹⁰⁶ Other controlled investigations that are needed include the efficacy of corticosteroids (topical or oral) in the prevention of respiration flares requiring antibiotics or improving radiographic abnormalities in chronic sinusitis.

NSAIDs

Rationale for use. ASA and NSAID trigger asthma/rhinosinusitis symptoms in susceptible individuals by mechanisms not fully elucidated. The proposed mechanisms for these adverse effects of ASA and the other NSAID have been reviewed recently¹⁰⁷ are beyond the scope of this discussion.

Aspirin and other NSAID exert mild but imperceptible¹⁰⁸ to no¹⁰⁹ increases in baseline NAR in humans. Placebo-controlled, double-blind studies have demonstrated moderate and significant effect of aspirin or other NSAIDs in (1) the inhibition of nasal pollen challenges in allergic subjects¹⁰⁹; (2) control of clinical symptoms accompanying allergic rhinitis but to a lesser degree than an antihistamine¹¹⁰; and (3) improvement in nasal symptoms and use of concomitant intranasal beclomethasone in subjects with aspirin-sensitive rhinosinusitis asthma (ASA-RSA).¹¹¹ Aspirin desensitization in 19 adults with eosinophilic aspirin-sensitive rhinitis, 79% of whom had nasal polyps, led to clinical improvement in 77%.¹¹² A retrospective chart review study noted that long-term continuous aspirin desensitization for 12 to 99 months ($n = 35$), compared with aspirin avoidance for 22 to 218 months ($n = 42$) in ASA-RSA patients, was associated with significantly fewer courses of antibiotics for sinusitis, fewer polypectomies, or supplemental sinus surgeries and less anosmia.¹¹³ The retrospective design and varied period of follow-up in the groups severely weaken the study's conclusions. Aspirin desensitization in ASA-RSA patients prevents the release of leukotriene C₄ and histamine into nasal lavage fluid, which is observed in nondesensitized ASA-RSA after oral ASA challenge.¹¹⁴ The frequent discontinuation of ASA in ASA-desensitized patients (46%, with almost 20% of these caused by adverse gastric reactions) combined with the persistent danger of invoking severe asthma and anaphylaxis during oral ASA desensitization relegates this form of therapy to research institutions equipped to deal with major complications, even if oral ASA desensitization was proved definitively beneficial for the treatment of chronic rhinosinusitis. Aspirin's reported capacity at therapeutic dosage (~1120 mg for a 70 kg adult) compared with placebo to significantly retard clearance of tracheobronchial secretions in 112 healthy subjects¹¹⁵ would temper enthusiasm for its use in

chronic sinusitis, should it be shown similarly to reduce nasal MCC.

Controlled clinical trials of ASA desensitization in sinusitis. There are none specifically studying sinusitis (see above for findings in asthma study). Desensitization to ASA in ASA-RSA by the inhalation route¹¹⁶ appears to be associated with considerably less severe complications than with oral ASA desensitization. Because evidence supports the efficacy of ASA desensitization in ASA-RSA syndrome, safer methods of ASA desensitization should be identified, including the possibility of nasal desensitization, to provide a possibly effective therapy to the 3% to 4% of adult asthmatic patients with ASA sensitivity.¹¹⁷

Future prospects

In addition to the inflammatory response triggered by infection in chronic infectious sinusitis, recent evidence implicates the eosinophil and its protein products as well as other cellular elements in causing the inflammation and hypersecretion that characterize many of the nonallergic inflammatory diseases of the sinuses. Activated eosinophils stimulate production of eicosanoids¹¹⁸ and platelet-activating factor¹¹⁹ that enhance glycoconjugate secretion and exert cytotoxic damage to sinus mucosa, which potentially allow increased penetration of pathogens. In addition, eosinophil products, mast cell mediators, and other inflammatory cell substances may stimulate release of neuropeptides, including the tachykinins,¹²⁰ from submucosal glands through sensory neurons and axon reflex activation. It is hoped that the future will unveil effective treatments to reduce eosinophil number and function, to regulate mucus hypersecretion by mucin gene expression regulation, and to antagonize the effects of proteases, eicosanoids, platelet-activating factor, tachykinins, and other mediators of inflammation.

SUMMARY

The relatively high prevalence and chronicity of chronic infectious and inflammatory sinusitis combined with the paucity of therapies with documented efficacy (antibiotics and surgical lavage) has led to a plethora of highly recommended but poorly documented ancillary treatments (Table II). With increasing interest and experimentation into the etiologic (infectious vs noninfectious causes), the inflammatory (mediators, neuropeptides, eosinophils and other cellular elements), secretory (mucous regulation) and glandular (induction and differentiation) components of chronic sinusitis, a better understanding of and improved therapies for chronic sinusitis should evolve in the not too distant future by directing energies to those areas recommended in Table I.

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DISCUSSION

Dr. Druce. We were interested in nasal blood flow. We found that just the repetitive installation of saline solution into the nose reduced nasal blood flow.

Dr. Rachelefsky. Is there a role for oral decongestants or mucoevacuants in the treatment of sinusitis? Do most people give oral decongestants for a patient with sinusitis? Who does? (16). Who doesn't? (4).