

Human nasal host defense and sinusitis

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Sinusitis is an exceptionally common disorder that affects an estimated 35 million Americans per year. The development of sinusitis requires both the presence of a virulent pathogen and the failure of the local immune system to prevent or effectively combat the infection. Identification of the components of the immune defense system of the upper respiratory tract and the possible areas of dysfunction that predispose to sinusitis may be important steps in the eventual prevention of this common disease. The nasal and sinus passages are lined by respiratory mucous membranes. Recent studies have identified some of the constituents found in mucus and their roles in human health and disease. However, the local immune system of the respiratory mucosa is largely unknown, and its role in sinusitis is conjectural. Nasal secretions include many proteins that serve important functions in local mucosal host defense. Most of these host-defense molecules are synthesized and secreted by serous cells in the submucous glands, and it appears that the serous cell is the resident antimicrobial cell in mucous membranes. Currently data suggest that serous cell secretion is abnormal in patients with recurrent sinusitis and that effective treatment leads to correction of the secretory abnormality along with improvement in sinusitis. (J ALLERGY CLIN IMMUNOL 1992;90:424-30.)

Key words: Host defense, secretory IgA, mucous membranes, sinusitis

Mucous membranes are named for their capacity to generate mucus. Respiratory mucous membranes begin at the nasal vestibule and continue through the nose, pharynx, larynx, trachea, bronchi, and bronchioles. Nasal airway secretions and their constituent proteins derive from epithelial cells (including goblet cells), submucosal glands (including both serous and mucous cells), blood vessels, and secretory cells resident in the mucosa (including plasma cells, mast cells, lymphocytes, and fibroblasts). Respiratory secretions consist of a mixture of mucous glycoproteins,¹ glandular products, and plasma proteins (Table I). Baseline, resting secretions include the following major proteins: albumin (representing about 15% of total protein), IgG (2% to 4%), s-IgA (15%), lactoferrin (2% to 4%), lysozyme (15% to 30%), nonsecretory IgA (about 1%), IgM (<1%), secretory leukoprotease inhibitor (10%), and mucous glycoproteins (about 10% to 15%).²

Careful immunohistochemical analysis has shown that plasma proteins such as albumin and IgG are

Abbreviations used

s-IgA:	Secretory IgA
NEP:	Neutral endopeptidase
MGP:	Mucous glycoproteins
PCF:	Periciliary fluid
ELF:	Epithelial lining fluid
SP:	Substance P
GRP:	Gastrin-related peptide
VIP:	Vasoactive intestinal peptide

found throughout the lamina propria of the mucosa, with an apparent increase in concentration at the basement membrane.³ Some albumin can also be found staining submucosal gland lumens and tracking between epithelial cells, is presumably being exported toward the airway lumen. In contrast, staining for lysozyme, lactoferrin, and s-IgA is seen exclusively in the serous cells, serous crescents, and ducts of the submucosal cells.^{4,5} More recently, several enzymes important in metabolizing neuropeptides have also been localized to the serous cells.⁶ NEP, which metabolizes SP and endothelin as well as other neuropeptides, is also found in glands as well as in the nasal epithelium and the endothelium of small blood vessels. Not only is NEP localized to serous cells, but NEP is also secreted in response to a variety of stimuli.

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1/0/38486

CONSTITUENTS OF HUMAN NASAL SECRETIONS AND THEIR FUNCTIONS
ELF

The secretory blanket consists of two separable layers; the surface mucous (or gel) layer and a deeper aqueous (or serous, periciliary) layer in which the base of the cilia is located. The concept of a two-layered ELF is quite old and dates back more than 50 years. In the nose, particles trapped in the surface mucous layer are transported by mucociliary action to the posterior pharynx at the rate of 1 cm/min. The surface mucous blanket is then swallowed and is constantly replaced about every 10 to 20 minutes under resting conditions. Analysis of lavage proteins indicates that only about 15% of the total protein is attributable to MGP, although this figure fails to take into account that MGP is at least 80% carbohydrate.⁷ Thus the mucous blanket of MGP is secreted constantly and is constantly removed and replaced. This rapid turnover contributes to the barrier functions of the mucous blanket. Microorganisms and particulate materials are trapped in the mucus and passively removed by these processes. The blanket is selective, because large particles never reach the mucous membrane, whereas smaller molecules do and are readily absorbed. Thus the mucous layer is a selective sieve.

The layer on which the mucus floats and in which the cilia beat is the periciliary or serous layer. Based on recently completed experiments, this layer of fluid appears to follow very different kinetics than does the mucous blanket. This PCF contains most of the aqueous proteins listed in Table I, many of which derive from the serous cells of the submucosal glands. The proteins within the PCF partially reconstitute themselves within 10 to 20 minutes after repeated lavages and may require 4 to 24 hours before they achieve resting concentrations.* The anterior portion of the nose is lined by about 100 µl of ELF, whereas each nostril is lined by 800 µl of PCF. The PCF does not turn over quickly, and the stability of this layer of fluid may provide many of the protective functions of secretions in host defense.

The capacity to actually measure the PCF with quantitation of secretory and plasma urea levels allows calculation of the actual molar concentrations of proteins in nasal secretions (Table II). It appears that this two-layered design of the ELF provides a superficial mucous blanket that traps and exports foreign materials away from the mucous membrane and a stable

TABLE I. Constituents of human nasal secretions

Mucous cell products
Mucous glycoproteins
Serous cell products
Lactoferrin
Lysozyme
S-IgA and secretory component
Neutral endopeptidase
Aminopeptidase
Uric acid
Peroxidase
Secretory leukoprotease inhibitor
Plasma proteins
Albumin
Immunoglobulins: IgG, IgA (monomeric), IgM, IgE
Carboxypeptidase N
Angiotensin-converting enzyme
Kallikrein
Indeterminate sources
CGRP
Urea
Inflammatory mediators
Histamine
TAME
PGD ₂
Bradykinin
LTC ₄
Tryptase
Major basic protein
Eosinophil-derived neurotoxin

Modified from Kaliner MA. Am Rev Respir Dis 1991;144:2-66.
TAME, Toluenesulfonylarginine methyl ester; PGD₂, prostaglandin D₂; LTC₄, leukotriene C₄.

TABLE II. Molar concentration of proteins in nasal secretions

	Baseline	Histamine stimulated	Methacholine
Albumin	0.76 µmol/L	96.6 µmol/L	0.59 µmol/L
IgG	0.22 µmol/L	27.6 µmol/L	0.38 µmol/L

Modified from Kaulbach HC, et al. Analysis of nasal epithelial lining fluid using urea as a marker (submitted for publication).

aqueous PCF, in which molecules providing important host-defense functions may be concentrated.

MGP

Table I lists the major proteins and other molecules found in nasal secretions. It is clear that this complex mixture of molecules serves several functions. Our current understanding of the roles and functions of respiratory secretions is summarized in Table III. Be-

*Kaulbach HC, White MV, Igarashi Y, Hahn BK, Emery B, Kaliner MA. Analysis of nasal epithelial lining fluid using urea as a marker. Submitted for publication.

TABLE III. Roles and functions of human nasal secretions

Protective functions
Antioxidant (uric acid)
Humidification
Lubrication
Waterproofing
Insulation
Provide proper medium for ciliary actions
Barrier functions
Macromolecular sieve
Entrapment of microorganisms and particulates
Transport and eliminate of entrapped materials
Host-defense functions
Extracellular source of IgA/IgG
Extracellular site for multiple enzyme actions
Antimicrobial functions
Lysozyme
Lactoferrin
IgA/IgG
Rapid deployment of multiple plasma proteins

Modified from Kaliner MA. Human nasal respiratory secretions and host defense. *Am Rev Respir Dis* 1991;144:S52-6.

cause the mucous membrane has no keratin layer to protect it from various exogenous stresses, mucus provides many of the protective functions of the outer layer of skin. Because of the large size of the MGP molecule (200,000 to 400,000 daltons) and capacity to polymerize extensively into a size greater than 2 million daltons,⁷ MGP provides a replaceable, flexible, continuous extracellular surface, which coats and protects the mucous membranes. This gelatinous layer insulates the epithelium, water-proofs it by trapping an aqueous layer beneath it, lubricates the surface, and humidifies the inspired air. Each MGP molecule absorbs waters of hydration onto itself, which provides a generous source of humidification for inspired air. Temperature transfer through the airway secretions to inspired air is facilitated by the gel-like structure of mucus, which allows for a gradual transfer of heat to inspired air while protecting the underlying mucosa from excessive cooling.

HOST-DEFENSE FUNCTIONS OF HUMAN RESPIRATORY SECRETIONS

Inspiration of toxic or infectious materials deposits these potential pathogens onto the mucous blanket of the nose. The effectiveness of nasal secretions to neutralize or eliminate potentially harmful pathogens is evident by the relative health that most of us enjoy as an ordinary part of life.

Immunoglobulins

The major specific mediators of host defense in secretions are the immunoglobulins. IgA and IgG are the major immunoglobulins in secretions, and they appear to act quite differently. IgG is a plasma protein that is distributed in the nasal mucosa by microvascular permeability. IgG is found diffusely throughout the mucosa but in highest concentration near the basement membrane.⁸ Analysis of IgG-producing plasma cells reveals that about 25% of the plasma cells in the human nasal mucosa produce IgG, whereas the remainder are IgA producing.⁸ IgA is produced locally by plasma cells located within 50 μ m of submucous glands. The locally produced IgA is dimeric and is joined by a J-chain before secretion. Dimeric IgA binds to secretory component produced by serous cells and forms s-IgA. s-IgA is transported transcellularly through the serous cells into glandular secretions and becomes a glandular secretory product. s-IgA acts primarily by binding microorganisms in the airway lumen and by preventing attachment of these potential pathogens to the mucosa. In contrast, IgG acts primarily in the mucosa itself to limit invasion by microorganisms that reach the epithelium. Although IgG is present in secretions (about 2% to 4% of total protein in baseline secretions), it is found in a much higher concentration in the tissue fluid itself. IgG levels in secretions are increased up to 125 times by the process of vascular permeability (Table II). Thus one could reason that one purpose of acute inflammation is to bathe the mucosa in an IgG-rich secretion.

The nonspecific antimicrobial properties of mucus and the presence of normal amounts of IgG must compensate adequately for the functions of s-IgA, because most IgA-deficient patients do not have symptoms and have a normal incidence of infections. In contrast, patients who are deficient in IgG or IgG subclasses usually require medical help because of recurring respiratory infections. Therefore it appears that the protective functions served in the mucosa by IgG are of greater importance in preventing the development of respiratory infections than is s-IgA.

Lysozyme and lactoferrin

Several nonspecific antimicrobial proteins in nasal secretions have broad-spectrum antimicrobial actions. Lysozyme is a relatively small protein (14,000 daltons) found in all body secretions. Fleming discovered lysozyme in human nasal secretions while he searched for molecules capable of killing bacteria.⁹ He recognized that lysozyme killed most bacteria found in the air but only some bacteria that ordinarily reside on

the mucosa. Thus lysozyme, which represents 15% to 30% of the protein normally found in nasal secretions, effectively prevents mucosal infections from most airborne bacteria. Lysozyme is synthesized and secreted by the serous cell of the submucosal gland.

Lactoferrin is another antimicrobial protein made by serous cells that is both bacteriostatic and bacteriocidal to susceptible bacteria.¹⁰ Lactoferrin binds iron, and presumably this action kills bacteria. Lactoferrin constitutes about 2% to 4% of nasal proteins.

There are multiple specific and nonspecific antimicrobial factors in human plasma. Processes that lead to increased microvascular permeability cause the outpouring of plasma proteins into the nasal mucosa and then into nasal secretions. The increased volume of secretions may lead to clearance of particulate materials, as well as the availability of increased amounts of IgG, albumin (which may nonspecifically bind particulate materials), and other plasma proteins. It has been suggested that this outpouring of plasma proteins might represent the first line of host defense at mucosal surfaces.¹¹

REGULATION OF HUMAN NASAL SECRETIONS
Adrenergic and cholinergic control

After washing the nose to remove existing secretions, the relative amount of proteins in nasal secretions is remarkably reproducible from patient to patient. However, initial washes reveal remarkable variability, which probably reflects the concentration of ELF over time. The innervation of the nose includes parasympathetic nerves that innervate the glands and vascular bed, sympathetic nerves that innervate the vascular bed, and sensory nerves that originate in the epithelium and arborize to include the vascular beds and glands.¹² Parasympathetic nerves are the major motor nerves in the nose. Stimulation of parasympathetic nerves leads to increased secretions, whereas the addition of cholinomimetics onto the nasal mucosa or the initiation of oral gustatory reflexes also leads to secretions.^{5, 13} Parasympathetic stimulation causes secretions enriched for the glandular proteins (Table IV), although plasma proteins are also included in these secretions.

When the relative amounts of proteins in secretions are determined by dividing the individual protein by the total protein concentration, a figure is generated that has been termed the "protein" percent. Cholinergic stimulation of glandular secretion may change the relative percent of lysozyme in secretions from 15% to 20% up to 30%; lactoferrin from 2% to 4% to 8%, and s-IgA from 15% to 25%. The plasma

TABLE IV. Nasal secretory responses

Protein	Stimulation	Response
Parasympathetic		
Plasma proteins		+
Glandular proteins		++
Histamine or allergen challenge		
Ipsilateral		
Plasma proteins		+++
Glandular proteins		+
Contralateral		
Plasma proteins		+
Glandular proteins		+++
Upper respiratory tract infection		
Early phase		
Plasma proteins		++++
Glandular proteins		+
Later stage		
Plasma proteins		+
Glandular proteins		+++

Modified from Kaliner MA. Human nasal respiratory secretions and host defense. *Am Rev Respir Dis* 1991;144:S52-6.

proteins found in glandular secretions do not change. Thus albumin remains at 15% of total protein and IgG at 2% to 4%.

Adrenergic stimulation of the mucosa either has no effect on secretions (β -adrenergic stimulation) or mildly stimulates glandular secretions (α -adrenergic stimulation).¹⁴ The effects of adrenergic stimulation have been studied both in vivo and in vitro with similar findings.¹⁴

Neuropeptides

Sensory nerves contain several associated neuropeptides, including calcitonin gene-related peptide, GRP, SP, and neurokinin A.¹⁵ The distribution of these neuropeptides has been carefully studied in the nasal mucosa by immunohistochemistry. Of the sensory nerves, all have some fibers that apparently innervate submucosal glands. However, calcitonin gene-related peptide and GRP (as well as the parasympathetic neuropeptide VIP) are most evident in regard to glandular innervation.¹⁶⁻¹⁸ The presence of neuropeptide receptors was examined in the nasal mucosa by binding iodine 125-labeled neuropeptides to their binding sites. It was found that GRP had the most intense binding to glands, whereas both VIP and SP also had gland receptors.¹⁹ The capacity of these neuropeptides to cause mucous and serous cell secretion of specific products has been examined in vitro with the use of human nasal turbinates in short-term culture. GRP and VIP were the most potent stimuli for glandular secre-

TABLE V. Chronic conditions that predispose to sinusitis

Allergic and nonallergic rhinitis
Cystic fibrosis
Common variable immunoglobulin deficiency
IgG subclass deficiency
IgA deficiency (only when combined with IgG deficiency)
Ciliary dyskinesia, Kartagener's syndrome, Young's syndrome
Aspirin sensitivity
Acquired immunodeficiency syndrome
Bronchiectasis
Rhinitis medicamentosa
Cocaine abuse
Wegener's granulomatosis

tion, although both SP and neurokinin A also had some activity.²

Bradykinin is a mediator generated by action of the plasma or tissue enzyme kallikrein on the substrate kininogen. Bradykinin has been found in nasal secretions,²⁰ has its receptors exclusively on blood vessels,²¹ and topical application onto the mucosa results in secretions rich in vascular proteins and is also associated with increased nasal blood flow.²²

ABNORMALITIES ASSOCIATED WITH SINUSITIS

Secretory abnormalities

Sinusitis may occur in otherwise normal individuals or the likelihood of developing sinusitis may be increased in association with the conditions listed in Table V. Evaluations to exclude these underlying problems are appropriate in subjects who have chronic sinusitis or frequently recurring disease. One recent study evaluated the capacity of patients who have recurrent sinusitis (two or more episodes for 2 or more years) to respond appropriately to topical methacholine or histamine challenge, evaluating and the constituents of the nasal secretions that resulted.²³ Several distinct abnormalities were discovered. Baseline washing of patients with sinusitis had an abnormally high concentration of the glandular proteins lysozyme and lactoferrin in relation to total protein, which suggests that glands were driven to secrete excessively in patients with chronic inflammation. Conversely, these same patients were unable to respond to cholinergic stimulation with a glandular response. The magnitude of the response included blunted secretion of glandular products as well as the passively transported

TABLE VI. An approach to the treatment of persistent sinusitis*

Hydration (6-8 glasses of water per day)
Antibiotics for 21 days, or longer
Topical long-acting decongestants, bid, for 2-3 wk
Nasal douche with saline solution with an ear bulb syringe
Topical corticosteroids (with decadron turbinaire):
3 sprays bid, for 1-2 wk
2 sprays bid, for 1-2 wk
1-2 sprays bid, until sinusitis is resolved; thereafter switch to other nasal steroid for long-term maintenance

bid, Twice daily.

*This approach is used only *after unsuccessful* treatment of sinusitis with more conventional approaches, such as decongestants and antibiotics, has failed.

plasma proteins ordinarily seen in glandular secretions.

The abnormal secretory response was restricted to cholinergic reactions as these patients responded normally to histamine stimulation with increased vascular permeability and glandular secretion. Thus the glands were likely to have been exposed long term to cholinergic stimulation and were therefore unable to respond to additional cholinergic stimulation but were still responsive to histamine-mediated responses. These data suggested the possibility that the glandular abnormality might have contributed to the disease by an inability of affected subjects to produce secretions rich in antimicrobial factors necessary to combat new or recurrent insults.

This suggestion was enhanced by the findings after effective treatment. Most of the patients received therapy as described in Table VI. After resolution of their sinusitis, they were restudied with the same provocations. Not only did the patients improve clinically, their baseline and stimulated secretory responses also returned to normal.

Another recent investigation indirectly adds support to the concept that nasal secretions help control mucosal infections. In a collaborative study conducted at the University of Pittsburgh, patients were experimentally infected with rhinovirus and nasal secretions collected during an ensuing upper respiratory tract infection.²⁴ Interestingly, the initial response consisted almost exclusively of increased vascular permeability that lasted 2 days into the infection. Secretions thereafter became enriched with glandular proteins as the urinary tract infection resolved. Our interpretation of these data is that the acute inflammatory response

causes the generation of vasoactive amines such as bradykinin, which cause the vascular response. However, as the initial inflammatory response matures, glandular secretion is stimulated either by cholinergic or peptidenergetic mechanisms. The antimicrobial-enriched secretions combine with local immune responses in the mucosa to clear the infection.

Nasal mucosal cellular immunity

The process of identifying which cells occupy the human nasal mucosa is just underway.²⁵ In the 200 μm beneath the epithelium in normal individuals, the predominant cell is the lymphocyte. Most of the lymphocytes are CD4^+ , and there is a predominance of $\text{CD4}^+:\text{CD8}^+$ cells. On average there are about 168 CD3^+ lymphocytes per 1000 μm of basement membrane. Of these, 117 are CD4^+ , and 46 are CD8^+ . There are also macrophages (16/mm of basement membrane) and plasma cells (27/mm of membrane). About 10 mast cells are also seen, which were overwhelmingly of the type of mast cells containing both tryptase and chymase. What changes occur in these populations of cells in patients with acute or chronic sinusitis is currently under investigation. Few publications describe the sinus mucosa, although one electron microscopic examination details a spectrum of changes ranging to extreme squamous metaplasia.²⁶ Another study describes desquamation of columnar cells, squamous metaplasia, and frank exfoliation.²⁷ Basement membrane thickening and mucosal edema were also noted, along with focal infiltration with eosinophils in the areas of greatest damage. About half of the samples stained for the presence of major basic protein, which was most marked in patients who had concomitant asthma. These findings suggested to the authors that chronic sinusitis resembled some of the finding seen in the airways of asthmatic patients and that the eosinophil might also play a role in chronic sinusitis.²⁷

SUMMARY AND CONCLUSIONS

Human respiratory secretions serve many critical functions; they protect the mucosa and provide essential host-defense roles. It appears that the serous cell in the submucosal glands is the source of most of the protective proteins that prevent infections of the mucosa. Although glandular secretions are an essential product of the mucosa, secretions are also derived from the vascular bed as a result of increased vascular permeability. These secretions can be recognized by a relative enrichment with vascular proteins, such as albumin and IgG. Analysis of secretory responses to topical histamine,³ allergen challenge,²⁸ and in the first

few days after an experimentally induced upper respiratory tract infection²⁴ reveals that vascular permeability is the underlying mechanism responsible. Thus in those circumstances in which patients complain most commonly of increased secretions (such as during a cold or in response to allergen exposure), it is really increased vascular permeability and not glandular secretions that is responsible. The proteins that increase in secretions as a consequence of increased vascular permeability include IgG, IgM, IgA, albumin, and many other plasma proteins. These proteins mediate both specific (IgG) and nonspecific (albumin) antimicrobial functions.

The sum results of stimulating nasal secretion is the outpouring of fluids capable of preventing or limiting infections, neutralizing toxic materials that may impact on the secretions, and the elimination of particulate materials that are trapped. Most humans have a limited number of viral infections and fleetingly few bacterial infections of their respiratory mucosa, speaking eloquently of the effectiveness of the host-defense mechanisms involved. In patients with recurrent sinusitis, cholinergic responses are abnormal, which results in a limited capacity to secrete mucus. Data show that the sinus epithelium in patients who have chronic sinusitis is infiltrated with eosinophils and that these cells may be involved in the chronic inflammatory nature of the disease. In otherwise normal individuals, we have no knowledge of mucosal defects that might predispose to sinus disease. In fact we really have an extraordinarily limited fund of knowledge about cellular immunity in the upper respiratory tract despite the obvious clinical importance of rhinitis and sinusitis.

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DISCUSSION

Dr. Druce. The effects that you see after infection are most likely generic effects on glands caused by the infectious process.

Dr. Kaliner. In essence there is no control for sinusitis other than sinusitis. However, the closest I can come to that is a collaborative study we just did with Phil Fireman and Jack Gwaltney, in which we looked at nasal proteins in normal volunteers treated with rhinovirus. They became sick, and those patients had dramatic changes in the secretory proteins. However, they were not reduced to the same magnitude as in patients with sinusitis.

Dr. Druce. Do you think patients who have IgA deficiency are usually sick because the IgA binds on the surface and IgG is submucosal?

Dr. Kaliner. We do not see many patients who have IgA deficiency who are sick. We examined all the blood bank IgA-deficient patients whom we have been able to locate throughout the National Institutes of Health, and none of them were sick unless they also had an IgG subclass deficiency.

Dr. Irvin. Do you believe in IgG-blocking antibodies?

Dr. Kaliner. Until we started doing the histologic studies, the answer was no. However, there is a lot of IgA in the mucosa. There are milligrams of IgG per gram of nasal tissue in the interstitium. So there is a substantial potential for IgG-blocking antibodies to bind allergen as it enters the mucosa.

Dr. Rachelefsky. What do topical nasal steroids do?

Dr. Druce. Two multicenter studies have addressed the issue of nasal steroids. I look at the use of nasal steroids on "healing" of acute sinusitis. The problem is how you define sinusitis, because if you just look at radiographic resolution, then indeed nasal steroids do not accelerate the rate of radiologic resolution. On the other hand, if you look at patients' well-being and the time it takes for them to feel better, that is a completely different issue that may be of value.