Chapter 2
Physiology and Host Immune Responses of the Nose and Sinuses

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Introduction

The nose and converging structures have several critical functions that are often trivialized until symptoms persist and interfere with the patient's daily activities. The nose is the body's heating, ventilation, and air conditioning (HVAC) system, as it humidifies, filters, and conditions air. These functions thereby protect the lungs from an influx of aeroallergens, air particulates, and other potentially deleterious air pollutants. The nose is the conduit for several important structures, including the paranasal sinuses and lacrimal duct. When nasal inflammation occurs, these small structures can become obstructed leading to a spectrum of clinical symptoms such as nasal congestion, postnasal drainage, sinus pressure or pain, headache, and ocular lacrimation and itching. In addition, the Eustachian tube also drains into the posterior pharynx. With allergic and/or nonallergic rhinitis, it is not unusual for patients to complain of ear plugging, popping, or pain consistent with Eustachian tube dysfunction. Although intact anatomic structures are essential for the normal functioning of the nose and sinuses, invisible structures buried within the nasal mucosa are equally if not more important for protecting the host from the external environment. This chapter will review the gross and microscopic anatomic and physiologic processes that are essential for normal functioning of the upper respiratory tract.

Phylogeny and Ontogeny of the Nose and Sinuses

The nose and sinuses are considered one organ even though phylogenetically the nose is primarily an olfactory organ, whereas the sinuses are speculated to have evolved as aids to facial growth and structure [1]. Interestingly although the ethmoid sinuses have been considered as part of the paranasal sinuses, the ethmoid bone is actually derived from the cartilaginous nasal capsule, and its main role may have been to protect the olfactory nose [1, 2]. In humans, the ethmoid labyrinth derived from the olfactory labyrinth contains only a very small amount of olfactory mucosa compared to other animal species, which have a much greater dependence on olfaction for their survival. This reduced need for olfaction led to retraction of the nose posteriorly and migration of the orbits anteriorly. These changes resulted in the disconnection of the frontal sinuses from the maxillary sinuses and the repositioning of the ethmoid bone between the paranasal sinuses [1]. The ethmoid bone is considered the most highly conserved region in the skull. Unlike the other paranasal sinuses, the ethmoid sinuses do not have defined walls or a well-defined ostium. They therefore do not meet the criteria of what constitutes a true sinus cavity [2, 3].

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In humans, the olfactory nose develops during week 5 of gestation on the frontal nasal process [1, 4]. By the end of week 6, these structures invaginate to form nasal pits which fuse posteriorly to form a nasal sac separated from the oral cavity by the nasal fin [1, 4]. During week 7, the nasal fin thins to form the oronasal membrane, which then ruptures to form an opening with the oral cavity referred to as the "primitive choanae" [1, 4]. The floor of the nasal fossa subsequently becomes the primary palate [1, 4]. By 6.5 weeks, the cartilaginous nasal capsule develops in connection with the olfactory structures and with the breakdown of the oronasal membrane forms a characteristic "m" shape. This is considered the beginning of the development of the paranasal sinuses [1, 4]. By weeks 9 and 10 of embryogenesis, six major furrows separated by ridges develop that are called the ethmoturbinals. The first ethmoturbinal regresses, leaving as its remnant the uncinate process [1, 4]. The second and third ethmoturbinals develop into the middle and superior turbinates, respectively, whereas the supreme turbinate develops from the fourth and fifth ethmoturbinals [1, 4]. The middle meatus and the hiatus semilunaris evolve from the first primary furrow, the superior meatus from the second furrow, and the supreme meatus from the third furrow [1, 4].

The paranasal sinuses develop after birth. The maxillary, frontal, and sphenoid sinuses evolve from epithelial diverticula that expand from the cartilaginous nasal capsule and become pneumatized [1, 2]. The maxillary sinuses are present at birth and expand throughout childhood. The sphenoid sinuses do not appear until 5 months after birth and then continue to develop throughout childhood [1, 5]. The last to develop are the frontal sinuses, which do not appear until 5–6 years of age and then continue to expand through adolescence [1, 5]. The frontal sinuses are believed to primarily assist in facial growth and architecture [1, 5]. The sizes of the paranasal sinuses vary due to the unpredictable development of the paranasal recesses [1, 5].

Anatomy of the Nose and Sinuses

External Nose

The nose and paranasal sinus complex are the result of fusion of the respiratory nose, the olfactory nose (including the ethmoidal labyrinths and olfactory clefts), and the paranasal sinuses [1]. The external nose is comprised of two nasal bones superiorly and two sets of paired cartilage inferiorly [6]. The respiratory nose is considered a channel. Its inferior wall is the floor of the nasal fossa; the superior wall is comprised of the roof of the rhinopharynx, the inferior edge of the middle turbinate, the tip of the nasal valve, and the vestibule; the lateral wall is made up of the turbinate wall of the maxillary sinus whereas the medial wall is the nasal septum [1]. The respiratory nose is comprised of the nasal vestibule, nasal valve, nasal chamber, and choanae [1].

The olfactory nose is comprised of two medial olfactory clefts and two lateral ethmoid labyrinths [1]. The human olfactory mucosa is limited to the olfactory clefts, but its exact distribution has not been well defined [1, 7–9]. The ethmoid labyrinth, which is devoid of olfactory mucosa, is divided from the olfactory cleft by the turbinate wall of the ethmoid labyrinth (TWEL) [1, 10]. The TWEL is comprised of turbinates, which traverse the entire ethmoid labyrinth and extend laterally to the lamina papyracea and superiorly to the lamina cribrosa (Fig. 2.1) [1, 10]. They are divided by air spaces that are further separated by small transverse septa that form the ethmoidal cells [1, 10]. The olfactory cleft is the narrow air space located below the olfactory groove, medial to the ethmoid labyrinth and lateral to the nasal septum (Fig. 2.1) [1]. The olfactory epithelium is limited to the upper part of the olfactory cleft which is further divided into an upper chamber called the olfactory fossa, which is the sensory cavity and the lower chamber which is called the olfactory vestibule [1]. Airflow is very slow through the olfactory cleft, which allows greater time to facilitate olfactory sensing [1, 11, 12].

Finally, the paranasal sinuses include the frontal, maxillary, and sphenoid sinuses. These are hollow, air-filled cavities, lined by thin respiratory mucosa with minimal to no glands or vascularization [1]. The only contact with the external environment is through the ostia [1]. The air composition in the sinuses remains relatively stable (17.5 % O_2, 2.2 % CO_2, 100 % relative humidity, and 34 ºC) with air exchange occurring between the nose and sinuses likely secondary to passive diffusion [1].

Vestibule

The vestibule is the most important structure of the nose for sensing nasal airflow. It is lined with stratified squamous epithelium, which transitions to pseudostratified columnar epithelium (Fig. 2.2) [6]. Vibrissae are thick hairs without piloerector muscles in the vestibule that filter out large particles [6]. Anterior nasal glands are present at the junction of the squamous and pseudostratified epithelial junction that secrete serous secretions which are atomized with sniffing [6]. In addition, the vestibule also contains thermoreceptors that cause decreased nasal resistance after inspiration of warm air and increased nasal resistance after inspiration of cold air [6, 13, 14].

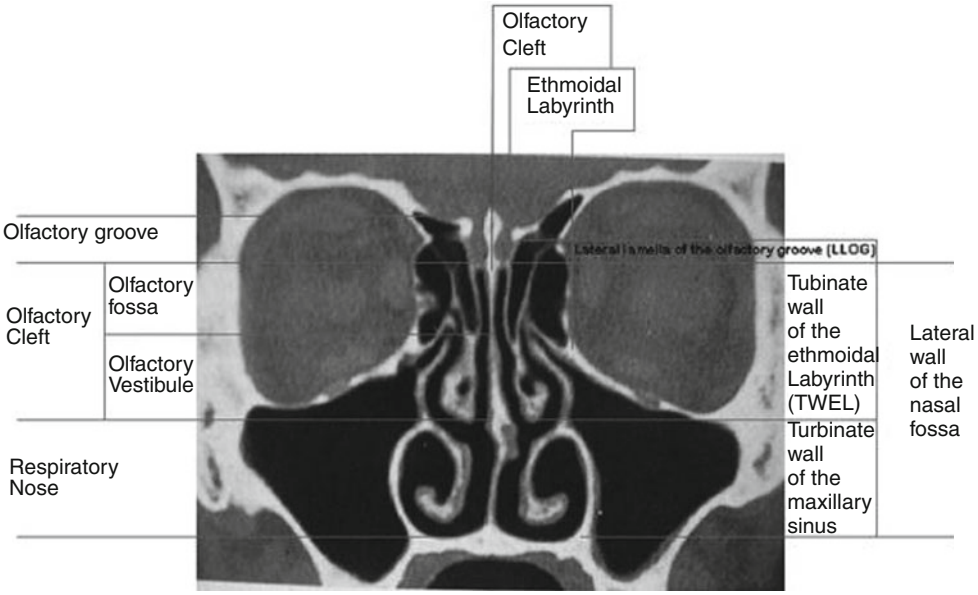

Fig. 2.1 Coronal CT scan of the sinuses (Reprinted from Jankowski [1]. With permission from John Wiley & Sons, Inc.)

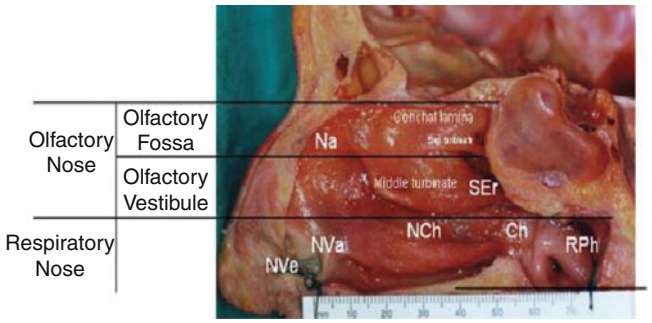

Fig. 2.2 Lateral wall of nasal cavity. *NVe* nasal vestibule, *NVa* nasal valve, *NCh* nasal chamber, *Ch* choana, *RPh* rhinopharynx, *Na* nasal attic, *SEr* sphenoidal ethmoidal recess (Reprinted from Jankowski [1]. With permission from John Wiley & Sons, Inc.)

Nasal Valve and Airflow

The nasal valve, located behind the nasal vestibule, has a cross-sectional area of 40 mm^2 which increases to 150 mm^2 in the nasal cavity (Fig. 2.2). Contraction of the dilator naris muscle leads to increased nasal airflow, manifested as nasal flaring [6, 15, 16]. The nasal valve is responsible for 50–75 % of inspired airflow resistance to the pulmonary alveoli [6, 17]. Airflow through the nasal valve is fastest as it streams through the middle turbinate (18 m/s) and slows significantly as it passes into the main part of the nasal cavity (2–3 m/s) [6, 15]. The slower airflow in the nasal cavity allows for maximal contact with the warmer nasal mucosa, which allows the ambient air to be warmed to 34 °C at resting rates of respiration. The greatest increase in temperature occurs anteriorly in the nasal valve [6, 18]. Relative humidity reaches 100 % in the nasopharynx.

Expiration lasts longer than inspiration and airflow is less laminar. Not surprisingly, the lowest temperatures are measured at the end of inspiration, whereas the highest mucosal temperature is at the end of expiration [6, 19]. Expiratory air cooling occurs primarily in the region of the inferior and middle turbinates [20].

Large volumes of airflow up to 30 L/min occur through the nose, but if larger volumes are necessary, then mouth breathing occurs. However, this can lead to significant loss of water and humidity [6, 21–23]. Physical exercise is the most common cause for increased nasal airflow [21, 22]. While sleeping, nasal airflow causes breathing to increase more in the nose compared to the mouth. Nasal obstruction can lead to abnormal breathing patterns, such as obstructive sleep apnea [24]. Several structural defects, such as septal deviation, enlarged turbinates, and adenoid hypertrophy, can impede nasal airflow which can lead to increased pulmonary resistance.

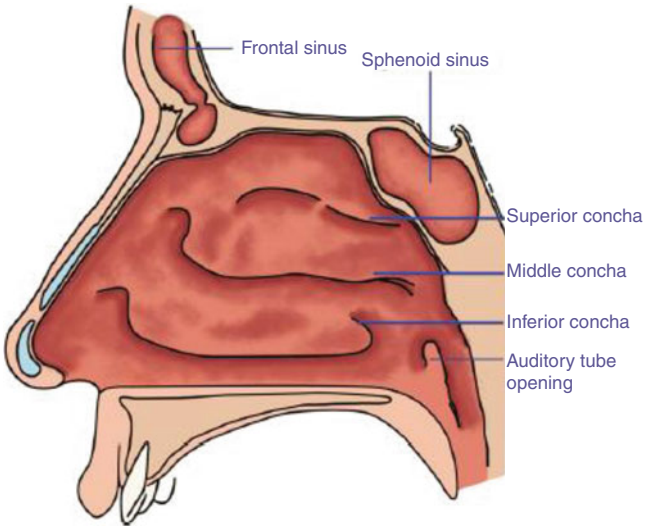

Fig. 2.3 Lateral wall of the nasal cavity illustrating turbinates

Normal individuals have relatively constant nasal airway resistance with alternating airflow in each nasal cavity known as the nasal cycle. The nasal cycle is regulated by the sympathetic nervous system as cervical sympathetic blockades extinguish this sequence [25]. The nasal cycle's pacemaker is believed to be located in the suprachiasmatic nucleus of the hypothalamus [6, 26]. Alternating airflow is the result of increased blood flow to the turbinates and septal tuberculum [6]. Typically, the nasal cycle goes unnoticed if the nasal cavity remains unobstructed, but can become quite apparent with the advent of nasal swelling from structural, infectious, or allergic problems [6, 27].

Nasal Septum and Turbinates

The nasal septum divides the nose into two cavities, thereby increasing the total mucosal surface in the nose (Fig. 2.1) [6]. The anterior tip of the septum is comprised of cartilage. The posterior bony section of the nose is made up of the vomer and the perpendicular ethmoid plate [6]. It is estimated that 90 % of the general public has a septal deviation to some degree or another; a straight septum is twice as common in women compared to men. Small anterior abnormalities can compromise nasal airflow much more dramatically than larger defects in the posterior cavity [6].

The turbinates emanate from the lateral nasal wall (Fig. 2.3). The inferior and middle turbinates are considered to be the functionally most important part of the nose [6]. Turbinates are comprised of a bony frame covered with respiratory epithelium [6]. The inferior turbinate plays an important role in protecting the lungs from the external environment and maintaining the normal physiology of the nose. In addition, several key structures empty under the middle and inferior turbinates. The lacrimal duct empties underneath the inferior turbinate. The anterior ethmoids, maxillary and frontal sinus ostia empty underneath the middle turbinate. Disruption of the middle and inferior turbinates, such as partial turbinectomies, can significantly impair their protective role [6].

Histology of the Nose and Sinuses

The nasal mucosa is lined with pseudostratified columnar epithelium, which contains mucosal secreting goblet cells and ciliated and nonciliated columnar cells with microvilli and scattered mast cells, eosinophils, neutrophils, and lymphocytes (Fig. 2.4) [6, 28]. Ciliated epithelium lines most of the airway from the nose to the respiratory bronchioles as well as the paranasal sinuses, Eustachian tube, and portions of the middle ear [6]. Cilia play an important role in mucous transport and are composed of a shaft (axoneme) made up of microtubules arranged as nine doublets surrounding two central singlets [29]. Each doublet has two dynein arms containing ATPase, which fuels their motion [6, 29].

Goblet cells are arranged perpendicularly to the epithelial surface and are important for secreting a mucosal blanket that protects the nose. The density of goblet cells increases from infancy to childhood. In adults, goblet cells are not found in the

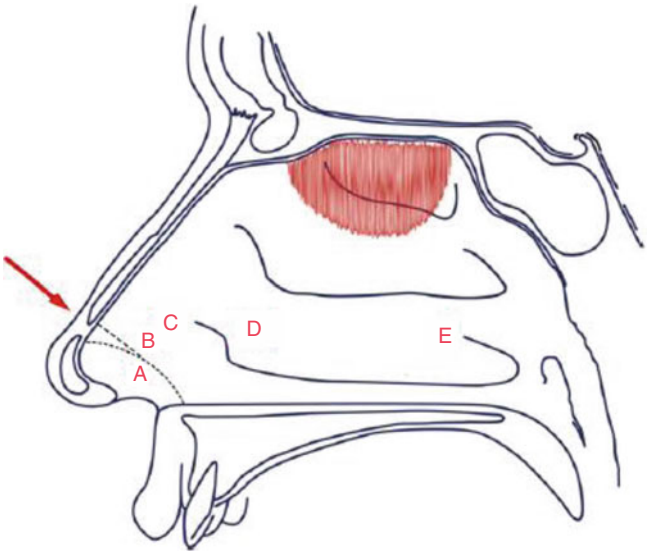

Fig. 2.4 Lateral wall of nose with letters representing histology at specific locations. *A* skin in nostril, *B* squamous epithelium without microvilli, *C* transitional epithelium with short microvilli, *D* pseudostratified columnar epithelium with few ciliated cells, *E* pseudostratified columnar epithelium with ciliated cells

squamous, transitional, or olfactory epithelia but are present in all areas of the pseudostratified columnar epithelium [6, 29]. There is a greater density of goblet cells in the inferior turbinate compared to the middle turbinate and septum. The density of goblet cells in these areas increases from anterior to posterior and inferior to superior. The mucosal barrier produced by goblet mucus-secreting cells provides an important protective layer composed of IgA and other mediators that protect the nose from infection and other external insults [30]. Columnar cells are covered by hundreds of microvilli that are distributed over the entire apical surface epithelium [6, 30]. They promote exchange processes across the epithelium. The microvilli are important for retaining moisture, which is important for ciliary function. Basal cells are important for providing adhesion between cells and anchoring columnar cells to the basement membrane [6]. Previously, studies have reported that basal cells may actually be progenitors for goblet cells, but this has not been reproduced by other investigators and is considered speculative.

The basement membrane separates the epithelium from the lamina propria. The submucosa is comprised of nerves, blood vessels, and glands. The glands in the submucosa produce the greatest amount of nasal secretions. The nasal mucosa does not contain lymphoid aggregates, and therefore, lymphocytes migrate to the nasal mucosa via the blood through tonsillar lymphoid tissue [6]. There are three types of submucosal nasal glands: (1) the anterior serous glands, (2) the seromucinous glands, and (3) the Bowman's glands. The anterior glands are important for moisturizing the nasal mucosa. The seromucinous glands produce the greatest amount of mucus in the nose. Bowman glands are serous glands located in the olfactory region, important for aiding in smell [6].

Mucociliary Clearance

Mucociliary transport is a physiologic mechanism of the nose important for clearing secretions and unwanted particulates. The mucus blanket is composed of secretions from goblet cells and submucosal glands. The mucus layer consists of a sol phase which is a watery periciliary layer and a gel phase which is closest to air (Fig. 2.5) [6]. Particles greater than 3 um are filtered primarily in the nasal valve region. Smaller particles between 0.5 and 3 um are filtered by the nasal mucosa and transported to the nasopharynx by ciliary flow [6]. Intranasal particle deposition occurs during inspiration and expiration [31]. The mucus blanket is also the first line of defense against bacterial and viral infections, largely due to the protective effect of IgA which is the major immunoglobulin in nasal secretions [30, 32]. IgA assists in preventing microorganisms from adhering to the nasal mucosa [6, 30]. Finally, the mucus blanket provides water for humidification [6, 30]. Daily mucus production is approximately 1 liter per day. The gel-like properties of mucus are due to being comprised of high molecular weight glycoproteins named mucin, which is composed of 80–90 % carbohydrate, 20 % protein, and 1–2 % sulfate bound to oligosaccharide side chains, to which water binds to form a matrix that lubricates the mucosa [32]. Mucin genes encode the protein backbones of mucins [33]. More than 16 are found to be expressed in the respiratory tract, but MUC5AC, MUC5B, and MUC2 appear to be the most important gel-forming mucins secreted in the airway [33]. Other components of mucus

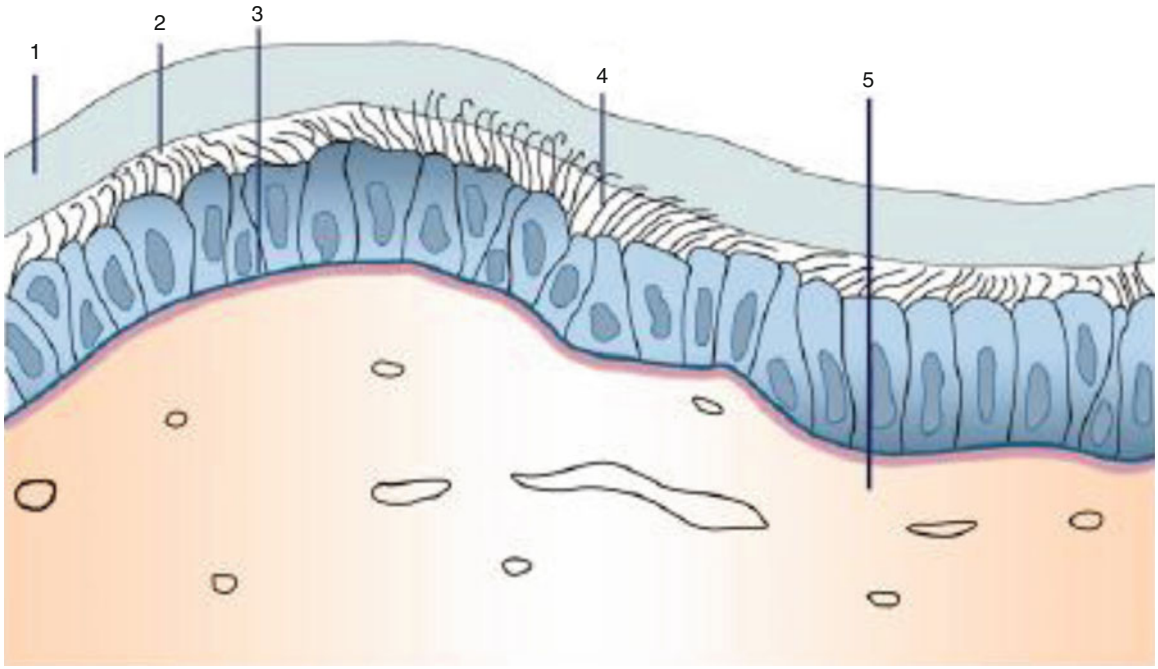

Fig. 2.5 Phases of the nasal airway mucus layer. *1* Gel phase, *2* sol phase, *3* basement membrane, *4* cilia, *5* submucosal layer

include IgG, IgE, albumin, bacteria, lactoferrin, lysozyme, ions, and cellular debris [6, 30]. Mucus moves posteriorly to the nasopharynx, except in the area anterior to the inferior turbinate where transport is anterior [6]. This transport mechanism can clear inhaled particles from the nasal cavity in 10–20 min. Mucociliary transport is increased with nasal irrigation. Clearance of secretions is also enhanced by nasal sniffing, sneezing, and nose blowing [6].

Cilia are all oriented in a similar direction and have a two-stroke pattern. The effector stroke is important for moving mucus. The recovery stroke is when the cilia bend and move in the watery sol phase [6]. Although patients with chronic rhinosinusitis are believed not to have differences in ciliary beat frequency compared to healthy individuals, they do have decreased numbers of ciliated cells and more ciliary disorganization and microtubular abnormalities [6]. Temperatures lower than 32 °C and higher than 40 °C can lead to decreased ciliary beating. Preservatives in nose sprays, such as benzalkonium chloride, can decrease mucociliary transport and cause ciliastasis [6, 34–36]. A number of structural problems in the nose, viral and bacterial infections, and genetic disorders such as cystic fibrosis and immotile cilia syndrome all have impaired mucociliary transport mechanisms leading to increased viscosity of secretions [6].

Vasculature

The nasal cavity blood supply comes from the internal and external carotid arteries. Branches of the internal carotid include the anterior and posterior ethmoid arteries and the ophthalmic artery. The sphenopalatine artery is a branch of the external carotid [6]. These vessels converge with branches of the facial artery and form a large triangle in the septum, which is the most common site of epistaxis in the nose [6, 37]. Veins run next to the arteries and empty into the pterygoid and ophthalmic venous plexi. Some drainage from veins occurs into the cavernous sinus, which can be a potential route for a spread of infection [6]. Arterial branches from the perichondral and periosteal arteries supply the subepithelial and glandular zones. These arteries move forward to the surface, branching off to form a cavernous plexi and ultimately a network of fenestrate capillaries in the subepithelium. These fenestrate capillaries are believed to be an important source of fluid for humidification [6].

Nasal airflow is regulated by alteration in blood flow to the turbinates and septum. Nasal congestion manifests as the result of changes in vascular tone, which leads to vascular engorgement in the sinusoids [6]. Vascular tone is regulated by receptors on blood vessels. When stimulated, the alpha-adrenoceptors cause vasoconstriction; specifically α-2-adrenoceptors are important for contracting nasal veins whereas the α-1-adrenoceptors cause constriction of nasal arteries [6]. A blockade of

cholinergic receptors results in drying nasal secretions. Histamine release, usually from mast cells and basophils in atopic individuals, leads to increase vascular permeability, glandular secretions, sneezing, and itching [6]. Blocking of H1, H2,and H3 receptors can lead to decreases in symptoms related to these physiologic changes [6].

Lymphatics

Lymphatic vessels in the nose drain to the external nose and along facial vessels to the submandibular lymph nodes. In contrast, lymphatics of the nasal fossae drain toward the nasopharynx [6]. Lymphadenopathy associated with rhinosinusitis is rare because the nasal-draining lymph nodes are buried deep along the vertebral bodies and cannot be palpated [6]. Lymphatic drainage in the maxillary sinus is unique in that it drains through the ostia as well as across the sinus wall through bony gaps [6, 38].

Nervous System

Sensory innervation of the nose involves the olfactory, ophthalmic, and maxillary branches of the trigeminal nerve [6]. Depolarized nociceptive C fibers release neuropeptides, including substance P, neurokinin A, and calcitonin gene-related peptide. These neuropeptides are potent vasodilators, resulting in increased vascular permeability [6, 39, 40]. Regulation of neurogenic inflammation occurs in part through chemoreceptors like transient response potential ion channels. These calcium ion channels are co-localized with other receptors like bradykinin-2-receptor, 5-lipoxygenase, and toll-like receptors. The complex interaction of these co-localized receptors can further enhance the parasympathetic response and down-modulate the sympathetic response, resulting in the physiologic responses observed in patients with allergic and nonallergic rhinitis [41, 42].

Sensory nerves regulate several nasal reflexes. The nasonasal reflex occurs when one side of the nasal cavity is stimulated, leading to bilateral efferent reflexes that can be observed in the contralateral nostril [43, 44]. The nasal ocular reflex occurs after chemical or mechanical stimulation of the nasal mucosa resulting in lacrimation [43]. The submersion reflex occurs when there is mucosal irritation, manifested as apnea, glottis closure, bradycardia, and vasoconstriction. The purpose of this reflex is to protect the heart and brain by the redistribution of blood to these organs [6]. Cooling of the skin causes nasal vasoconstriction, whereas heating of the skin causes an increase in nasal temperature [6, 45]. Finally, a nasobronchial reflex has also been described; irritation of the nasal mucosa has been demonstrated to increase lower airway hyperresponsiveness [6]. Treatment of upper airway inflammation has been shown to decrease lower respiratory tract airway hyperresponsiveness [46]. However, the definitive mechanism of this neurogenic reflex connecting the upper and lower respiratory tracts remains elusive.

The parasympathetic nerve supply originates in the midbrain and travels with fibers of the seventh cranial nerve. After synapsing in the sphenopalatine ganglion, they are distributed to mucosal and submucosal branches [6]. Postganglionic branches contain acetylcholine and neuropeptides, including vasoactive intestinal peptide and secretoneurin [6, 47]. Parasympathetic nerve stimulation causes glandular secretion and vasodilation [6, 48].

The sympathetic nerve supply originates in the hypothalamus. They synapse with the superior cervical ganglion and travel to the carotid plexus to join the parasympathetic fibers from the seventh cranial nerve to form the vidian nerve [6]. The sympathetic fibers do not synapse in the sphenopalatine ganglion [6]. Sympathetic responses are mediated by adrenoceptors stimulated by norepinephrine and neuropeptide Y [6, 49]. Stimulation of the sympathetic nervous system leads to vasoconstriction, resulting in decreased nasal airway resistance [6].

The olfactory epithelium is covered by a layer of mucus rich in immunoglobulins, lactoferrin, and lysozyme that protect against infection [6, 50]. The olfactory and trigeminal systems interact to inhibit or activate one another [6]. The field of *olfaction* has dramatically grown with the discovery of a superfamily of approximately 1,000 odorant receptor (OR) genes, located in multiple clusters on all but two of the 24 human chromosomes [51]. These *OR* gene clusters comprise 17 gene families, four of which contain greater than 100 genes each [51, 52]. It has been estimated that the *OR* gene superfamily comprises 1–3 % of the entire genomic complement of genes. It is likely to be the largest gene superfamily in the genome of any species [52]. The OR genes are members of the 7-transmembrane domain G-protein-coupled receptor (GPCR) superfamily [52]. In situ hybridization studies indicate that each *OR* gene is expressed in approximately 1 out of every 1,000 olfactory epithelial (OE) neurons, suggesting that each OE neuron expresses only one OR gene [53]. Interestingly, 63 % of

human OR genes are nonfunctional pseudo-genes, which increase the likelihood for the presence of OR genetic polymorphisms [51, 53].

Odorant-binding proteins help transport odorant molecules through hydrophilic mucus to the olfactory epithelium where they can bind to OR [52]. This binding sends an impulse through axons that pass through the cribriform plate and into the CNS to synapse with the olfactory bulb [52]. Neuronal projections travel from the olfactory bulb to a number of regions in the brain important for olfactory sensory processing [6]. Not surprising, olfaction is not as well developed in humans as it is in animals who depend on smell for survival [6]. In humans, the estimated percent of blood flow to the olfactory region is 10 %. Olfaction can be impaired by a number of conditions, including allergic and nonallergic rhinitis, nasal polyposis, viral infections, vitamin A or thiamin deficiency, or other structural abnormalities resulting from developmental disorders, malignancy, or trauma [6]. Recently, loss of olfaction has been demonstrated to be an early diagnostic indicator for the onset of Parkinson's and Alzheimer's disease [54].

Innate Immune Responses in the Nose

The nasopharynx is colonized with normal flora that act as commensal organisms to prevent colonization of the host with more pathogenic organisms, thereby preventing disease [55]. Gram-positive organisms, including *Streptococci viridians*, *Staphylococcus epidermidis and aureus*, and *Corynebacterium*, and gram-negative organisms, such as *Moraxella* and *Haemophilus* (*influenza and parainfluenza*), can be found in the nasopharynx with some regularity in normal hosts [55]. Colonization of these organisms varies with age [55]. For example, children less than 2 years of age harbor the above organisms more commonly than adolescent-aged children. In contrast, the paranasal sinuses are considered sterile cavities that are protected by anatomic and local mucosal defense mechanisms. These low virulent organisms can paradoxically cause disease when local protective innate immune responses become impaired [55].

There are several natural protective mechanisms in the nose that are part of the innate immune response. Because the nasal epithelium provides a weak protective barrier, innate immunity plays a very important role to prevent infection and other pathologic inflammatory responses [30]. The nasal mucus acts as a protective barrier against the invasion of microorganisms and injury by toxic agents. Mucociliary transport is an essential first line of defense for elimination of microorganisms [30]. Alterations of the viscoelastic properties of the nasal mucous lead to stasis and abnormal mucociliary clearance, increasing the risk of infection [30, 56].

In addition, nasal secretions are rich in lysozyme, which has potent anti-bactericidal or bacteriostatic activity against some gram-positive bacteria and enhances lytic activity of antibody-activated complement on some gram-negative bacteria such as *E. coli* [30, 55]. Lactoferrin is an iron-binding protein in nasal secretions that inhibits bacterial growth of organisms that depend on iron for their metabolism, such as facultative and aerobic gram-positive and -negative bacteria as well as *Candida albicans*, which increases in the presence of secretory IgA [30, 55]. Neither lysozyme and lactoferrin have any effect against viral infections [30]. Lactoperoxidase acts on peroxide and oxidized forms of thiocyanate to form molecules that are toxic to bacteria [55].

Other important molecules include secretory leukoprotease inhibitor, uric acid, peroxidase, aminopeptidase, secretory phospholipase A2, and defensins [30]. Human beta-defensin (hBD)-1 is expressed constitutively in epithelial cells and have broad antibacterial and antifungal activity; hBD-2 and 3 are expressed in response to bacterial and other forms of inflammation [55]. Nitric oxide is present in high concentrations in the nasal cavity and sinuses and also plays an important role in defense [30]. The complement system consists of a network of over 30 proteins that play a critical role in the nasal innate immune response by assisting with opsonization by phagocytes of viruses and bacteria, activation of phagocytic cells, and lysis of bacteria and infected cells [30].

Nonspecific immune responses occur if the above initial defense systems are broken down. These immune responses are manifested as the release of bioactive and chemotactic factors resulting in increased migration of inflammatory cells into the mucosa, increased vascular permeability, and hyperemia [30]. Increased blood flow carries numerous plasma proteins to the nasal mucosa including immunoglobulins, complement, and proteases and helps to rid the nasal cavity of microorganisms [30]. Table 2.1 summarizes the specific and nonspecific mechanical, humoral, and cellular defense mechanisms in the nose.

Toll-like receptors (TLRs) are transmembrane proteins that function as pathogen-recognizing receptors (PRRs) capable of interacting with conserved domains on microorganisms, referred to as pathogenesis-associated molecular patterns (PAMPs) [55]. PAMPs include protein (TLR4, 5), lipid or lipoprotein (TLR1, 2), and nucleic acid (TLR9) motifs [55]. Activation of TLRs results in activation of NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) and transcription resulting in subsequent production of a spectrum of proinflammatory cytokines (including IL-1α, IL-6, IL-12, TNFα), anti-inflammatory cytokines (including IL-10, TGF-β), and chemokines (including RANTES, MIP-1, IL-8). These cytokines and chemokines provide nonspecific protection to the host [55].

Table 2.1 Defense mechanisms of the upper airways

Defense	Humoral	Cellular
Mechanical	Mucus	Ciliary epithelium
Nonspecific immune responses	Complement, lysozyme, lactoferrin	Granulocytes, macrophages
Specific immune responses	Immunoglobulins	Lymphocytes

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Bacterial clearance requires recruitment and activation of inflammatory cells such as neutrophils and macrophages at the site of inflammation [30]. Recruitment and activation require a well-coordinated series of events, including increased expression of leukocyte and vascular adhesion molecules and the establishment of chemotactic gradients generated by the release of proinflammatory cytokines and chemokines [30]. Acute inflammation initially manifests as increased neutrophils, which migrate to the site of inflammation within 24 h, followed by the appearance of macrophages and lymphocytes [30]. Neutrophils have toxic granules containing proteolytic enzymes that, when released, can cause oxidative damage of surrounding tissue leading to inflammation [30]. The oxidative burst created by neutrophils, manifested as increased nitric oxide levels, is an important protective mechanism against unwanted invasive microorganisms [30].

Adaptive Immunity

The humoral adaptive immune response plays an important role in combating infection as well as eliciting specific IgE-mediated responses in susceptible individuals. Mucosa-associated lymphoreticular tissue (MALT) is an aggregate collection of lymphoid cells present throughout the nasopharynx, bronchi, and gastrointestinal tract [55]. In the nasopharynx, dendritic cells process foreign antigens for a presentation and activation of T- and B-lymphocytes [55]. Antigen-stimulated B-lymphocytes migrate to mucosal lymphoreticular tissue where they expand and differentiate into specific immunoglobulin-producing plasma cells [55]. Immunoglobulins are formed in response to proteins as well as the polysaccharide bacterial capsules of organisms like *Haemophilus influenza B* and *Streptococcus pneumoniae* [30].

Elicitation of a specific IgE-mediated allergic response in a genetically susceptible person first requires antigen exposure leading to sensitization, followed by a latency period that can be of a variable length of time [57]. Specific IgE antibodies are bound to high affinity IgE receptors (FcεRI) on mast cells. After re-exposure to the sensitizing allergen, the antigen-binding sites of specific IgE antibodies on mast cells recognize the eight to nine amino acid-relevant sensitizing peptides and are cross-linked, leading to mast cell activation and the release of preformed (such as histamine, platelet activating factor) and newly formed (such as leukotrienes, prostaglandins) bioactive mediators. These bioactive mediators cause vascular and neuroreflex responses characteristic of allergy symptoms, including nasal congestion, postnasal drainage, rhinorrhea, nasal and ocular itching, and sneezing [57].

Pathogenesis of Chronic Rhinosinusitis

Chronic rhinosinusitis (CRS) is a condition characterized by persistent inflammation of the mucosa in the nose and paranasal sinuses [58]. This condition encompasses both polypoid and non-polypoid forms of disease. In a small subset of patients, genetic disorders (such as Kartagener's syndrome and cystic fibrosis) and systemic autoimmune disorders (such as Wegener's granulomatosis and sarcoidosis) account for the underlying inflammation, leading to chronic rhinosinusitis [58]. However, most cases of chronic rhinosinusitis are idiopathic. Proposed mechanisms for CRS included obstruction of the osteomeatal complexes, impaired mucociliary transport, atopy, microbial resistance, and biofilm formation [58, 59]. The *Alternaria* "fungal hypothesis" proposes that *Alternaria*, a common ascomycete fungi genus, is the primary pathogenic trigger of all forms of CRS. In contrast, the *Staphylococcus aureus* "superantigen hypothesis" proposes that colonizing *S. aureus* release superantigenic toxins that can induce direct T and B cell immune responses [58, 60–68]. The primary support for the *Alternaria* hypothesis is the hyperreactivity of peripheral blood mononuclear cells in response to stimulation with supraphysiologic doses of *Alternaria* antigen [58, 69–71]. However, there is little in vitro, in vivo, or clinical evidence to support the fungal hypothesis as the cause of chronic sinus disease [58, 72]. With respect to the superantigen hypothesis, there is currently no evidence to support a role for superantigens causing CRS. Currently, they are considered more a modifier rather than a cause of disease [58, 73].

The immune barrier hypothesis proposes that compromises of the nasal epithelium physical barrier, mucociliary transport, the innate and adaptive immune responses induced by environment irritants, and colonizing and pathogenic organisms lead to chronic inflammation and CRS [58]. Recent evidence supports a role for mutations in genes significant for coding

proteins important for epithelial structure and function in CRS [58, 74, 75]. Evidence for impaired barrier disruption includes decreased tight junction proteins and increased ion permeability in patients with CRS compared to normal controls [58]. This observation is supported by a decrease in SPINK5, a gene that encodes the protease inhibitor LEKT1 (important for maintenance of epithelial barrier function) [58, 74, 75]. A deficiency of this protease inhibitor could lead to increased susceptibility to the intrinsic protease activity of bacteria, fungi, and allergens like dust mites, thereby rendering the host more vulnerable to penetration by foreign proteins and leading to increased inflammation from innate and adaptive immune responses [58, 74, 75]. Similarly, antiproteases like LEKT1 protect epithelial surface receptors (referred to as protease activated receptors or PARS) from exogenous proteases [58, 76]. Protease activity receptor stimulation could lead to increased cytokine and chemokine release and effector cell recruitment to the nose, leading to impaired immune responses [58, 76]. Recent evidence suggests that S100 proteins, which are antimicrobial proteins, are reduced in patients with CRS [58, 77]. CRS has been postulated to be in part caused by a deficiency of these proteins, which are important for antibacterial and antifungal activity, neutrophil and lymphocyte recruitment, and wound healing [58, 74, 75].

Interestingly, toll-like receptor-2 (TLR2) mRNA has been found to be decreased in patients with cystic fibrosis nasal polyps; TLR2 and TLR9 mRNA are decreased in patients with CRS with nasal polyps [58, 78–81]. However, data relating the pathogenic role for TLR and CRS are inconsistent and still remain a theoretical mechanism [58]. IL-22 secreted by Th17 and Th1 cells activates epithelial cells by binding to IL-22R [58, 82, 83]. It has been shown that patients with CRS with nasal polyps have decreased IL-22R and therefore a decreased IL-22 response [58, 84]. This deficiency remains yet another way the innate immune response can be impaired.

Epithelial cells likely play a major role in the pathogenesis of CRS, likely due to their ability to regulate activation of T cells as well as produce cytokines that can activate B cells, dendritic cells, T cells and chemokines that can attract effector cells to the nasal tissue [58, 80]. Epithelial cells also produce and release thymic stromal lymphopoietin (TSLP) in response to viruses such as rhinovirus, which cause T cells to differentiate into Th2 cells. Interestingly, TSLP has been demonstrated to be increased in those individuals who have a deficiency of the protease inhibitor LEK1 [58, 85].

It is clear that numerous immune components and pathways are involved in the pathogenesis of the various forms of rhinosinusitis. These immune mechanisms are discussed in greater detail in Chap. 3.

Conclusions

The upper respiratory tract is a complex anatomic, neurologic, and vascular network that provides structural, physiologic, and immune defense barriers to protect the host from the external environment. When one or more of these processes break down, then many predictable and at times unpredictable medical consequences can occur. Correct diagnosis and appropriate treatment of patients with allergic, nonallergic, or mixed rhinitis to prevent unchecked nasal inflammation will often prevent or ameliorate the progression to chronic rhinosinusitis. Future research investigating the pathogenesis and mechanism(s) of rhinitis subtypes and CRS will provide better opportunities for developing novel therapies to improve our management of this common clinical condition.

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