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Review Article

Physiology and pathophysiology of respiratory mucosa of the nose and the paranasal sinuses

Abstract

In this review, anatomy and physiology of the respiratory mucosa of nose and paranasal sinuses are summarized under the aspect of its clinical significance. Basics of endonasal cleaning including mucociliary clearance and nasal reflexes, as well as defence mechanisms are explained. Physiological wound healing, aspects of endonasal topical medical therapy and typical diagnostic procedures to evaluate the respiratory functions are presented. Finally, the pathophysiologies of different subtypes of non-allergic rhinitis are outlined together with treatment recommendations.

Keywords: physiology, pathophysiology, mucociliary clearance, non-allergic rhinitis, nasal cycle

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1 Introduction

Respiratory mucosa of nose and paranasal sinuses are subject of daily routine of the ENT specialist. Restoration of the respiratory function is the aim of both conservative and surgical therapies. Therefore, the role of respiratory mucosa has been put into the centre of this paper. For ventilation aspects, it is referred to the article of Lindemann and Keck. From the perspective of clinical relevance, profound knowledge and innovative research results regarding anatomy (with embryology), physiological functions and their diagnostic tests are presented. Due to the amount of different pathophysiologies, only selected disorders are summarised with regard to their impaired function of the respiratory mucosa and therapy strategies are outlined. To facilitate coherent reading, references to the more surgically orientated papers are included.

2 Embryology

During the 6th week of embryological development, ectodermal thickened parts of the frontobasal prominence invaginate resulting in two symmetrical nasal placodes. Nasal pits divide the placodes (*Fovea nasalis*) into medial and lateral nasal processes [1]. This deepens, becoming the nasal sac – an ectodermally lined cavity, which is divided into two halves by the primary septum. Between weeks 6 and 7, a membrane separates the oral cavity from the primitive choanae. This resolves due to immigration of mesenchymal cells. The mesenchymal septum (secondary septum) grows caudally, merging with the palate and enlarging the embryonic structures of the nose. In weeks 7 and 8, first cartilaginous cells are identified, including parts of the turbinates. Starting in the 3rd month, mucosal lining migrates into the lateral nasal wall priming the development of the paranasal sinuses. By cell differentiation and maturation of the respiratory mucosa, detection of glands is possible after the 4th month of intrauterine development. During the 5th month of fetal development, ossification of the nose starts, including the previously cartilaginous areas of the turbinates. Influenced by various transcriptional factors, including Sox [2], cells differentiate further into the various cell types included in respiratory mucosa. For ciliogenesis and their pathophysiologies, several influencing factors play their part to a certain extent [3]. In animal models, the regulation of ciliogenesis is proven for FoxJ1, TTC25-GFP, Mig12-GFP, OFD 1, Ftm and Talpid3 [4], [5], [6]. Deletion of Talpid3, which works via the hedgehog signaling pathway, will inhibit the development of cilia completely [6], while disorders of the to hedgehog signaling pathway alone result in abnormal or degenerated cilia. A specific disruption of Talpid3 has been suggested as animal model for primary ciliary dyskinesia with polycystic kidneys [6]. For anchorage and orientation of cilia, further factors have been identified, such as FoxJ1 [4].

3 Anatomical and histological structures of the respiratory mucosa

Dorsally to the vestibulum nasi, which is lined with squamous epithelium, lies the nasal cavity. This is coated with 120 cm^2 of pseudostratified columnar ciliated epithelium. The respiratory mucosa shows a thickness of 0.3–5 mm. Three (rarely four) turbinates protrude into the nasal cavity showing the thickest respiratory mucosa on their medial surface. In respiratory mucosa, several **specific cell types** can be identified. All cells are attached on the basal membrane. *Basal cells* lie on the membrane and show non contact with the epithelial surface. Their specific morphologic features are desmosomes for cell adhesion.

Columnar cells represent up to 70% of the epithelium and have 300–400 microvilli on their surface. The general principle of microvilli is the increase in surface area to retain moisture and to prevent drying of the surface [7]. Another 20–50% of epithelial cells are ciliated cell possessing 200–300 cilia on their surface, which are the morphological substrate of the mucociliary clearance. *Cilia* are 5 to 10 µm long and 250 nm thick and sheated in a plasma membrane. Within cilia, nine double tubules are arranged around two sheated central tubules. An inner sheath surrounds the central tubules. Outer pairs of microtubules (A and B-tubules) are connected to each other by nexin bridges and dynein arms and to the central pair by radial spokes. Bending of the cilia occurs as an ATP-consuming mechanism, called "sliding filament mechanism". Existence of non-motile cilia is discussed in cells without central double tubules acting as sensory antenna. Cilia are covered by a 10–15 µm thick layer of mucus, filling also the spaces between cilia [8]. In respiratory mucosa, goblet cells and seromucous glands in the adjacent connective tissue are typically found. *Goblet cells* represent 5–15% of cells in the respiratory mucosa and produce secretions for the endonasal mucus together with the submucosal glands. Next to their form, existence of microvilli and a small opening, called stoma, are their characteristics. They differentiate out of non-ciliated cells [9]. In connective tissue, 20–80 *anterior serous glands* with 2–20 mm long ducts opening into small crypts are visible. Their importance is unclear [10]. About 90,000 *seromucous glands* possess ducts lined by cubical epithelium and are organised in two layers. Moreover, 20–50 intraepithelial mucous glands are detected around a central lumen. Their contribution to mucus production is regarded as small.

At the anterior septum, epithelium is underlined by a 1.5 mm thick tissue of convoluted vessels, called Locus Kieselbachii. In addition, venous plexus are seen in the area of the inferior turbinate and the nasal septum, acting as swell bodies during the nasal cycle.

Dimensional orientation for healthy respiratory mucosa in a biopsy indicate a subepithelial capillary network with a diameter of 0.025 mm, below a 1.6–10 µm thick basal membrane covered with a epithelium showing 40–100 µm height. Ciliated cells have a height of 15–20 µm and a width of 15 µm. Human cilia are about 6 µm long and 0.3 µm thick. Microvilli are 0.5–4 µm long and about 0.1 µm thick. These reference data are limited due to a high degree of variation depending on the endonasal localisation of cells.

As migrating cells, more T- than B-lymphocytes are detectable in subepithelial healthy tissue. The ratio of T-helper to regulatory T-cells (T-suppressor cells) is subepithelial 3:1 and in deeper layers 2:1 [11]. Natural killer cells are rare. 50% of IL-5-positive cells and 100% of IL-6 positive cells are mast cells [12].

3.1 Vascular supply

Branches of the maxillary artery are responsible for the arterial supply, including the sphenopalatine artery, the posterior lateral nasal artery and the infraorbital artery. Venous blood drainage occurs along the facial vein after unification of the supratrochlear and supraorbital veins.

3.2 Lymphatic vessels

Superficial and deep lymphatic vessels (15–200 µm) can be demonstrated in respiratory mucosa, which lead in the middle nasal meatus to the natural ostium of the maxillary sinus. Their density decreases from top to bottom of the middle nasal meatus; their number is higher in the paranasal sinuses than the nose. Several connections are visible between lymphatic vessels and the vascular supply [13]. More lymphatic vessels begin at the nasal floor and the turbinates and converge in the medal inferior area of the turbinates. From this area, lymphatic vessels pass retropharyngeally and to the parapharyngeal space, reaching lymph nodes of both anatomic areas [14].

3.3 Innervation und regulation

Autonomic innervation takes place via the posterior ethmoidal nerve. Sympathetic innervation of the nasal mucosa is supplied via branches of the superior cervical ganglion passing along with the nerve of the pterygoid canal [15]. Hypothalamic stimulation will provoke a vasoconstriction [16]. Glands of the nasal mucosa, as well as the vessels, have a direct parasympathetic innervation leading to direct parasympathetic increase of nasal secretions via transsudation and exsudation [17]. Various cotransmitters were detected in nasal respiratory mucosa [18]. Parasympathetic neurons have mostly vasointestinal peptide (VIP) as cotransmitter to acetylcholine [19]. VIP is stimulating secretions (more serous than mucous) and vasodilatating at arterial and sinusoidal vessels [20]. Sympathetic neurons contain neuropeptide Y (NPY) as key cotransmitter to noradernaline and innervate predominantly arterioles and arteriovenous anastomoses. Liberation of NPY results in prolonged vasoconstriction, together with decongestion of venous sinusoidal vessels [21]. Substance P acts as Co-transmitter for Neurokinin A [22] and Calcitonin Gene-Related Peptide (CGRP) at arteries. The high number of cotransmitters is regarded as a possibility to adjust congestion of the nose delicately. Its disturbance may contribute to the aetiology of various, non-allergic rhinitis disorders [23].

An additional way of regulation is provided by endothelial nitric oxide synthase (NO-Synthetase; NOS; producing NO in the tissue) located in capillaries and arterioles near glands and nerve fibres around seromucous glands. As cotransmitter in parasympathetic nerve fibres, nitric oxide (NO) shows a neuromodulating and vasodilatating effect stimulating also seromucous glands [24]. As a con-

sequence, both via nerve fibres and the endothelium, the degree of endonasal congestion can be altered [24].

4 Physiology of respiratory mucosa

Every day about 12,000 litre airflow is passing through the adult nose [25] and being hydrated (cf. article of Lindemann and Keck http://www.egms.de/en/journals/cto/2011-9/cto000072.shtml) and filtered. The nose is of extreme importance to protect the distal airways from deterious influence of gas, aerosol and pathogens. The nose and paranasal sinuses also act as area of voice resonance and produce nitric oxide (NO) for regulation of lower airways. Finally, the nose acts as chemosensoric organ responsible for smelling.

4.1 Cleaning function

The nasal passage filters 95% of particles with a diameter of more than 15 µm out of inspired air [25]. The cleaning function for pollen and dust of smaller dimensions is severely diminished but not abolished [26]. Liquids inhaled as aerosol will be eliminated from the upper airway if inspirited through the nose to 95% (mouth: 50%). Dosage of inhaled gas measured in the pulmonary alveoli will be diminished from 6–10% during mouth breathing to 0.9% during nasal breathing [27].

4.1.1 Sneeze reflex

Sneezing aims for elimination of particles from the nose. This reflex is most complexly coordinated affecting also the solitary nucleus [28]. Typically, sneezing will be provoked by foreign bodies in the anterior parts of the nose, which stimulate H1-receptors of trigeminal C-fibres [29]. After inspiration [30] ceases to allow glottic closure, sudden contraction of abdominal and breast muscles happens. After glottal opening, liquid drops or foreign bodies are tossed from the nose at velocities of 50 m/s [31]. This type of reflex can be triggered by light called photic sneeze reflex.

4.1.2 Nasolacrimal reflex

Nasolacrimal reflex results after chemical or mechanical stimulation of the nasal respiratory mucosa in increased lacrimal secretion. Afferent, C-fibre nociceptive neurons run together with the trigeminal nerve to the superior salivary nucleus, continuing via the geniculate ganglion, the large superficial petrosal nerve and through the pterygoid canal to the sphenopalatine ganglion. Cholinergic fibres reach together with the maxillary nerve the lacrimal gland [29]. Stimulation of one side leads also to a physiological, weaker reaction contralaterally [28] (for more information regarding reflexes: [32]).

4.2 Unspecific defense mechanism

Static and dynamic mechanisms (structure of the epithelium, configuration of endonasal airflow) and regulated physical and chemical mechanisms (structure and content of nasal mucus, mucociliary clearance, nasal cycle, plasma extravasation by NO [33]) assist in immune defense. Epithelial cells have a key position as a physical barrier and are the mainly responsible cells for maintaining the mucociliary transport. Respiratory mucosa of the nose is characterised by a high enzymatic activity, especially of the cytochrome P450 system [34]. NO, produced mainly by the mucosa of the sinuses and released at the surface, is discussed to have bactericidal effects in the airway [35].

4.2.1 Mucociliary clearance (MCC)

Mucociliary clearance is defined as cleaning of upper and lower airway by interaction of nasal mucus (about 200 g or 2 litre/day produced by the respiratory mucosa) [36] and ciliary beating. Number, structure and coordinated stroke of the cilia are as important as the biochemical, physical and chemical properties of the mucus. Nasal mucus has a weak, flexible, three-dimensional network formed from linear, hydrated mucin molecules. This is enhanced by disulfide bonds and secondary chemical connections between ions [37]. To prevent infections, mucus is slightly acid with a physiological pH-value of 5.5–6.5 and has a small capacity as chemical buffer. Via hydroxyl- (OH-) groups and oligosaccharide chains, negatively charged groups, the highly hydrated form of nasal mucus and the embedded network of linear and flexible glycoproteins, nasal mucus may form unspecific secondary connections, e.g. with pathogens or drugs. Viscoelasticity, adhesive and cohesive properties of nasal mucus are mainly determined by the glycoprotein compound [37]: They comprise a protein backbone covalently bound to oligosaccharide chains at a molecular mass of about 200 Kilodalton (kDa) and are responsible for the negative electric charge of the nasal mucus.
Optimal mucociliary clearance is achieved at 37 ° Celsius and 100% relative humidity (absolute: 44 mg/dm^3). Nasal Mucus is about 10–15 µm thick [38] and has two layers: the lower, 6 µm thick liquid layer (also called: periciliary liquid) is covered by the more viscous gel phase. The gel phase is structured by embedded mucin. Height of the liquid layers has tremendous effect of the efficiency of the ciliary stroke [39]. Nasal mucus contains 90% water and glycoproteins as well as ions (cf. Table 1). It is produced by submucosal, seromucous glands, goblet cells, transsudation of blood plasma, mucosal tissue fluid and tear fluid. Due to transsudate, most proteins detectable in serum may also be demonstrated in nasal secretions. In cases of local inflammation, the amount of transsudate and their respective proteins will increase.

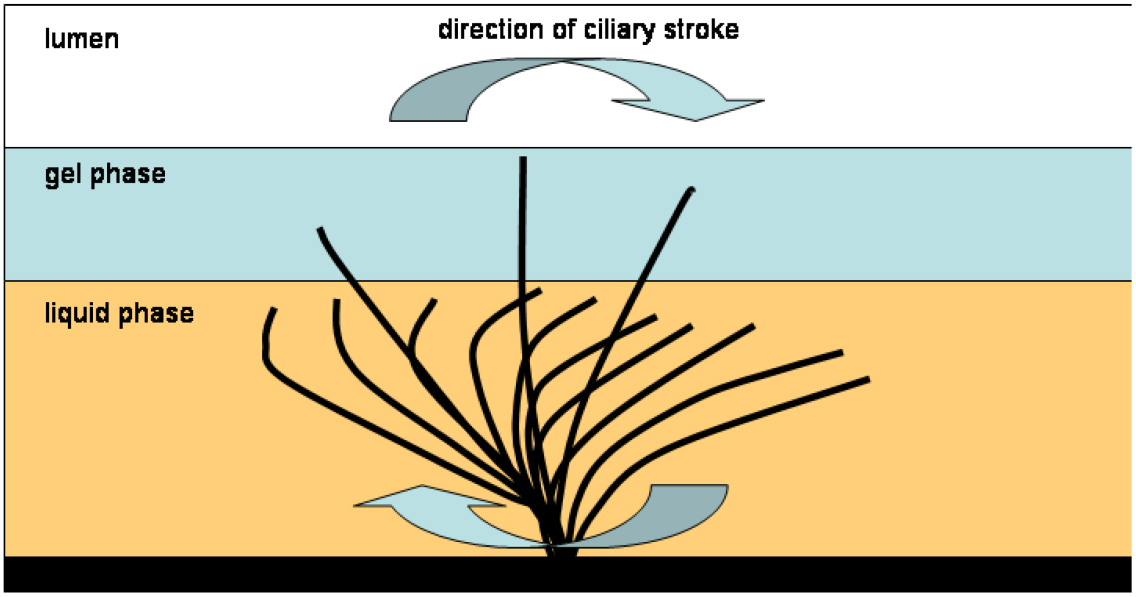

Figure 1: Schematic drawing of the ciliary stroke in nasal mucus (modified by [10])

Table 1: Concentration of ions in the nasal mucus [36]

Electrolyte	Concentration
sodium	128 to 150 mmol
potassium	17 to 41 mmol
calcium	4 mmol
magnesium	5 mmol
chloride	139 mmol

Due to the coordinated, metachronous ciliary stroke (cf. Figure 1), the mucus layer will be moved at a velocity of 2–25 mm/min [40]. In detail, control of the ciliary beat frequency is unknown. However, ciliary beat frequency will increase if cells are exposed to NO or a mechanical, calcium-mediated stimulus [41], whereas IL-13 will decrease the frequency [42]. In addition, intensive physical activity will decrease mucociliary clearance [43].

Particles bound to the mucus layer will be transported towards the pharynx passing the hiatus semilunaris. A second stream runs from the sphenoid sinus to the posterior ethmoid towards the choanae. Within a paranasal sinus, mucociliary clearance will always be orientated towards the primary natural opening [44], while accessory ostia are bypassed by the mucociliary clearance.

Next to water and electrolytes, immune globulin (Ig) G and A can be detected in high concentrations in nasal mucus. Secretoric Ig-A (up to 80% Ig-A1; among others against Coxsackie viruses and polio virus) is an obligatory ingredient and may provide up to 50% of the total protein of nasal secretions [45]. It is secreted into the tissue from plasma cells located near the basal membrane of the glands to bind and neutralise the antigen. Due to this effect, Ig-A is discussed as an important factor in pathogenic microbiological colonisation of respiratory mucosa.

Ig-G is synthesised in nasal submucosa and secreted after muscarinergic stimulation or exposition to histamine [46]. In physiology, Ig-M is not detectable, while Ig-E levels are below serum concentration. Moreover, lipids (e.g. surfactant [0.8%] and carboanhydrase [1%]) may be detected.

Application of sodium-chloride leads to increase of ciliary beat frequency [47] and thereby improvement of mucociliary clearance. According to a Cochrane review [48], salt concentration is of minor importance. On the other hand – depending on the pathophysiology – hypertonic solutions in chronic rhinosinusitis and isotonic salty solutions in acute sinusitis may be beneficial [49].

4.3 Humoral mechanisms

Unspecific substances for immune defense are localised in the epithelium and in nasal secretions. These include lysozyme (attacks peptidoglykans in the cell wall of gram positive bacteria), lactoferrin (inhibits bacterial growth) [50] and oligosaccharides (bind bacteria) [51]. Furthermore, neutrophil granulocytes produce proteases and hydrolases to destroy the cell membrane of bacteria and viruses. The 20 proteins of the complement system are detectable in blood and in tissue. They destroy foreign structures and marker pathogens for phagocytosis. The kinin-kallikrein system activates an inflammatory response after viral invasion by vasodilatation. Intracellular interferon impedes viral replication and inhibits ongoing viral infection.

4.4 Cellular mechanisms

Neutrophil granulocytes, monocytes and macrophages are cellular components of the host defense using phagocytosis in the subepithelial tissue of the nose and sinuses. Immigrated natural killer cells destroy infected cells. Under physiologic conditions, importance of cellular mechanisms is subordinated to unspecific components of immune defense. In case of pathogen invasion, multiple immunocompetent cells immigrate, and increase the importance of cellular defense. The specific immune

Table 2: Normal microbiological findings in the nose of adults

	Araujo et al. [309]	Gordts et al. [310]	Gwaltney [311]	Kirtsreesakul et al. [312]	Klossek et al [313]	Overall
N	23	52		90	139	**304**
Rate of detection		75%		94.5%	81.3%	**84.3%**
Corynebacterium spp.		23%		9.3%	20%	**15.8%**
Gram-negative Bacteria			13			
H. influenzae			20%		1.4%	**0.7%**
coagulase-negative Staphylococcus	56%	35%		61.6%	50%	
Neisseria meningitidis			15%			
S. aureus	39%	8%	12%	11.6%	12%	**13.2%**
Str. pneumoniae	9%		20%		1.4%	**1.3%**

Table 3: Normal microbiological findings in the nose of children

	Gordts et al. [310]	Gwaltney [311]
N	52	
Rate of detection	75%	
Diphteroids		40%
Gram-negative Bacteria		6%
H. influenzae	40%	45%
M. catarrhalis	34%	
Neisseria meningitidis		5%
S. aureus		40%
Str. pneumoniae	50%	70%
Str. pyogenes		25%

system in nasal respiratory mucosa is part of the lymphatic system (*mucosa-associated lymphatic tissue;* MALT).

4.5 Nasal cycle

Nasal cycle is defined as spontaneous and reciprocal change of nasal congestion without change of the total nasal airflow. It was first described by R. Kayser in 1895 [52]. According to literature, nasal cycle can be detected in 70–90% of humans [53], [54].

The nasal cycle is regulated by the hypothalamus [55], with efferents running along the vidian nerve and showing an asymmetrical activity in controls [56]. Changes of volume in the erectile tissue of the septum, the inferior and middle turbinates and even in the paranasal sinuses can be demonstrated [57].

The working and resting phase can be easily distinguished. During the working phase the nasal passage is characterised by an increased hydraulic diameter, passage of nasal airflow and turbulence, while resistance is decreased. During resting phase resistance is raised, while hydraulic diameter, transnasal airflow and turbulence are diminished [53]. Mucociliary clearance is enhanced by factor 2.5 in a working phase in comparison to the contralateral resting phase [58]. Resting phase allows gathering of mucosal moisture [59], [60]. Mucosal cleaning and regeneration as well as improved host defense are discussed as advantageous during the evolution, eventually leading to the development of the nasal cycle [61].

If analysed more closely, contralateral working and resting phases with regular change ('classical type') can be differentiated from parallel working and resting phases ('in-concert type') and undefined phases ('irregular type'). The frequency of nasal cycle phase classified as classical type decreases with age [62]. There is a high amount of variation in the duration of phases reported (duration of phase: 1.6 h [54] 1–2.5 h [63]; 1.5–10 h [64]; 2.5 h [65], 2.9 h [66], 3–4 h [67]; 3–5 h [68]; 4.3 h [69]; 1–5–10 h [53]; 7 h [70]). A relationship to the individual duration of rapid eye movements (REM) in sleep has been demonstrated [71].

The change from one phase to another happens quite rapidly within a few minutes. This is helpful in distinguishing changes of nasal congestion caused by the nasal cycle from those due to change of body position [68], [72], [73], [74], or physical activity mediated though the adrenergic sympathetic system.

4.6 Microbiological colonisation

In the nose, a physiologic, multi-microbial colonisation exists. Specific articles are summarised in Table 2 and Table 3. Normal microflora and pathogens are differentiated from each other by their ability to release a Th1/2-mediated immune reaction. Commensal bacteria may pass the epithelial barrier and will only evoke a minimal T-cell activation without effects on regulatory T-cells (CD25FoxP3) [75].

Paranasal sinuses are sterile under physiologic conditions [76]. In 50 cultures obtained during nasendoscopy of 25 healthy controls, 32 bacteria were detected such as Staphylococcus aureus, coagulase-negative Staphylococci, Corynebacteria and Propionibacterium acnes [77].

After sinus surgery, detection rate increased to 97% in patients with clinically normal endoscopic findings. Here, coagulase-negative Staphylococci (69%), Corynebacteria (25%), S. aureus (31%) and Pseudomonas aeruginosa (3%) can be identified [78]. Fungus is also part of normal microflora of nose and paranasal sinuses. While 20% of postnatal babies have a positive fungal culture in nasal secretions, this detection rate increased to 94% at the age of 4 months [79].
Methods of choice to detect colonisation are endoscopically guided aspirate specimens or sinus punctures. In comparison to the latter, accepted as gold standard, cultures from the middle nasal meatus showed a sensitivity of 80% and specificity of 100% with regard to their detection rate (positive predictive value: 100%; negative predictive value 78.6%). If analysed prospectively, results will match in 88.5%, suggesting that endoscopically guided aspiration will be sufficient while resulting in minor burden for the patient [80].
In 70% of people working in a hospital, S. aureus can be detected in a nasal swab. To facilitate defense of the respiratory mucosa, exposure to commensal bacteria has been evaluated. Medical doctors may terminate their colonisation with methicillin-sensitive S. aureus, if inoculated with Corynebacteria spp., also decreasing the risk of methicillin-resistant S. aureus infection [81].

4.7 Regeneration and wound healing

The detailed sequence of wound healing of the nasal respiratory mucosa is delicately regulated [82]. In the following, relevant procedures during course of wound healing with evident clinical aspects will be presented.
Aim of wound healing is structural and functional repair of the tissue defect. Fundamental differences between partial and full-thickness defects (affecting all layers) of respiratory mucosa have been reported [83]: Preservation of the basal membrane results in rapid restoration of normal epithelial height [84], while its destruction will lead to a repair process taking weeks to months [84]. Deeper wounds will also result in scar formation, with its extent being quite variable [85]. Duration of wound healing of respiratory mucosa is estimated as 6 months, and sometimes even longer [86]. Physiological wound repair happens in different stages, which may temporarily overlap and macroscopic appearances show fluent transition. The stages are regulated by a variety of cytokines and growth factors.

4.7.1 Temporal sequence of wound healing

Based on the endoscopic aspect of the wound area, the stages of blood crusting (until day 10), obstructive lymphoedema (until day 30), and mesenchymal growth (up to three months) can be distinguished with subsequent scar formation [87].

Coagulation and haemostasis

The trauma leads to vessel injury and release of blood. Thrombocytes aggregate and release PDGF (Platelet-derived Growth Factor). In parallel, vasoconstriction occurs to diminish the injury of the vessel wall. Platelets activate the coagulation cascade to close the defect with a thrombus [88]. Subsequently, the thrombus dehydrates and resolves into crusts. Neutrophil granulocytes immigrate and release pro-inflammatory cytokines. This leads to vasodilatation and increase of vessel permeability with oedema formation. Platelets integrated into the fibrin net chemotactically attract macrophages [89], fibroblasts and endothelial cells to the defect [90]. Due to repeated microtraumata, this coagulation cascade may be activated on several occasions during the first one to two weeks [91].

Inflammatory phase

Next to neutrophil granulocytes, the thrombus is dissolved by immigrated monocytes and macrophages. Neutrophils release more proliferative cytokines (e.g. Transforming Growth Factor (TGF)-α, TGF β 1, IL-1). Cell migration shows a peak for neutrophil granulocytes after 2 days, for monocytes and macrophages after 4–5 days, and for lymphocytes after six days. Monocytes differentiate to tissue macrophages and eliminate microorganisms and debris. They also regulate enzymatic tissue disaggregation. Macrophages control the transition from the inflammatory to the proliferative phase by production of growth factors, such as tumor necrosis factor (TNF)-α [90].

Proliferative phase

The defect will be filled with granulation tissue. This happens by proliferation of connective tissue, with synthesis, degradation, and alteration of collagen, angiogenesis, production of glycosaminoglycans and epithelial coverage. In addition, osteoneogenesis can be observed [86], [92], [93]. This phase starts about three days after the initial trauma and lasts for at least 2–3 weeks. Fibroblasts produce among other substrates collagens, a main component of the extracellular matrix (ECM) in wounds detectable since day three after injury [94]. Collagen bundles are built by rearrangement of collagen fibril orientation. Due to better organisation of collagen, resistance of the wound against shear is increased. One year after injury, remodelling processes of collagen are still detectable. Due to the close molecular connections of fibroblasts, ECM and collagen synthesis, fibroblasts are regarded as main source of adhesions.
As early as 24 hours after epithelial injury [95], epithelial cells migrate concentrically at a velocity of 20 µm/h [92] into the defect [92], [96]. Until epithelial closure, depending on the defect's size more than two weeks will pass [97]. In parallel, changes in ECM proteins, such as matrix metalloproteinases (MMPs) and release of more cytokines take place. MMP-9 (see below) is of special interest. Re-

innervation of mucosal glands of the paranasal sinuses is detectable after 4–8 weeks [98].

Phase of remodelling

During this phase, granulation tissue is replaced by scar formation. "Airway remodelling" is frequently used as general term for continuous adaptation of mucosa during the course of a chronic inflammation (e.g. bronchial asthma or chronic sinusitis). In contrast, remodelling in wound healing is defined as a process of collagen degradation, conversion and synthesis and has a limited duration. Type-3 collagen is replaced by the more firm type-1 collagen. This process starts after 48–72 hours and is detectable by increased rate of mitosis and hyperplasia at the wound edges with increased activity of MMPs [95]. Continuous synthesis of firm collagen, its stabilization with cross-linking and the aggregation to thicker bundles as well as its coordinated orientation, increases the strength of the reconstruction.
Three months [99] to two years [100] takes "wound healing", if the duration is measured as time interval from injury (e.g. during surgery) to accomplishment of the optimal and final functional result. Especially in adults [101], the regenerated tissue shows less serous glands [97] with increased number of excretory ducts [102]. Subepithelial stroma of the regenerated tissue is thicker and the number of vessels is increased [103]. Only slightly more than half of all patients show a normal mucociliary clearance 18 months after sinus surgery if evaluated with nuclear medicine techniques [104].

4.7.2 Relevance of matrix Metalloproteinase-9 (MMP-9) as indicator of wound healing

MMP-9 belongs to the family of matrix metalloproteinases, which may activate each other in-vitro synergistically. This matrix metalloproteinases is a type IV collagenase and is also called Gelatinase B [105]. After a stimulus, e.g. an injury, a 92 kDa proenzyme is released which can be activated by removal of the propeptide resulting in the active 82 kDa enzyme [106]. MMP-9 is detectable only during the first days after injury. Generally, increased levels of MMP-9 determined in wound secretion are associated with problems in reepitheliasation [107], [108].
With regard to sinus surgery, MMP-9 was presented as predictive marker for healing quality. High concentrations of MMP-9 go together with worse healing quality and distinct oedema [109].

4.7.3 Risk factors for deteriorated wound healing

Wound healing is above all, complicated by local disturbances like hypoxia [110] or low-nutrition. Systemic disorders (e.g. diabetes mellitus (see below), tumours, immune deficiencies [111], cystic fibrosis, primary ciliary dyskinesia, aspirin intolerance, bronchial asthma, gastroesophageal reflux, autoimmune diseases), cytotoxic or immunosuppressive medication, allergic disposition or active or passive smoking [112] may impede wound healing.
This may result in exceeding granulation tissue, which favours adhesion formation.
Eosinophilic histology was identified as risk factor for frontal ostium restenosis after type III drainage according to Draf [113]. Unfortunately, practical benefit of this finding is limited due to the high frequency of eosinophilic inflammation in chronic sinusitis.

4.8 Rhinologic functional diagnostics

4.8.1 Anterior rhinoscopy

During anterior rhinoscopy, blood vessel pattern and quality of nasal mucosa with colour and properties of secretion are evaluated. To facilitate better estimation of nasal congestion, inspection before and after decongestion is mandatory. Endonasal resistance is assessed based on configuration and extent of ventilated nasal areas. Bachmann's test (introduction of a cotton-tipped swab in the upper nasal valve) as well as Cottle's test, enlarge the area of the nasal isthmus. They are rated as too unreliable and observer dependent to diagnose isthmus stenosis. Visual judgement of the inflow areas has been recommended [114], but is also observer dependent.

4.8.2 Endoscopy und videoendoscopy

During standardised nasendoscopy, after inspection of the inferior nasal meatus, the middle nasal meatus with middle turbinate, the anterior wall of the sphenoid sinus, sphenoethmoidal recessus and the superior nasal meatus with olfactory groove are inspected. As videoendoscopy [115] digital documentation is possible for analysis by independent observers [116].

4.8.3 Clinical imaging

The clinical importance of imaging modalities such as computer tomography (CT) and magnetic resonance imaging (MRI) lies in the possibility to verify mucosal swelling of the sinuses [117]. Extent and type of sinusitis [118], presence of invasive processes such as neoplasia and invasive fungal sinusitis (MRI: [119]) or non-invasive fungal sinusitis [120] can be evaluated. A positive aspect is its high reliability up to a time interval of more than 120 days [121]].
The relative importance of sonography is limited to follow-up of acute sinusitis and special problems during pregnancy and childhood. Sensitivity and specificity of ultrasound of the sinuses is not sufficient for detection of mucosal swelling in clinical routine [122]. For the same reason, employment of conventional x-rays in chronic sinusitis is discouraged [117].
Innovative studies report a high resolution of optical coherence tomography with regard to nasal mucosa [123],

suggesting this technique as most interesting alternative in future.

4.8.4 Diagnostic tests of mucociliary clearance in-vivo

Saccharin test

For this most commonly employed global assessment of mucociliary clearance, saccharin particles (usually a few crystals) are placed on the head of the inferior turbinate. Time intervall until the patient reports a sweet gustatoric sensation is measured. This technically easy and inexpensive test is lacking any side-effect. It may be employed in children, but is dependent on a normal sense of taste. A time interval from placement of saccharin to taste sensation of ≤30 min. is regarded as physiological; a time interval exceeding one hour as pathological [124]. Repeated measurements may vary by about 6 min. [125]. The long duration of this test is commonly regarded as disadvantagous. As modification, application of a solution has been suggested, shortening the transport time to about 10 min [126].

Nuclear medical tests

Using technetium 99, mucociliary clearance can be evaluated by means of nuclear medicine [127]. This sensitive method comes along with increased technical effort [128] and radioactive contamination, but is due to its reliability [129] still employed for special questions [130], [131].

Particle tests

Titanium dioxide (TiO2) is a 500 µm TiO2 particle, which can be placed on the mucosa to measure its velocity (in mm/min) in vivo. Standardised reference values have been reported for the nasal floor, employment is due to the small weight supposed to be possible on the whole area of respiratory mucosa. The short duration of this test is favourable [132]. In analogy to earlier studies using resin [128], [133], this test is believed to particularly evaluate the gel phase of the nasal mucus. General advantage of tests employing particles are: independence of the sense of taste, short duration of testing, and in some cases less technical effort and less costs.

4.8.5 In-vitro tests for parts of mucociliary clearance

Ciliary beat frequency (normal range: 7–12 Hz) can be determined after removal of ciliated cells (e.g. by nasal curettage or brushing [134]) using a phase-contrast microscope. An average value for at least four cells should be calculated when this frequently employed technique is reported [47], [135]. To increase reliability and allow for quicker analysis, a specially developed digital photometry has been reported [136].

If a hereditary disorder of cilia function is suspected, cell culture of ciliated cells has been recommended [137]. This time-consuming technique is only available in very few centres, but shows nearly ideal sensitivity and specificity [138].

Ingredients of nasal mucus can be evaluated in-vitro using ELISA [139], [140]. As well, the determination of certain cytokines is possible in nasal secretions [141]. However these techniques are not employed in clinical daily routine.

Mucosal biopsy may be subjected to conventional histology to aid in differential diagnoses and to assess inflammatory activity (based on the number of inflammatory cells). Furthermore, biopsies may facilitate more precise classification of chronic rhinitis (eosinophil/neutrophil inflammation). In addition, scanning electron microscopy can be used to visualise the ultrastructural surface of respiratory mucosa and nasal mucus. It is not appropriate for specific detection of biofilms [142].

Using transmission electron microscopy (TEM), changes within the cilia going together with altered dynein structures are reliably detected. Gathering specimens is reliably accomplished by nasal brushing [134]. Costs and expenditure of time are unfavourable. Furthermore, TEM is highly specific in detection of biofilms but at the cost of immense work load [142].

Confocal laser scanning microscopy (CLSM) [51] is a less costly technique to detect biofilms with superior sensitivity and specificity. For CLSM, the specimen is incubated with fluorescent cell markers (e.g. Soty 9 and Propidium Iodide as differential staining for living and dead cells). Afterwards, it is inspected three dimensionally using a laser beam. Different wavelengths of the laser stimulate the cell markers, resulting in coloured light emission depending on the functional state of the cells. Analysing the surface of larger specimens can be accomplished in short time and with reasonable workload [51], [143].

4.8.6 Rhinomanometry (RMM)

Rhinomanometry (RMM) allows objective measurement of nasal airflow synchronous to nasal breathing based on the transnasal pressure difference. Airtight placement of a pressure hose at the nostril (e.g. by sticky tape) elongates the pressure column to the choanae and serves as reference value for the examined contralateral side [144]. Deformities of the nasal inflow area should be avoided, due to their associated measurement error. If measured in accordance to the recommended setting [144], [145] before and after decongestion, nasal obstruction can be rated at a pressure difference of 150 Pa as flow velocity or resistance (R=ratio of pressure difference and flow velocity; cf. Table 4) [114]. One-sided reference values are discussed controversially in international literature [146]. As a consequence, total flow of >900 ml/sec at 150 Pa were reported as lower limit of normal [146]. In contrast to classical “anterior RMM“, “posterior RMM“ allows the measurement even in patients with septal perforation after placement of a pressure hose in the

Table 4: Classification of unilateral nasal obstruction using rhinomanometry [114]

Degree of obstruction	Flow velocity [cm³/s] at 150 Pa	Resistance [sPa/cm³] at 150 Pa
Not obstructed	>500	<0.3
Minimally obstructed	300–500	0.3–0.5
Moderately obstructed	180–300	0.5–0.8
Severely obstructed	<180	>0.8

mouth, but is prone for measurement errors caused by positioning of the soft palate in relation to the back wall of the pharynx.
The relevance of RMM in rhinology has been documented [144], but is limited due to missing age-stratified reference values [147]. Measurement error may reach 15% [148] and normal rhinomanometry can be obtained in 25% of patients with obvious pathological findings [149].

4.8.7 Rhinoresistometry (RRM)

Employing fluid dynamics, rhinoresistometry is a refinement of rhinomanometry [144], [150]. Measurement technique and protocol are identical to anterior RMM. To sum up, nasal resistance can be classified at a flow velocity of 250 cm³/s according to the reference values indicated in Table 5. In addition to the information availably by RMM, RRM aims at objectively detecting the aetiology of nasal obstruction. The value of RRM is still discussed controversially due to missing prospective studies.

Table 5: Classification of unilateral nasal obstruction using rhinoresistometry [114]

Degree of obstruction	Resistance [sPa/cm³] at 250 cm³/s
Not obstructed	<0.17
Minimally obstructed	0.18–0.35
Moderately obstructed	0.36–0.70
Severely obstructed	>0.70

As parameter for the inner width of the nasal cavity and endonasal friction, hydraulic diameter is indicated. After decongestion, the hydraulic diameter in a normal nose should measure ≥6 mm. This parameter can also be used for objectively evaluating changes in endonasal congestion. [151]. The comparison of a measured and a calculated graph allows objective assessment of inspiratory nasal wing collapse. Deviation of both graphs at flow velocities ≥500 cm³/s is regarded as pathological [152]. Endonasal turbulence is presented as a graph in relation to flow velocities and calculated as friction coefficient λ (normal after decongestion λ > 0.025) for both nasal sides separately.
Measurement process of RRM is reliable [152] and is aiming to objectively differentiate certain aetiologies of nasal obstruction (mucosal changes, cartilaginous/bony findings, pathological inspiratory nasal valve collapse, changes in endonasal turbulence). Results of rhinomanometry and rhinoresistometry correlate well [151].

4.8.8 Acoustic rhinometry (AR)

For acoustic rhinometry, sound is applied endonasally and based on its reflection the dimensions of the nasal cavity are calculated. Measurements should be performed under standardised circumstances [144] to secure its high reliability (measurement error: 2–4% [148], [153]). Volume and diameter of two typical locations, the internal isthmus (I-notch [mean cross-sectional area 1; MCA1] and the head of the inferior turbinate (Conchal notch [mean cross-sectional area 2; MCA2]) can be calculated [144], to geometrically determine extent and localisation of a stenosis. The nasal diffusor can be measured by the gain in diameter from I-notch to the the spacious area posterior to the C-notch [53]. Measurements distal to a severe stenosis are unreliable [154]. Reference values have been published for several groups of patients (Caucasian adults [155], [156], [157] and children [156], [158], [159]; Asian adults [155], [160] and children [161]).

4.8.9 Long-term rhinoflowmetry (LRM)

Oxygen cannulas are placed in the nostril near the floor of the nasal vestibule. Nasal airflow can be recorded for 24 hours via a portable device. Graphical presentation facilitates detailed insight into changes of nasal congestion over time including definition of the type of nasal cycle and measurement of the duration of working/resting phase [54], [64]. The aim is to objectively assess pathological mucosal swelling under conditions of daily living [64].

4.8.10 Measurement of nasal expiratory nitric oxide (NO)

Human cells produce nitric oxide (NO) from arginine by the enzymes NO-synthases [162]. Nitric oxide is produced in the nasal cavity [162], but first and foremost in the paranasal sinuses [162]. It has anti-bacterial, as well as anti-viral properties and regulates mucociliary clearance via control of nasal secretions [163], [164]. Measurement of nasal NO [in parts per million; ppm] is influenced by lower airways [165], local and systemic diseases and their therapy [166], compliance [167], nasal cycle [168], anatomy [169] and technical aspects [170]. Valid measurement protocols have been reported [171] for compliant patients [169] and infants [172]. Reliable reference values do not exist due to high interindividual variation [173].

Using nasal NO measurement, patients with chronic rhinosinusitis with polyps can be distinguished from those without polyps or healthy controls [174] and treatment effects can be monitored [175]. Most significant differences to a normal population can be obtained in patients with primary ciliary dyskinesia or cystic fibrosis [176], suggesting nasal NO as non-invasive screening tool for these diseases [177].

4.9 Special aspects to functions of respiratory mucosa

4.9.1 Particularities of children

Children in Western industrial nations suffer from 6–8 viral upper airway infections per year [178] with 5–13% developing bacterial sinusitis [179], [180]. This frequency, together with the common problems of adenoid hyperplasia favouring nasal blockage and susceptibility to local inflammation, complicate effective diagnosis of chronic rhinitis. No epidemiological data is available for non-allergic chronic rhinitis in children. In newborn and infants, a connatal hypothyroidism, a (usually autoimmune) thyreoiditis [181], or an infection with Chlamydia (usually acquired during birth) may results in symptoms of nasal obstruction [182]. Children, whose mother is heroin addicted, show nasal complaints often due to structural changes of cilia [183]. In children below the age of 12, a sweat test is mandatory to exclude cystic fibrosis in case endonasal polypoid tissue [184]. If simultaneously chronic bronchitis, sinusitis and otitis are present, a primary ciliary dyskinesia (immotile ciliary syndrome) or Kartagener syndrome should be taken into consideration [184].
In infants suffering from recurrent infections, (humoral) immunodeficiencies should be taken into account. With an incidence of 1:700 Ig-A deficiencies due to a B-cell-defect are most often diagnosed [185]. Besides, there exists evidence that in children gastroesophageal reflux is an confounding factor for recurrent upper airway infections [186]. During puberty, sexually transmitted diseases [187] (e.g. syphilis [188]) and hormonal fluctuations may result in rhinologic functional disturbances [189].
For diagnostics in and follow-up of paediatric patients, acoustic rhinometry is recommended. Growth-induced increase of airflow or decrease of resistance measured with rhinomanometry can be estimated by comparison with body weight development. Using this technique, pathophysiological effects can be distinguished from growth-induced ones.

4.9.2 Particularities of geriatric patients

During aging, nasal mucosa shows signs of atrophy with decrease of goblet cells and thickening of the basal membrane [190]. This repair is mirrored in increased expression of caspase-3, an apoptotic marker [191]. In parallel, elasticity of nasal mucosa decreases, by part due to a decreasing level of oestrogen. Accordingly, in postmenopausal women, substitution using a nasal spray has been recommended [192], [193].
Results on the effect of age on mucociliary clearance are contradicting: While some studies showed no effect on mucociliary clearance [194], [195], others were able to demonstrate a decrease of ciliary beat frequency with increase of saccharin transit time as equivalent of deterioration of mucociliary clearance in old age [196]. Viscosity of nasal secretion increases and causes post nasal drip with consecutive repeated clearing of the throat.
As structural change of respiratory mucosa in old age, single instead of double tubules were detected using transmission electron microscopy. In rhinoscopy, a wide nasal cavity with quite dry nasal mucosa lining is typically seen. Increased turbulence despite objectively free nasal passages may result in a feeling of nasal obstruction (paradoxical nasal blockage). Accordingly, endonasal volume and areas of MCA1 and MCA2 are enlarged [197]. Prevalence of endonasal polyps increases with age [198]. Also, primary atrophic rhinitis is associated with aging [199]. Due to the frequent medication with multiple drugs, rhinitis medicamentosa has a high relevance as differential diagnosis [199], [200]. As therapy, topical steroids (sometimes under addition of propylene glycole), expectorant drugs to stimulate exocrine glands and nasal douching with saline are recommended [184].

4.9.3 Influence of diabetes mellitus on the respiratory function

In diabetics, upper airway infections do not occur more frequently than in healthy subjects [201]. There exists controversial discussion whether the diabetic nose is more frequently colonised by pathogens, such as S. aureus [202].
Much clearer is the situation in diabetics undergoing dialysis: These have in 53.4% (non-diabetics: 18.6%) a nasal colonisation with methicillin-sensible and in 19% with methicillin-resistant S. aureus (MRSA; non-diabetics: 6.0%). In addition, if a patient has a central-venous catheter, his risk of endonasal colonisation of S. aureus is 35 times increased in comparison to patients with arterio-venous fistula [203].
A polymorphism of vitamine D receptor in diabetics has also been associated with colonisation of S. aureus [204]. Moreover, concentration of the bactericidal nasal NO is decreased in insulin dependent diabetes mellitus [166]. In parallel, diabetics have an increased resistance measured by RMM. This increase is more pronounced before than after decongestion, indicating a chronic state of increased congestion.
Chronic congestion is also favoured by mucociliary clearance, the latter being reduced in diabetics [205], [206] due to alcalised pH-values of nasal secretions [207]. Insulin-dependent diabetes mellitus and diabetes lasting for more than ten years result in further deterioration of mucociliary clearance [207].
Diabetics have more frequent clinical signs of a dry nose [208] and are at a higher risk to suffer from non-invasive

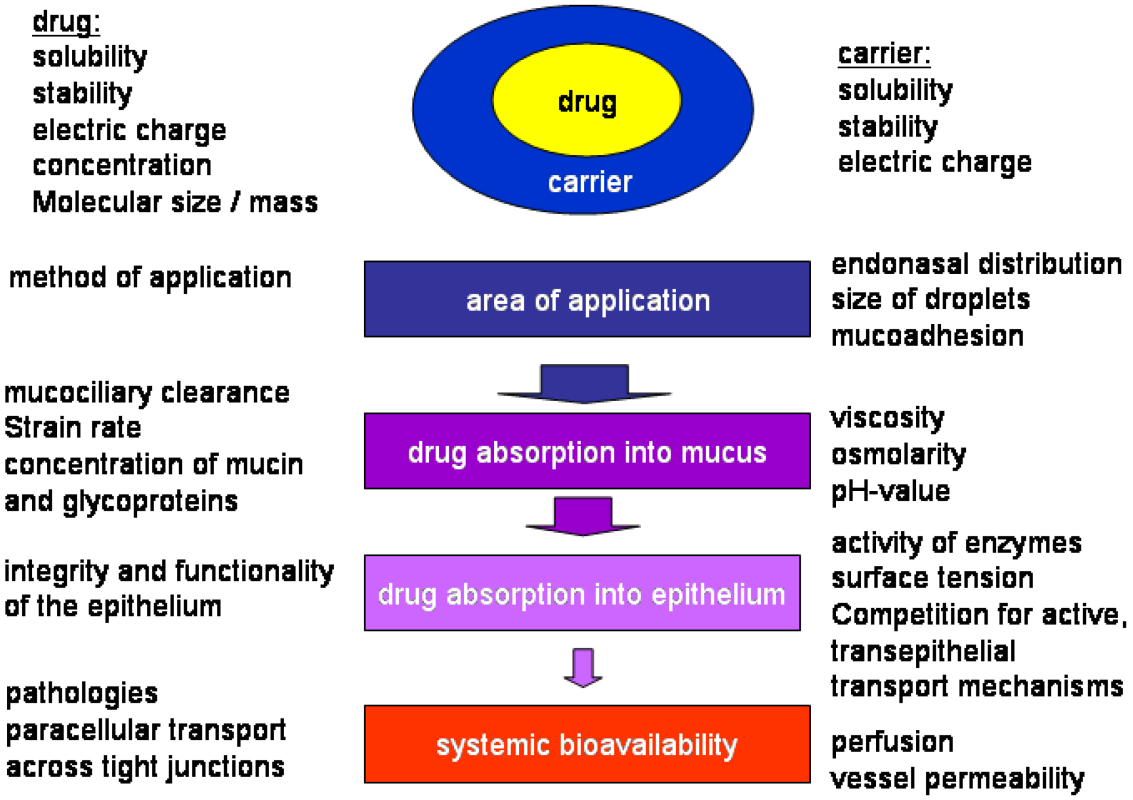

Figure 2: Influencing factors on the mode of action of topically applied endonasal medication

[209] or invasive [210] fungal sinusitis [211]. A topical moistening by employment of nasal douching and oil has been recommended as therapy or prophylaxis, respectively [208].

4.9.4 Nasal respiratory mucosa as area of drug application

If topical drug application is discussed, it is of special importance to distinguish pharmacokinetics and pharmacodynamics. The pharmacokinetic science describes effects of the human body on the drug, while pharmacodynamics aims at studying the effect of the drug on the human body. In the following, special pharmacokinetic aspects are elaborated on.

Distribution of drugs in the nose and the paranasal sinuses

Use of nasal spray transports only a small part of the dosage to the paranasal sinuses, while the biggest part is deposited in the inferior meatus and on the head of the inferior turbinate [212]. For optimal application with regard to the frontal sinus, Vertex-to floor position has been recommended [213]. Effectivity of dexamethasone nasal drops in this position has been demonstrated with prevention of frontal ostium restenosis [214]. Unfortunately, compliance to employ this position is limited by existing co-morbidities (e.g. diseases of the cervical spine). In contrast, inhalation devices using alternating pressure waves reach the paranasal sinuses reliably within three minutes near the ostium [215].

Another application form is nasal douching being well-tolerated by 80% of patients. To rinse a paranasal sinus effectively, an ostium with a diameter of 3.95 mm is necessary [216]. Postoperatively, nasal douche is a reliable mode of application [215], [217]. To rinse the frontal sinus, a maximal forward bending ("Vertex to floor-position") with maximal volume of the employed squeeze bottle is recommended. Generally, nasal douching should be performed with high volume and low pressure [218].
An additional innovative method of topical therapy is the employment of drug-releasing stents [219]. Releasing dexamethasone, granulation formation [96] and osteoneogenese [93] are decreased significantly, without impeding reepithelialisation. While stents may provoke a local foreign body reaction with biofilm formation, they can reliably provide topical application to inaccessible areas of the upper airways.

Aspects regarding resorption and absorption of medication in nose and sinuses

Mucociliary clearance limits the dosage of topically applied drugs (cf. Figure 2). Particle transport of MCC restricts application duration of topical medication to an estimated 20–30 min. [220], [221]. In addition, mechanical activity of cilia destroys drug molecules [37], [220]. Moreover, nasal mucus is a barrier to diffusion [222], [223]. Molecular size and electric charge are decisive for the diffusion capacity of a drug [222], [224]. With regards to this background, microemulsions were developed to increase resorption into nasal mucus [225].

Mucins of the gel phase conjugate drugs and change their absorption properties. This may be taken advantage of by supply of lipophil pro-forms of the active substances [226]. Alternatively, medication influences mucin secretion [227] and it viscosity [228]. For drugs interacting with glycoproteins of nasal mucus [229], this property may limit drug permeation [230]. Especially charged particles with the capacity to build hydrogen bonds and lipophil particles are affected [231].

Nasal mucosa is well permeable for hydrophilic substances and lipophilic ones below a molecular mass of 1000 Da [232], [233], because the nasal membrane has pores with dimensions of 3.9 to 8.4 Å. Transcellular transport is possible for lipophil substances, while charged hydrophilic drugs are mainly transported paracellularly [234]. Paracellular transport happens via tight junctions (TJ) or the zonula occludens (ZO) [234]. Connections between goblet cells or goblet cells and ciliated cells are rated as loose [234], [235]. Besides, they show a high variation of permeability [236]. Many substances are inactivated by the high enzymatic activity (local "first-pass effect") of nasal mucosa during the process of absorption [234]. Carrier systems (e.g. chitosan [135], [237]), are employed to enhance nasal bioavailability. In parallel, a strategy has recently been developed to intraoperatively employ resorbable, medication-releasing application systems to increase the applicated dosage. Possiblities of technical refinement of modified systems are limited, as mucosal function should not be harmed.

Nasal drugs have to be well tolerated, exert beneficial effect on ciliary function and if applicable should show good dispensing properties (if applicated as nasal spray) and/or a high degree of adhesion (for better resorption).

5 Chronic rhinitis – selected disorders

In the following section, selected typical forms of chronic rhinitis will be discussed. Allergic rhinitis is differentiated from non-allergic forms. 57% of patients with chronic rhinitis suffer from a non-allergic form [238]. Classification of non-allergic rhinitis is still controversially discussed and quite complex [184]. Some non-allergic, non-infectious forms of rhinitis with a pathophysiology closely connected to nasal respiratory mucosa are summarised here. With regards to different non-allergic forms, it is referred to two elaborative and recent publications [184], [239].

5.1 Rhinitis medicamentosa

Rhinitis medicamentosa, also called drug-induced rhinitis, is defined as pathological congestion or the nasal mucosa with nasal blockage, nasal drainage (anterior rhinorrhea and post nasal drip) and optional sneezing. It occurs as a direct consequence of drug intake, with the classical disorder developing after prolonged use of decongesting nasal drops [240]. Due to its high prevalence, rhinitis medicamentosa is of special significance among the various subtypes of non-allergic rhinitis. Incidence is estimated as 6–9% in patients with nasal obstruction [241], [242] and 1–7% [241] of unselected patients in an ENT office.

Reported drugs that may possibly cause rhinitis medicamentosa (cf. Table 6) belong to various groups of drugs. In 1931, this disorder was first reported by Fox [243]. As pathophysiology, respiratory mucosa becomes accustomed to the drug, with the latter resulting in minor [244] and shorter [245] drug-induced effect (hyporeactivity). It remains unknown whether this is a consequence of tissue hypoxia with reactive hyperaemia due to vasodilatation [246], a negative presynaptic feedback mechanism at α-2-receptors [247], and/or change of vasomotoric tonus by increased activity of cholinesterase [248], [249]. Based on structural deformities, increased permeability [250] and secretion of glands [251] were reported.

The risk to suffer from rhinitis medicamentosa is gender independent and it most commonly affects middle aged adults. The postulated increased susceptibility of patients with chronic inflammation of nasal respiratory mucosa [252] failed to be proven [253]. The risk to acquire this disease dramatically increases if topical sympathomimetics are applied three times a day for more than 10 days [245], [253], [254] or night-time application exceeds 4 weeks [245], [255].

Decongestants used to have benzalkonium chloride as a preservative. This quartery ammonium compound is capable of destroying cell walls of microorganisms. In-vitro, toxic effects on cilia [252], deterioration of granulocyte chemotaxis and phagocytosis [256] and of neutrophil defense [257] have been reported. Because benzalkonium chloride aids development of drug-induced rhinitis [253], [258], aggravates its symptoms [241], [259] and may provoke rhinitis medicamentosa if used alone [260], only a few formulations in Europe are still available containing benzalkonium chloride [240].

Structural changes in rhinitis medicamentosa include damage and loss of cilia [261], metaplasia [261] and epithelial oedema [262], tears in the basal membrane [261] and openings in subepithelial endothel [250], [261] together with vasodilatation [241]. Moreover, hyperplasia of goblet cells [251], [262] and infiltration of inflammatory cells [263] were demonstrated probably as equivalent of reparative changes with increased expression of epithelial growth factor [263]. As complication, septal perforation may occur [264]. If not adequately treated, this disease leads to secondary atrophic rhinitis up to frank clinical picture of ozaena [265].

Careful history taking with questions regarding last topical and complete current medication is the key element to diagnose this disorder. For therapy planning, detailed history of previously unsuccessful therapeutic trials is helpful. Clinical examination should be performed in the early morning to provide the typical clinical picture with congested nasal mucosa in nasendoscopy after last topical medication on the previous evening [241]. Nasendoscopy is also beneficial to detect structural changes,

Table 6: Typical indication, group of drugs and ingredients, which may trigger a drug-induced rhinitis (modified [254, 260, 263, 266])

After systemic application:	
diuretic	Amylorid Hydrochlorothiazid
high blood pressure drug	ACE inhibitor beta blocker alpha-adrenergic blocker (Doxazosin, Phentolamine, Prazosin) Imidazoline (Clonidine) Guanethidine Hydralazine / Dihydralazine Methyldopa (Reserpine)
drugs for erectile dysfunction	Phosphodiesterase Inhibitor (Sildenafil citra, Tadalafil, Vardenafil)
hormones	Oestrogen Oral contraceptives
pain reliever	Acetylsalicylic acid Non-steroideal anti-inflammatory drugs (NSAIDs)
psychotropic drugs	Benzodiazepine (Chlordiazepoxide) Tricyclic antidepressant (Amitriptyline) Classical neuroleptics / Phenothiazin (Chlorpromazine, Thioridazine) Atypical antipsychotic / Risperidone
Others	Tropane Alkaloids (Cocaine) Anticonvulsant (Gabapentin) Cyclosporine
After topical application:	
Sympathomimetic drugs	Amphetamine (Norephedrine, Amphetamine) Alkaloids (Ephedrine, Pseudoephedrine, Mescaline, Caffeine) α1-adrenergic receptor agonist (Phenylephrine)
Imidazoline	Clonidine Naphazoline Oxymetazoline Xylometazoline
Other	Benzalkonium chloride

which eventually may have led to the use of nasal drops. For apparative diagnostics, anterior rhinomanometry, acoustic rhinometry and measurement of mucociliary function have been recommended [266].

For successful therapy, identification and elimination of the causative drug is decisive. The patient has to be informed of the underlying pathophysiology to improve compliance ("counselling") [267]. Sudden stop of intake leads to a rebound-swelling. In severe cases, separate cessation of application on both nasal sides is mandatory. Topical application of steroids (in severe cases starting before cessation of the causative agent) is able to effectively diminish rebound-swelling [268], [269]. Onset of decongestive effect is expected 4–7 days after start of steroid use [262]. A surgical procedure like a turbinoplasty may ease withdrawal for the patient (reported success rate of 88% for laser turbinoplasty [270]), but will not cure the disease. After repeated turbinoplasty due to prolonged abuse of decongestants, a surgically caused nasal dryness may develop. Therefore a three month time interval between cessation of abuse and surgical correction has been recommended [241].

The necessity to diagnose and possibly treat the underlying pathology, initially leading to abuse of decongestants, is not to be underestimated [241]. The underlying disorder for topical medication resulting in rhinitis medicamentosa is in 30% of cases an episode of upper respiratory tract infection, in 22% a non-allergic, non-infectious rhinitis, in 16% allergic rhinitis, in 30% structural deformities (such as septal deviation, endonasal polyps, posttraumatic pathologies), and in 3% hormonal changes [271].

For prevention, avoidance of benzalkonium chloride is mandatory [259]. Patients have to be aware of their persistent susceptibility to develop relapse of rhinitis medicamentosa even one year after onset of successful treatment [272]. Furthermore, control visits every three months have been recommended. During infection, short-term use (up to 3 days) of nasal decongestants at lower concentrations may present a preventive strategy.

5.2 Atrophic rhinitis, anterior rhinitis sicca and ozaena

Atrophic rhinopathy is characterised as a chronic inflammation of unclear aetiology, leading to atrophy and decay of the entire endonasal mucosa and the underlying bone. A primary form, foremost occurring in developing countries and showing spontaneous development, is distinguished from a secondary form after rhinologic surgical procedures (especially: turbinoplasty), trauma, infection, granulomatous inflammation, or radiation [273]. For the primary form, six times more females than males are af-

fected in developing countries. Patients live 1.5 times more often in rural areas than in urban ones [274]. A genetic component has been reported [275] with incidence decreasing in recent years [276]. A vetenerian type of primary atrophic rhinitis is often seen in pigs, resulting in development of multiple veterinary vaccines against the causative pasteurella multocida toxin [277].

Endonasal crust formation (usually on the middle turbinate), epithelial metaplasia with loss of cilia and superinfection of nasal mucosa (with detection of Klebsiella ocaena in 65–100% [274], [278]) are visible. In addition, vasodilatation [274] and changes in bone formation including osteitis of the turbinate bony may occur [278]. As a consequence, MCA1 is enlarged [279]. A classical smell develops and polyp formation, chronic dacryocystitis [280], scar-induced stenosis of the choanae [281], or pharyngitis sicca [282] are possible. The endpoint of atrophic rhinitis is called ozaena ('stink-polyp'). The patient does not realise his odour, but complaints about anosmia [283].

Histologically, increased activity of caspace-3 in the epithelium and subepithelial glands has been demonstrated as indicator for apoptosis [284]. Absolute quantity and chemical quality of phospholipids (with surfactant) is decreased [285]. Therefore, a lack of surfactant has been suspected as aetiopathogenesis of atrophic rhinitis [285]. By application of angiogenetic inhibitors, a similar disorder can be provoked in a recently reported animal model [286].

Anterior rhinitis sicca is not easily distinguished from atrophic rhinitis, but affects only the mucosa of the anterior septum with elsewhere in the nasal cavity presenting normally configurated mucosa. In case of perichondritis, ulcer formation up to septal perforation may occur. Patients report of nasal dryness, itchiness and crust formation. Aetiology is unknown. Physical, chemical (e.g. snuff, cocaine), and mechanical irritation (digital manipulation) are discussed.

Based on a progressively deteriorated mucociliary clearance, differentiation of rhinitis sicca to atrophic rhinitis is possible. For diagnosis, endoscopy, histological and microbiological examination, imaging and allergy tests are mandatory [273], because 60% have a sinusitis [274] and 85% an allergic disposition. Endonasal resistance if below normal, which is called "paradoxical nasal obstruction" in case of subjective nasal blockage [273]. At a sensitivity of 95% (specificity: 77%) an atrophic rhinitis is diagnosed, if the patient's suffers from chronic sinusitis for more than six months and shows an additional two out of five features. These include: nasal bleeding, anosmia, purulent rhinorrhea, chronic upper airway infection, and having had two or more sinus surgeries [287].

Next to an infectious aetiology (due to Klebsiella ozaenae and Bacillus foetidus [273], [282]), environmental, endocrinologic and allergic-immunologic causes have been suspected [274], [282]. Atrophic rhinitis occurs more commonly near desserts [282] in patients with a relatively wide nasal cavity [288]. In parallel, surgical procedures narrowing the nose (up to its closure) cure the disease. From this background, disturbance of endonasal airflow was estimated as underlying pathophysiology. Accordingly, atrophic rhinitis was called a consequence of nasal cycle deterioration [289], [290].

With regards to treatment, no prospective controlled studies have been reported [291]. Empiric conservative treatment consists of local application of dexpanthenol and oil to resolve the crusts and to stimulate the regeneration of nasal mucosa. Sesame and soja oil improve ciliary beat frequency in contrast to essential oils [292]. Additional nasal douching, occasionally under supplementation of glucose (up to 25%), sole inhalation and sleeping next to an opened window have been recommended [293]. Antibiotics (rifampicin: [294]) have been used in case of purulent secretion [295] or as adjunct to surgical procedures (aminoglycoside: [296]), without being able to cure the disease [273]. Even closure of the nostrils e.g. by an obturator, has been suggested [297].

5.3 Vasomotor rhinitis

Vasomotor rhinitis (also called: hyperreflectoric rhinitis) is a disorder diagnosed by exclusion. Among non-allergic rhinitis, this subgroup is most common, affecting 60% of patients [298]. Aetiology is unclear with both episodical and perennial clinical manifestations occurring. A cholinergic course, going together with increased nasal secretion ('Runner'), can be distinguished from a clinical course characterised by nasal obstruction ('Blocker') mediated by nociceptive nerve fibre.

Reported trigger mechanisms include cold air [299], change of temperature, food (spices, alcohol), physical activity, smoke, dust and automobile exhaust.

Histologically, a strong expression of NO-synthetase is detected in subepithelial smooth muscle cells of the cavernous sinus [300]. Moreover, intense staining with 3-Nitrotyrosin, a product of NO-metabolism [300]. SP, CGRP, and VIP are increased, while IL-12 is diminished. Eosinophilic findings contradict the presence of vasomotor rhinitis [291].

A missing change of endonasal resistance after application of oxymetazoline supports diagnostically the hypothesis of etiologic changed autonomic innervation [301] and is helpful for posing the diagnosis. Measurements of heart frequency show a relative, parasympathetic hyperreactivity [302]. Based on standardised questionnaires, void of symptoms in spring and in presence of cats, missing allergic diseases of the parents, symptoms associated with perfumes and scents and age of first manifestation show a predicative value for suffering from vasomotor rhinitis [303].

Topical antihistamines [304], glucocorticoids [305] and ipatropium bromide are very effective in treating vasomotor rhinitis [298]. Interestingly, in a subgroup with complaints triggered by wind and change of temperature, Fluticasone treatment showed no significant benefit [306]. Locally injected botulinum toxine (I0 international units) improves subjective complaints of patients with vasomotor rhinitis for eight weeks [307]. Vidian neurec-

tomy is reported to achieve five year lasting cessation of symptoms in 80% of patients. Acupuncture used in a placebo-controlled phase III study, showed a positive effect on a nasal symptom score [308].

6 Conclusion

Respiratory mucosa of the nose and paranasal sinuses exerts various functions, with their complex morphological and functional correlations becoming increasingly well understood.

Derangement of the respiratory function is one of the most frequent disorders of human beings. Due to available treatments with antibiotics and effective topical steroids, frequency of disorders is changing. Previously less common subtypes of chronic rhinitis gain increased importance. To encourage detailed pathophysiological understanding, selected disorders have been presented with their treatment options.

Early diagnostics and differentiated treatment can prevent continuous loss of function and development of consecutive disorders. This may help to avoid increased treatment costs. In this way, diagnosis and therapy of respiratory function gain next to their inherent individual importance increased relevance from the perspective of society.

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